

Table SI. Detailed information of 443 differential proteins in BDE 4th and 8th Ger and HOC group (filtered with threshold value of expression fold change >2 or < 0.5 and P<0.05).

Protein	P-value BDE 4 th and 8 th Ger/HOCs Ratio		Regulated type	Length (kDa)
Poly(U)-binding-splicing factor PUF60	1.432	0.001	UP	564
Formin-binding protein 4	1.819	0.001	UP	1031
Ubiquitin carboxyl-terminal hydrolase 10	1.529	0.001	UP	792
Nuclear inhibitor of protein phosphatase 1	1.670	0.002	UP	351
Glutamate-rich WD repeat-containing protein 1	1.977	0.002	UP	446
28S ribosomal protein S28, mitochondrial	1.379	0.002	UP	186
TGF-beta-activated kinase 1 and MAP3K7-binding protein 1	2.795	0.002	UP	502
28S ribosomal protein S26, mitochondrial	1.890	0.003	UP	200
N-terminal Xaa-Pro-Lys N-methyltransferase 1	1.641	0.003	UP	223
Ubiquitin thioesterase otulin	9.714	0.004	UP	352
Vacuolar protein sorting-associated protein 37B	2.087	0.005	UP	285
MKI67 FHA domain-interacting nucleolar phosphoprotein	1.390	0.005	UP	317
Ubiquitin-conjugating enzyme E2 variant 1	1.688	0.005	UP	147
Phosphatidate cytidyltransferase, mitochondrial	2.778	0.005	UP	337
28S ribosomal protein S23, mitochondrial	1.800	0.006	UP	177
H/ACA ribonucleoprotein complex non-core subunit NAF1	3.349	0.006	UP	489
Signal-induced proliferation-associated protein 1	1.303	0.007	UP	1037
THO complex subunit 6 homolog	1.422	0.007	UP	341
Cystatin-B	2.182	0.007	UP	98
Suppressor of SWI4 1 homolog	1.546	0.008	UP	470
TATA box-binding protein-like protein 1	4.638	0.008	UP	186
Diphosphoinositol polyphosphate phosphohydrolase 1	1.339	0.008	UP	168
Polyglutamine-binding protein 1	12.375	0.009	UP	263
Malonate--CoA ligase ACSF3, mitochondrial	25.564	0.009	UP	583
Phosphatidylinositol 4-phosphate 3-kinase C2 domain-containing subunit alpha	1.482	0.009	UP	1686
28S ribosomal protein S16, mitochondrial	2.353	0.010	UP	135
Ubiquitin-associated protein 2-like	1.228	0.010	UP	1107
Ribosomal protein S6 kinase beta-2	11.010	0.010	UP	485
6-phosphogluconolactonase	1.580	0.010	UP	257
Arpin	2.269	0.010	UP	226
Pantothenate kinase 4	1.386	0.010	UP	820
Activator of 90 kDa heat shock protein ATPase homolog 1	1.471	0.011	UP	338
60S ribosome subunit biogenesis protein NIP7 homolog	1.738	0.012	UP	180
40S ribosomal protein S17	1.459	0.012	UP	135
Ubiquitin carboxyl-terminal hydrolase 25	1.675	0.012	UP	1055
Forkhead box protein K1	2.265	0.013	UP	719
Hydroxymethylglutaryl-CoA synthase, cytoplasmic	1.788	0.014	UP	520
Transportin-2	1.260	0.014	UP	887
Barrier-to-autointegration factor	10.379	0.014	UP	89

Transcription elongation factor SPT5	1.414	0.014	UP	1082
Mediator of RNA polymerase II transcription subunit 20	1.572	0.014	UP	212
Cleavage and polyadenylation specificity factor subunit 3	1.886	0.015	UP	684
Mitogen-activated protein kinase 1	1.358	0.015	UP	358
60S ribosomal protein L23	1.916	0.015	UP	140
ATP-dependent RNA helicase DHX8	6.542	0.015	UP	1244
Structural maintenance of chromosomes protein 2	3.565	0.015	UP	1191
Methionine aminopeptidase 2	1.584	0.015	UP	478
Peptidyl-prolyl cis-trans isomerase FKBP3	1.313	0.015	UP	224
Ribonuclease P protein subunit p29	1.835	0.015	UP	221
Testis-expressed protein 10	1.468	0.016	UP	928
WD repeat-containing protein 75	1.901	0.016	UP	830
Jupiter microtubule associated homolog 2	2.163	0.016	UP	190
Torsin-1A-interacting protein 2, isoform IFRG15	1.914	0.017	UP	131
Probable ATP-dependent RNA helicase DDX49	1.359	0.017	UP	480
RNA-binding protein 15	1.548	0.018	UP	962
Peroxisomal membrane protein PMP34	2.030	0.018	UP	307
Probable ATP-dependent RNA helicase DDX46	1.605	0.018	UP	1032
ADP-ribosylation factor-like protein 2	1.305	0.018	UP	184
Neuroguidin	2.632	0.018	UP	315
Flap endonuclease 1	7.703	0.018	UP	378
DNA repair protein RAD50	3.415	0.019	UP	1312
Gem-associated protein 5	3.363	0.019	UP	1502
Signal recognition particle 19 kDa protein	1.589	0.019	UP	144
ARF GTPase-activating protein GIT2	1.477	0.020	UP	708
DCN1-like protein 1	1.432	0.020	UP	259
Glutaredoxin-1	5.100	0.021	UP	107
Protein phosphatase 1G	1.554	0.021	UP	542
Rapamycin-insensitive companion of mTOR	1.238	0.021	UP	1708
Annexin A5	1.413	0.022	UP	319
Activating signal cointegrator 1	1.925	0.023	UP	581
Splicing factor U2AF 35 kDa subunit	1.517	0.023	UP	239
Heat shock protein 105 kDa	1.884	0.023	UP	858
Cleavage and polyadenylation specificity factor subunit 7	1.349	0.023	UP	471
Annexin A3	1.285	0.024	UP	323
Mediator of DNA damage checkpoint protein 1	14.740	0.025	UP	1707
Histone acetyltransferase type B catalytic subunit	63.701	0.025	UP	416
Zinc finger C2HC domain-containing protein 1A	1.624	0.025	UP	324
tRNA methyltransferase 10 homolog A	6.149	0.025	UP	328
Armadillo repeat-containing X-linked protein 3	1.465	0.026	UP	379
28S ribosomal protein S11, mitochondrial	2.116	0.026	UP	191
Cytochrome c oxidase subunit 4 isoform 1, mitochondrial	1.435	0.026	UP	169

28S ribosomal protein S10, mitochondrial	2.254	0.026	UP	160
Josephin-2	7.328	0.026	UP	188
Regulatory-associated protein of mTOR	1.430	0.027	UP	1335
Cyclin-dependent kinase inhibitor 2A	4.528	0.028	UP	168
Nucleoredoxin	1.257	0.028	UP	435
28S ribosomal protein S18b, mitochondrial	1.440	0.029	UP	254
Peptidyl-prolyl cis-trans isomerase A	1.446	0.029	UP	164
CAD protein [Includes: Glutamine-dependent carbamoyl-phosphate synthase	1.828	0.029	UP	2225
SUN domain-containing protein 2	2.178	0.029	UP	731
Methylated-DNA--protein-cysteine methyltransferase	3.573	0.030	UP	211
Muscleblind-like protein 1	1.213	0.030	UP	341
Tyrosine-protein kinase Fer	1.247	0.030	UP	823
Nascent polypeptide-associated complex subunit alpha	1.463	0.030	UP	215
Signal-induced proliferation-associated 1-like protein 3	1.452	0.030	UP	1776
Metastasis-associated protein MTA3	2.218	0.031	UP	591
Cordon-bleu protein-like 1	1.425	0.034	UP	1273
Uncharacterized protein C6orf203 homolog	1.946	0.034	UP	240
La-related protein 1	1.665	0.034	UP	1072
N-alpha-acetyltransferase 50	1.918	0.034	UP	169
40S ribosomal protein S24	1.609	0.034	UP	133
ADP-sugar pyrophosphatase	1.607	0.034	UP	218
Negative elongation factor A	8.183	0.034	UP	530
THO complex subunit 3	1.217	0.034	UP	351
Ankyrin-2	2.989	0.035	UP	3898
Exportin-T	1.209	0.035	UP	963
Mitogen-activated protein kinase 14	1.592	0.035	UP	360
Intraflagellar transport protein 122 homolog	3.296	0.035	UP	1182
Histone-lysine N-methyltransferase SETD2	4.826	0.035	UP	2537
Protein Red	1.444	0.035	UP	557
Mitotic spindle assembly checkpoint protein MAD2A	3.441	0.035	UP	205
Protein quaking	1.426	0.035	UP	341
Homer protein homolog 3	1.247	0.036	UP	356
Nuclear factor 1 C-type	9.460	0.037	UP	439
Protein MEMO1	1.608	0.037	UP	297
RNA-binding protein 39	1.461	0.037	UP	530
Symplekin	1.613	0.037	UP	1284
Phospholipid hydroperoxide glutathione peroxidase	1.395	0.037	UP	197
DNA topoisomerase 2-alpha	1.959	0.038	UP	1528
Phosphatidylinositol transfer protein alpha isoform	1.333	0.038	UP	271
DDB1- and CUL4-associated factor 7	1.521	0.039	UP	342
Protein arginine N-methyltransferase 7	5.703	0.040	UP	692

Nucleoporin Nup37	1.568	0.040	UP	326
TBC1 domain family member 1	1.242	0.040	UP	1255
Arginine/serine-rich coiled-coil protein 2	5.981	0.041	UP	376
Something about silencing protein 10	2.498	0.041	UP	469
Glomulin	1.370	0.041	UP	596
WD repeat domain phosphoinositide-interacting protein 3	1.275	0.041	UP	344
Cyclin-dependent kinase 13	10.995	0.041	UP	1511
Deoxyhypusine hydroxylase	1.770	0.042	UP	302
Elongin-B	1.633	0.043	UP	118
Armadillo repeat-containing protein 6	3.204	0.043	UP	468
RWD domain-containing protein 1	1.936	0.044	UP	243
Peptidyl-prolyl cis-trans isomerase F, mitochondrial	2.235	0.044	UP	206
Bystin	1.674	0.045	UP	436
Mesenteric estrogen-dependent adipogenesis protein	1.513	0.045	UP	303
26S proteasome non-ATPase regulatory subunit 13	1.314	0.045	UP	376
28S ribosomal protein S7, mitochondrial	1.388	0.045	UP	242
Splicing factor 3A subunit 3	1.293	0.046	UP	501
Nuclear cap-binding protein subunit 2	1.722	0.046	UP	156
Probable ATP-dependent RNA helicase DDX27	1.815	0.046	UP	760
Guanine nucleotide exchange factor MSS4	1.947	0.047	UP	123
rRNA 2'-O-methyltransferase fibrillarin	2.401	0.047	UP	327
Casein kinase II subunit alpha'	1.275	0.047	UP	350
Transcription termination factor 2	12.113	0.047	UP	1138
SWI/SNF complex subunit SMARCC2	1.550	0.047	UP	1213
Polymerase delta-interacting protein 3	1.512	0.048	UP	420
A-kinase anchor protein 8	1.946	0.048	UP	687
Serine/threonine-protein kinase PRP4 homolog	2.092	0.048	UP	1007
Charged multivesicular body protein 3	1.346	0.048	UP	224
Ferredoxin-2, mitochondrial	4.193	0.048	UP	174
Large proline-rich protein BAG6	1.526	0.048	UP	1154
28S ribosomal protein S24, mitochondrial	23.185	0.048	UP	167
Exosome complex component RRP4	1.465	0.048	UP	293
Eukaryotic translation elongation factor 1 epsilon-1	1.317	0.048	UP	174
Protein phosphatase 1 regulatory subunit 12B	1.666	0.048	UP	976
Protein prune homolog 2	4.592	0.049	UP	3084
Fas apoptotic inhibitory molecule 1	1.652	0.049	UP	179
Serine/arginine repetitive matrix protein 2	1.969	0.049	UP	2703
U4/U6 small nuclear ribonucleoprotein Prp3	1.439	0.049	UP	683
E3 ubiquitin-protein ligase TRIM47	1.223	0.049	UP	641
ATP-dependent RNA helicase DDX18	2.178	0.050	UP	660
Macrophage-expressed gene 1 protein	0.083	0.010	DOWN	713
Oxysterol-binding protein-related protein 9	0.648	0.021	DOWN	736

Endoplasmic reticulum mannosyl-oligosaccharide 1,2-alpha-mannosidase	0.492	0.048	DOWN	658
Probable 2-oxoglutarate dehydrogenase E1 component DHKTD1, mitochondrial	0.604	0.013	DOWN	921
Adenylyltransferase and sulfurtransferase MOCS3	0.164	0.027	DOWN	460
Exocyst complex component 6B	0.747	0.023	DOWN	810
Canalicular multispecific organic anion transporter 2	0.125	0.015	DOWN	1523
A-kinase anchor protein 5	0.009	0.001	DOWN	745
FERM, ARHGEF and pleckstrin domain-containing protein 1	0.184	0.017	DOWN	1048
Calpain-2 catalytic subunit	0.750	0.028	DOWN	700
Syntenin-1	0.338	0.042	DOWN	299
Collagen alpha-1(XV) chain	0.055	0.006	DOWN	1367
Tyrosine-protein phosphatase non-receptor type 9	0.630	0.042	DOWN	593
Exocyst complex component 7	0.511	0.017	DOWN	697
Sialidase-1	0.149	0.034	DOWN	409
Mitochondrial import inner membrane translocase subunit TIM44	0.233	0.017	DOWN	452
Neutral amino acid transporter A	0.318	0.005	DOWN	532
Syndecan-4	0.397	0.001	DOWN	198
Rho GTPase-activating protein 6	0.094	0.033	DOWN	987
OX-2 membrane glycoprotein	0.263	0.032	DOWN	278
Ninjurin-1	0.120	0.040	DOWN	152
Integrin beta-5	0.405	0.035	DOWN	798
Cathepsin S	0.005	0.001	DOWN	340
14-3-3 protein sigma	0.424	0.003	DOWN	248
Electrogenic sodium bicarbonate cotransporter 1	0.212	0.004	DOWN	1079
Palmitoyl-protein thioesterase 1	0.326	0.036	DOWN	306
Target of Myb protein 1	0.378	0.009	DOWN	492
Signal transducing adapter molecule 2	0.767	0.030	DOWN	523
Tripeptidyl-peptidase 1	0.443	0.027	DOWN	562
Coronin-1A	0.014	0.004	DOWN	461
Collagen alpha-1(IV) chain	0.420	0.022	DOWN	1669
Fructose-bisphosphate aldolase C	0.075	0.036	DOWN	363
cAMP-dependent protein kinase catalytic subunit alpha	0.668	0.001	DOWN	351
Integrin alpha-M	0.011	0.005	DOWN	1153
Ectonucleotide pyrophosphatase/phosphodiesterase family member 1	0.507	0.010	DOWN	906
Low affinity immunoglobulin gamma Fc region receptor II	0.057	0.006	DOWN	330
Apolipoprotein E	0.025	0.003	DOWN	311
Lysozyme C-2	0.027	0.003	DOWN	148
Superoxide dismutase	0.770	0.009	DOWN	222
Small integral membrane protein 1	0.577	0.039	DOWN	78
Fibronectin	0.076	0.030	DOWN	2477

Keratin, type II cytoskeletal 8	0.086	0.048	DOWN	490
Integrin beta-2	0.004	0.000	DOWN	771
Inositol 1,4,5-trisphosphate receptor type 1	0.386	0.046	DOWN	2749
Beta-glucuronidase	0.108	0.008	DOWN	648
Intercellular adhesion molecule 1	0.060	0.025	DOWN	537
Complement C1q subcomponent subunit B	0.016	0.002	DOWN	253
CD44 antigen	0.231	0.033	DOWN	778
Interleukin-4 receptor subunit alpha	0.066	0.008	DOWN	810
Lysosomal protective protein	0.436	0.020	DOWN	474
Methanethiol oxidase	0.064	0.029	DOWN	472
Receptor-type tyrosine-protein phosphatase alpha	0.821	0.027	DOWN	829
Cathepsin D	0.282	0.049	DOWN	410
Syndecan-1	0.207	0.031	DOWN	311
Lysosomal acid phosphatase	0.398	0.018	DOWN	423
Myristoylated alanine-rich C-kinase substrate	0.750	0.049	DOWN	309
Alpha-mannosidase 2	0.613	0.047	DOWN	1150
Sodium- and chloride-dependent glycine transporter 1	0.567	0.047	DOWN	692
Adenylosuccinate synthetase isozyme 1	0.012	0.001	DOWN	457
Macrophage scavenger receptor types I and II	0.005	0.001	DOWN	458
Dipeptidase 1	0.158	0.042	DOWN	410
Macrosialin	0.002	0.000	DOWN	326
Protein NEDD1	0.668	0.020	DOWN	660
Thromboxane-A synthase	0.009	0.001	DOWN	533
Fibulin-2	0.079	0.032	DOWN	1221
Natural resistance-associated macrophage protein 1	0.028	0.003	DOWN	548
Mannosyl-oligosaccharide 1,2-alpha-mannosidase IA	0.031	0.003	DOWN	655
Glutathione peroxidase 3	0.134	0.030	DOWN	226
Programmed cell death protein 2	0.442	0.009	DOWN	343
Aldehyde dehydrogenase, mitochondrial	0.769	0.019	DOWN	519
Tyrosine-protein kinase SYK	0.095	0.015	DOWN	629
Rab GDP dissociation inhibitor alpha	0.725	0.006	DOWN	447
Arylsulfatase A	0.431	0.007	DOWN	506
V-type proton ATPase catalytic subunit A	0.516	0.035	DOWN	617
V-type proton ATPase subunit d 1	0.608	0.048	DOWN	351
Alpha-2-macroglobulin receptor-associated protein	0.494	0.036	DOWN	360
Ectonucleoside triphosphate diphosphohydrolase 1	0.012	0.001	DOWN	510
Toll-like receptor 7	0.074	0.009	DOWN	1050
VIP36-like protein	0.595	0.022	DOWN	347
Protein transport protein Sec61 subunit gamma	0.748	0.023	DOWN	68
Ras-related protein Rab-8B	0.438	0.012	DOWN	207
4-aminobutyrate aminotransferase, mitochondrial	0.066	0.015	DOWN	500
Ras-related protein Rab-1A	0.812	0.039	DOWN	205

V-type proton ATPase 16 kDa proteolipid subunit	0.477	0.037	DOWN	155
Serine/threonine-protein phosphatase 2B catalytic subunit alpha isoform	0.775	0.032	DOWN	521
Acid sphingomyelinase-like phosphodiesterase 3a	0.012	0.004	DOWN	445
3-beta-hydroxysteroid-Delta	0.831	0.006	DOWN	230
Ena/VASP-like protein	0.051	0.021	DOWN	414
Isochorismatase domain-containing protein 2A	0.586	0.017	DOWN	206
Vacuolar protein sorting-associated protein 45	0.624	0.033	DOWN	570
Aminopeptidase N	0.007	0.002	DOWN	966
Bone morphogenetic protein 1	0.130	0.035	DOWN	991
Complement C1q subcomponent subunit A	0.075	0.009	DOWN	245
Collagen alpha-1(VIII) chain	0.124	0.000	DOWN	744
Aquaporin-1	0.033	0.011	DOWN	269
Complement C1q subcomponent subunit C	0.137	0.029	DOWN	246
Ras-related C3 botulinum toxin substrate 2	0.017	0.002	DOWN	192
Basement membrane-specific heparan sulfate proteoglycan core protein	0.130	0.001	DOWN	3707
Platelet glycoprotein 4	0.020	0.007	DOWN	472
Neutrophil cytosol factor 1	0.051	0.006	DOWN	390
SLAM family member 5	0.096	0.011	DOWN	329
Scavenger receptor cysteine-rich type 1 protein M130	0.028	0.003	DOWN	1121
Zinc transporter SLC39A7	0.643	0.004	DOWN	476
Putative phospholipase B-like 2	0.588	0.045	DOWN	594
NLR family member X1	0.253	0.017	DOWN	975
Hexokinase-3	0.004	0.000	DOWN	922
Ceroid-lipofuscinosis neuronal protein 5 homolog	0.229	0.010	DOWN	341
Divergent protein kinase domain 2A	0.441	0.027	DOWN	430
Phosphofurin acidic cluster sorting protein 2	0.098	0.012	DOWN	862
Transmembrane anterior posterior transformation protein 1	0.450	0.010	DOWN	564
N-acetylgalactosamine-6-sulfatase	0.078	0.017	DOWN	520
Zinc transporter 9	0.145	0.038	DOWN	567
Palmitoyltransferase ZDHHC20	0.644	0.011	DOWN	380
Ganglioside GM2 activator	0.548	0.023	DOWN	193
Glutaryl-CoA dehydrogenase, mitochondrial	0.622	0.032	DOWN	438
Lymphocyte antigen 75	0.250	0.018	DOWN	1723
Syntaxin-binding protein 3	0.739	0.035	DOWN	592
Glutathione S-transferase theta-2	0.173	0.028	DOWN	244
Arginase-1	0.002	0.000	DOWN	323
Plastin-2	0.010	0.002	DOWN	627
Adhesion G protein-coupled receptor E1	0.027	0.003	DOWN	931
Fibrillin-1	0.038	0.011	DOWN	2873
NADPH:adrenodoxin oxidoreductase, mitochondrial	0.629	0.036	DOWN	494
Growth arrest-specific protein 6	0.189	0.031	DOWN	674

Macrophage mannose receptor 1	0.006	0.001	DOWN	1456
Pregnancy zone protein	0.116	0.019	DOWN	1495
Versican core protein	0.023	0.002	DOWN	3357
Serum paraoxonase/lactonase 3	0.508	0.048	DOWN	354
Retinal dehydrogenase 2	0.061	0.024	DOWN	518
Dystroglycan	0.300	0.027	DOWN	893
Sialoadhesin	0.009	0.004	DOWN	1695
ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 2	0.034	0.022	DOWN	311
UDP-glucuronosyltransferase 1-6	0.729	0.023	DOWN	531
C-type mannose receptor 2	0.700	0.002	DOWN	1479
Tyrosine-protein phosphatase non-receptor type 13	0.121	0.036	DOWN	2453
Endothelial protein C receptor	0.079	0.028	DOWN	242
All-trans-retinol 13,14-reductase	0.266	0.008	DOWN	609
Raftlin	0.825	0.006	DOWN	554
Protein wntless homolog	0.492	0.004	DOWN	541
Protein CASC4	0.516	0.001	DOWN	435
Nucleoporin NUP188 homolog	0.727	0.013	DOWN	1759
Nesprin-1	0.718	0.011	DOWN	8799
Ubiquitin carboxyl-terminal hydrolase MINDY-1	0.216	0.031	DOWN	468
F-box only protein 22	0.429	0.013	DOWN	402
Echinoderm microtubule-associated protein-like 2	0.274	0.001	DOWN	649
Coiled-coil domain-containing protein 93	0.717	0.043	DOWN	629
Tumor necrosis factor ligand superfamily member 18	0.139	0.017	DOWN	173
Ubiquitin-protein ligase E3C	0.732	0.007	DOWN	1083
Phosphatidylinositol 5-phosphate 4-kinase type-2 beta	0.466	0.010	DOWN	416
Calcium-transporting ATPase type 2C member 1	0.163	0.043	DOWN	918
Uroplakin-3b	0.026	0.015	DOWN	275
ADP-ribosylation factor-like protein 5A	0.389	0.043	DOWN	179
N-acetylglucosamine-6-sulfatase	0.514	0.014	DOWN	544
Phospholipase D4	0.010	0.001	DOWN	503
Mitochondrial Rho GTPase 1	0.690	0.045	DOWN	631
Transmembrane 9 superfamily member 4	0.580	0.036	DOWN	643
Calcium-binding mitochondrial carrier protein Aralar1	0.742	0.018	DOWN	677
Coagulation factor XIII A chain	0.012	0.002	DOWN	732
Protein FAM49A	0.244	0.030	DOWN	323
Exopolyphosphatase PRUNE1	0.654	0.001	DOWN	454
Neutral cholesterol ester hydrolase 1	0.271	0.035	DOWN	408
LHFPL tetraspan subfamily member 6 protein	0.451	0.041	DOWN	200
Golgi resident protein GCP60	0.482	0.050	DOWN	525
Trifunctional enzyme subunit alpha, mitochondrial	0.674	0.016	DOWN	763
Copine-3	0.532	0.022	DOWN	533
T-complex protein 11-like protein 1	0.627	0.011	DOWN	509

Complex I assembly factor TIMMDC1, mitochondrial	0.594	0.029	DOWN	285
ADP-ribosylation factor-related protein 1	0.419	0.032	DOWN	201
RAD50-interacting protein 1	0.491	0.016	DOWN	792
Chondroitin sulfate N-acetylgalactosaminyltransferase 2	0.389	0.010	DOWN	542
Endonuclease domain-containing 1 protein	0.029	0.003	DOWN	501
Vacuolar protein sorting-associated protein 52 homolog	0.664	0.045	DOWN	723
E3 ubiquitin-protein ligase Itchy	0.588	0.005	DOWN	864
Latent-transforming growth factor beta-binding protein 1	0.068	0.032	DOWN	1712
Synaptojanin-1 (EC 3.1.3.36)	0.660	0.049	DOWN	1574
Myosin light chain 6B	0.037	0.004	DOWN	207
Membralin	0.042	0.005	DOWN	574
BMP-binding endothelial regulator protein	0.134	0.046	DOWN	685
Rho GTPase-activating protein 18	0.810	0.041	DOWN	663
Fermitin family homolog 3	0.016	0.002	DOWN	665
Dynamin-1-like protein	0.727	0.034	DOWN	742
Serine/threonine-protein kinase Nek9	0.581	0.039	DOWN	984
Leucine-rich repeat-containing protein 25	0.032	0.004	DOWN	297
Nck-associated protein 1-like	0.044	0.005	DOWN	1134
Very-long-chain (3R)-3-hydroxyacyl-CoA dehydratase 3	0.537	0.022	DOWN	362
Shootin-1	0.086	0.023	DOWN	631
EMILIN-2	0.008	0.001	DOWN	1074
ATP-dependent RNA helicase DDX54	0.603	0.029	DOWN	874
SEC14-like protein 4	0.094	0.011	DOWN	403
Exocyst complex component 1	0.616	0.007	DOWN	894
TBC1 domain family member 22A	0.591	0.036	DOWN	516
Apolipoprotein B receptor	0.052	0.027	DOWN	942
Fibrinogen gamma chain	0.031	0.019	DOWN	436
39S ribosomal protein L50, mitochondrial	0.034	0.004	DOWN	159
Solute carrier family 35 member F6	0.417	0.023	DOWN	372
Coiled-coil domain-containing protein 115	0.140	0.034	DOWN	180
Group XV phospholipase A2	0.623	0.018	DOWN	412
Translocating chain-associated membrane protein 1	0.762	0.003	DOWN	374
RUS1 family protein C16orf58 homolog	0.599	0.048	DOWN	466
Haloacid dehalogenase-like hydrolase domain-containing 5	0.339	0.012	DOWN	419
Transmembrane protein 205	0.481	0.007	DOWN	189
Egl nine homolog 1	0.658	0.046	DOWN	400
Acyl-CoA:lysophosphatidylglycerol acyltransferase 1	0.581	0.039	DOWN	370
Serotransferrin	0.004	0.000	DOWN	697
cGMP-dependent 3',5'-cyclic phosphodiesterase	0.060	0.007	DOWN	939
Endothelial cell-selective adhesion molecule	0.092	0.050	DOWN	394
Tubulointerstitial nephritis antigen-like	0.064	0.008	DOWN	466
Serine/threonine-protein kinase 26	0.315	0.050	DOWN	416

GTPase IMAP family member 4	0.130	0.016	DOWN	328
EMILIN-1	0.061	0.011	DOWN	1017
N-acetylneuraminate cytidylyltransferase	0.297	0.014	DOWN	432
Transmembrane glycoprotein NMB	0.004	0.002	DOWN	574
Histone chaperone ASF1A	0.236	0.008	DOWN	204
Prenylcysteine oxidase	0.483	0.003	DOWN	505
39S ribosomal protein L20, mitochondrial	0.617	0.025	DOWN	149
Exosome complex component RRP46	0.522	0.015	DOWN	235
Vitamin K epoxide reductase complex subunit 1	0.630	0.023	DOWN	161
IST1 homolog	0.674	0.045	DOWN	362
EEF1A lysine methyltransferase 1	0.209	0.047	DOWN	214
Phosphoacetylglucosamine mutase	0.750	0.046	DOWN	542
Transmembrane emp24 domain-containing protein 10	0.559	0.023	DOWN	219
Plasminogen receptor	0.628	0.034	DOWN	147
GRIP and coiled-coil domain-containing protein 1	0.298	0.009	DOWN	778
SUN domain-containing protein 1	0.606	0.004	DOWN	913
Nitric oxide synthase-interacting protein	0.436	0.003	DOWN	301
Esterase OVCA2	0.557	0.045	DOWN	225
Adipocyte plasma membrane-associated protein	0.533	0.012	DOWN	415
LysM and putative peptidoglycan-binding domain-containing protein 2	0.043	0.001	DOWN	215
Coiled-coil domain-containing protein 91	0.599	0.025	DOWN	442
Glycine amidinotransferase, mitochondrial	0.077	0.005	DOWN	423
Trimeric intracellular cation channel type B	0.098	0.012	DOWN	292
AP-2 complex subunit beta	0.703	0.046	DOWN	937
Armadillo repeat-containing protein 8	0.461	0.000	DOWN	673
Matrix remodeling-associated protein 8	0.707	0.016	DOWN	442
Sushi domain-containing protein 2	0.156	0.027	DOWN	820
Pre-mRNA-splicing factor SYF1	0.423	0.048	DOWN	855
N-acetylneuraminate lyase	0.007	0.001	DOWN	320
ATP synthase subunit d, mitochondrial	0.829	0.006	DOWN	161
MICOS complex subunit Mic26	0.112	0.042	DOWN	198
Fibroblast growth factor 23	0.018	0.002	DOWN	251
Sciellin	0.476	0.020	DOWN	652
Allograft inflammatory factor 1-like	0.352	0.045	DOWN	150
Secretory carrier-associated membrane protein 2	0.570	0.039	DOWN	329
Trafficking protein particle complex subunit 4	0.721	0.026	DOWN	219
Reticulon-3	0.761	0.031	DOWN	964
Hematopoietic prostaglandin D synthase	0.121	0.015	DOWN	199
Glycosylated lysosomal membrane protein	0.127	0.009	DOWN	404
Pleckstrin	0.021	0.002	DOWN	350
Leucine zipper transcription factor-like protein 1	0.459	0.042	DOWN	299

P2X purinoceptor 4	0.070	0.042	DOWN	388
Sphingomyelin phosphodiesterase 3	0.057	0.012	DOWN	655
Prolargin	0.019	0.006	DOWN	378
Ras GTPase-activating-like protein IQGAP1	0.712	0.043	DOWN	1657
Sacsin	0.639	0.018	DOWN	4582
Peroxisomal biogenesis factor 3	0.662	0.010	DOWN	372
Spastin	0.250	0.034	DOWN	614
Microfibrillar-associated protein 5	0.056	0.032	DOWN	164
Tumor necrosis factor receptor superfamily member 10B	0.049	0.006	DOWN	381
A disintegrin and metalloproteinase with thrombospondin motifs 5	0.036	0.006	DOWN	930
Interferon-activable protein 202	0.477	0.028	DOWN	445
Thymidine kinase 2, mitochondrial	0.763	0.004	DOWN	270
Zinc finger E-box-binding homeobox 2	0.496	0.046	DOWN	1215
Transmembrane emp24 domain-containing protein 2	0.638	0.036	DOWN	201
Serine protease HTRA1	0.071	0.042	DOWN	480
Periplakin	0.597	0.031	DOWN	1755
Glycosylphosphatidylinositol anchor attachment 1 protein	0.584	0.037	DOWN	621
MAGUK p55 subfamily member 2	0.026	0.003	DOWN	552
Prostaglandin F2 receptor negative regulator	0.164	0.019	DOWN	879
Type-1 angiotensin II receptor-associated protein	0.575	0.011	DOWN	161
Maleylacetoacetate isomerase	0.389	0.017	DOWN	216
Exostosin-like 3	0.089	0.010	DOWN	918
Reversion-inducing cysteine-rich protein with Kazal motifs	0.093	0.041	DOWN	971
Pantetheinase	0.021	0.007	DOWN	512
Platelet factor 4	0.018	0.002	DOWN	105
Glycogen	0.693	0.018	DOWN	738
Angiopoietin-related protein 4	0.052	0.031	DOWN	410
General vesicular transport factor p115	0.666	0.035	DOWN	959
Myotubularin	0.405	0.012	DOWN	603
Uroplakin-1b	0.040	0.021	DOWN	260
Oxidoreductase HTATIP2	0.595	0.009	DOWN	242
Cytokine receptor-like factor 3	0.712	0.005	DOWN	442

BDEs, bile duct epithelial cells; Ger, generation; HOCs, hepatic oval cells; LFQ, label-free quantification.

Table SII. Functional annotation of 30 differential proteins with cell differentiation in BDE 4th and 8th Ger and HOCs group by NCBI.

Protein name	Length (kDa)	Function
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of pre-fusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078,</p>

		<p>ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791,</p>

		ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.; FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation. {ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.
Interleukin-4 receptor subunit alpha	810	FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.
Protein NEDD1	660	FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265). {ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.
Protein phosphatase 3 catalytic subunit alpha	521	FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone

		<p>formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259,</p>

		ECO:0000269 PubMed:25801429, ECO:0000305}.
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity).</p> <p>{ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release</p>

		<p>into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with</p>

		Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell

		growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	<p>FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate</p>

		<p>from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU</p>

		<p>nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2,</p>

		<p>RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity.</p> <p>{ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are</p>

		<p>present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity).</p>

		<p>Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing.</p>

		<p>{ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis.</p> <p>{ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>

Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of prefusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an</p>
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		<p>anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples</p>

subunit alpha		to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK</p>

		<p>signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in</p>

		<p>cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity).</p> <p>{ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the</p>

		<p>hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+)</p>

		and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein

		<p>degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating</p>

		<p>glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'-hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs</p>

		<p>(miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF</p>

		<p>stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity.</p> <p>{ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in</p>

		HOX gene regulation (By similarity). {ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.
Activating signal cointegrator 1	581	FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.
Histone-lysine N-methyltransferase SETD2	2537	FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of

		<p>elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelinization (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>

TBC1 domain family member 1	1255	FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.
Mesenteric estrogen-dependent adipogenesis protein	303	FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic

		<p>interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of prefusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094). {ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B,</p>

alpha		<p>ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>

Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317,</p>

		ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm

		<p>diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGA5:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734</p>
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		(PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959). {ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.
Versican core protein	3357	FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.
All-trans-retinol 13,14-reductase	609	FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation,

		migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival

		<p>of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}.; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the</p>

		<p>myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required</p>

		<p>for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783,</p>

		<p>ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal	581	<p>FUNCTION: Transcription coactivator which associates with nuclear</p>

cointegrator 1		<p>receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3</p>

		<p>(PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>

Mesenteric estrogen-dependent adipogenesis protein	303	FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during

		<p>inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of pre-fusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated</p>

		<p>by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>

Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792,</p>
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		ECO:0000269 PubMed:8627154}.
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for</p>

		<p>the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGA5:ITGB1 and ITGA5:ITGB3. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
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Versican core protein	3357	FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.
All-trans-retinol 13,14-reductase	609	FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte

protein		differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes

		(By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle

		<p>progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>

Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1,</p>
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		IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen</p>

		<p>receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
<p>Histone-lysine N-methyltransferase SETD2</p>	<p>2537</p>	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling</p>

		(PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome</p>

		<p>topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during</p>

		<p>systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains</p>

		<p>circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768} .;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+)</p>

		<p>levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in</p>

		<p>the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone</p>

		<p>morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779,</p>

		<p>PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
<p>Calcium-transporting ATPase type 2C member 1</p>	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.</p>
<p>Exopolyphosphatase PRUNE1</p>	454	<p>FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.</p>
<p>Adipocyte plasma membrane-associated protein</p>	415	<p>FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.</p>
<p>Fibroblast growth factor 23</p>	251	<p>FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By</p>

		similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6,

		a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of</p>

		<p>molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
Cleavage and polyadenylation specificity factor subunit 3	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending</p>

		<p>on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating</p>

		<p>different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By</p>

		<p>similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
<p>Histone-lysine N-methyltransferase SETD2</p>	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2,</p>

		ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of</p>

		<p>neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma</p>

		<p>membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.; FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094). {ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating</p>

		<p>VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+)</p>

		<p>release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases</p>

		<p>proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating</p>

		<p>TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of</p>

		MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central

		nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains

		and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}.; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon</p>

		<p>stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
<p>Mitogen-activated protein kinase 1</p>	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions</p>

		<p>in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of</p>

		<p>mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650,</p>

		ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development</p>

		<p>(PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit</p>

		<p>the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis</p>

		<p>(PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of prefusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude</p>

		<p>and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May</p>

		<p>dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a</p>

		<p>prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription</p>

		<p>factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779,</p>

		ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.</p>
Exopolyphosphatase PRUNE1	454	<p>FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.</p>
Adipocyte plasma membrane-associated protein	415	<p>FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.</p>
Fibroblast growth factor 23	251	<p>FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.</p>
P2X purinoceptor 4	388	<p>FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression</p>

		of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	FUNCTION: Transcriptional regulator involved in different processes

		<p>such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909,</p>
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		ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.
Cleavage and polyadenylation specificity factor subunit 3	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular</p>

		<p>organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading</p>

		<p>to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is</p>

		<p>capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development</p>

		<p>(PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and</p>

		<p>PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing</p>

		<p>the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog</p>

		<p>(Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2</p>

		<p>processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and</p>

		SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.
Transmembrane anterior posterior transformation protein 1	564	FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.
Fibrillin-1	2873	FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).

		<p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By</p>

		<p>similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.</p>
Exopolyphosphatase PRUNE1	454	<p>FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.</p>
Adipocyte plasma membrane-associated protein	415	<p>FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.</p>
Fibroblast growth factor 23	251	<p>FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.</p>
P2X purinoceptor 4	388	<p>FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.</p>

Exostosin-like 3	918	<p>FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.</p>
Vacuolar protein sorting-associated protein 37B	285	<p>FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.</p>
Ubiquitin-conjugating enzyme E2 variant 1	147	<p>FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684,</p>

		<p>PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
Cleavage and polyadenylation specificity factor subunit 3	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and</p>

		<p>poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the</p>

		<p>Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity.</p> <p>{ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872,</p>

		<p>PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and</p>

		<p>by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP</p>

		<p>mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the</p>

		<p>activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of pre-fusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982,</p>

		<p>ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215} .;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity).</p>

		<p>Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin</p>

		<p>activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8;</p>

		inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.
Transmembrane anterior posterior transformation protein 1	564	FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.
Fibrillin-1	2873	FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity). {ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver

		<p>in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By</p>

		similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity).

		{ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate

		<p>kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	<p>684</p>	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage</p>

		<p>product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of</p>

		<p>translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493} .;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity.</p> <p>{ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and</p>

		<p>spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch</p>

		<p>DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070,</p>

		ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.
TBC1 domain family member 1	1255	FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.
Mesenteric estrogen-dependent adipogenesis protein	303	FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036,

		ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of pre-fusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259,</p>

		<p>ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p>

		<p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation</p>

		<p>(PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>

Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity).</p> <p>{ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of</p>

		<p>adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation</p>

		and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.

Ubiquitin-conjugating enzyme E2 variant 1	147	<p>FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}.; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate</p>

		<p>(PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
Cleavage and polyadenylation specificity factor subunit 3	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'-hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive</p>

		<p>and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and</p>

		<p>phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity.</p> <p>{ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to</p>

		<p>splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an</p>

		<p>essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce</p>

		apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.
TBC1 domain family member 1	1255	FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.
Mesenteric estrogen-dependent adipogenesis protein	303	FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion

		<p>molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby</p>
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		ameliorating atherosclerosis (PubMed:32883094). {ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in</p>

		<p>promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription</p>

		<p>factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the</p>

		differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGA5:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the</p>

		<p>hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255).</p> <p>{ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.</p>
Calcium-transporting ATPase type 2C member 1	918	<p>FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing</p>

		cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of

		<p>NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as</p>

		<p>a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction</p>

		<p>with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint.</p>

		<p>Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p>

		{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during</p>

		<p>angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family</p>

member 1		protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.
Mesenteric estrogen-dependent adipogenesis protein	303	FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036). {ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM)

		<p>(PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9</p>

		<p>and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation</p>

		<p>of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543,</p>

		ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both</p>

		<p>structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via</p>
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		interaction with Olfr734 receptor (PubMed:31798959). {ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.
Versican core protein	3357	FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.
All-trans-retinol 13,14-reductase	609	FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1.

		Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction

		<p>activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.</p>
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle</p>

		<p>(PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and</p>

		<p>pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692,</p>

		ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.; FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.
RNA-binding protein 15	962	FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity). {ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.
Activating signal cointegrator 1	581	FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and

		<p>NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
<p>Histone-lysine N-methyltransferase SETD2</p>	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation</p>

		<p>of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric	303	<p>FUNCTION: Involved in processes that promote adipocyte</p>

estrogen-dependent adipogenesis protein		differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages</p>

		<p>via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of pre-fusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094). {ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic</p>

		<p>differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein</p>

catalytic subunit alpha	<p>phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
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SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as</p>

		<p>elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	FUNCTION: May play a role in intercellular signaling and in connecting

		cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.
All-trans-retinol 13,14-reductase	609	FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.

Fibroblast growth factor 23	251	<p>FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.</p>
P2X purinoceptor 4	388	<p>FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.</p>
Exostosin-like 3	918	<p>FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.</p>
Vacuolar protein sorting-associated protein 37B	285	<p>FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.</p>
Ubiquitin-conjugating enzyme E2 variant 1	147	<p>FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral</p>

		RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of

		<p>FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential</p>

kinase 1	<p>component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity).</p> <p>{ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1.</p>
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		Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen</p>

		<p>receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation (PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.</p>
<p>Histone-lysine N-methyltransferase SETD2</p>	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral</p>

		<p>defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625, ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.</p>
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes</p>

		<p>that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as</p>

		<p>a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in</p>

		<p>numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in</p>

		<p>cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNMI1L inducing DNMI1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals (By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154).</p> <p>{ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune</p>

		<p>response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not seem to be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors</p>

		<p>(GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGAV:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward</p>

		all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix

		mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	<p>FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925). Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.</p>
Exostosin-like 3	918	<p>FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.</p>
Vacuolar protein sorting-associated protein 37B	285	<p>FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.</p>
Ubiquitin-conjugating enzyme E2 variant 1	147	<p>FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250,</p>

		ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	<p>FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both 'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}.; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.</p>
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair</p>

		<p>(PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression (By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.</p>
<p>Cleavage and polyadenylation specificity factor subunit 3</p>	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
<p>Mitogen-activated protein kinase 1</p>	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse</p>

		<p>biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative</p>

		<p>splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
Activating signal cointegrator 1	581	<p>FUNCTION: Transcription coactivator which associates with nuclear receptors, transcriptional coactivators including EP300, CREBBP and NCOA1, and basal transcription factors like TBP and TFIIA to facilitate nuclear receptors-mediated transcription. May thereby play an important role in establishing distinct coactivator complexes under different cellular conditions. Plays a role in thyroid hormone receptor and estrogen receptor transactivation (By similarity). Also involved in androgen receptor transactivation (PubMed:12077347). Plays a pivotal role in the transactivation of NF-kappa-B, SRF and AP1. Acts as a mediator of transrepression between nuclear receptor and either AP1 or NF-kappa-B. May play a role in the development of neuromuscular junction (By similarity). May play a role in late myogenic differentiation</p>

		(PubMed:27008887). Also functions as part of the RQC trigger (RQT) complex that activates the ribosome quality control (RQC) pathway, a pathway that degrades nascent peptide chains during problematic translation (By similarity). {ECO:0000250 UniProtKB:Q15650, ECO:0000269 PubMed:12077347, ECO:0000269 PubMed:12390891, ECO:0000269 PubMed:27008887}.
Histone-lysine N-methyltransferase SETD2	2537	<p>FUNCTION: Histone methyltransferase that specifically trimethylates 'Lys-36' of histone H3 (H3K36me3) using dimethylated 'Lys-36' (H3K36me2) as substrate (PubMed:18157086, PubMed:20133625). It is capable of trimethylating unmethylated H3K36 (H3K36me0) in vitro (By similarity). Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation (PubMed:18157086, PubMed:20133625). Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A (By similarity). Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction (By similarity). Required for DNA double-strand break repair in response to DNA damage: acts by mediating formation of H3K36me3, promoting recruitment of RAD51 and DNA repair via homologous recombination (HR) (By similarity). Acts as a tumor suppressor (By similarity). H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A (By similarity). H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase (By similarity). Required during angiogenesis (PubMed:20133625). Required for endoderm development by promoting embryonic stem cell differentiation toward endoderm: acts by mediating formation of H3K36me3 in distal promoter regions of FGFR3, leading to regulate transcription initiation of FGFR3 (PubMed:25242323). In addition to histones, also mediates methylation of other proteins, such as tubulins and STAT1 (PubMed:27518565). Trimethylates 'Lys-40' of alpha-tubulins such as TUBA1B (alpha-TubK40me3); alpha-TubK40me3 is required for normal mitosis and cytokinesis and may be a specific tag in cytoskeletal remodeling (PubMed:27518565). Involved in interferon-alpha-induced antiviral defense by mediating both monomethylation of STAT1 at 'Lys-525' and catalyzing H3K36me3 on promoters of some interferon-stimulated genes (ISGs) to activate gene transcription (By similarity). {ECO:0000250 UniProtKB:Q9BYW2, ECO:0000269 PubMed:18157086, ECO:0000269 PubMed:20133625,</p>

		ECO:0000269 PubMed:25242323, ECO:0000269 PubMed:27518565}.
Protein quaking	341	<p>FUNCTION: RNA-binding protein that plays a central role in myelination (PubMed:10864952, PubMed:11917126). Also required for visceral endoderm function and blood vessel development (PubMed:11892011, PubMed:16470614). Binds to the 5'-NACUAAAY-N(1,20)-UAAAY-3' RNA core sequence (PubMed:16041388). Acts by regulating pre-mRNA splicing, mRNA export, mRNA stability and protein translation, as well as cellular processes including apoptosis, cell cycle, glial cell fate and development (PubMed:10535969, PubMed:12467586, PubMed:11297509, PubMed:11917126, PubMed:15568022). Required to protect and promote stability of mRNAs such as MBP and CDKN1B which promotes oligodendrocyte differentiation (PubMed:10535969, PubMed:15568022). Participates in mRNA transport by regulating the nuclear export of MBP mRNA (PubMed:12467586). May also play a role in smooth muscle development (PubMed:14706070). {ECO:0000269 PubMed:10535969, ECO:0000269 PubMed:10864952, ECO:0000269 PubMed:11297509, ECO:0000269 PubMed:11892011, ECO:0000269 PubMed:11917126, ECO:0000269 PubMed:12467586, ECO:0000269 PubMed:14706070, ECO:0000269 PubMed:15568022, ECO:0000269 PubMed:16041388, ECO:0000269 PubMed:16470614}.; FUNCTION: Isoform 1 is involved in regulation of mRNA splicing of MAG pre-mRNA by acting as a negative regulator of MAG exon 12 alternative splicing. {ECO:0000269 PubMed:11917126}.; FUNCTION: Isoform 3 can induce apoptosis, while heterodimerization with other isoforms results in nuclear translocation of isoform 3 and suppression of apoptosis. {ECO:0000269 PubMed:11297509}.; FUNCTION: Isoform 4 acts as a translational repressor for GLI1. {ECO:0000269 PubMed:16198329}.</p>
TBC1 domain family member 1	1255	<p>FUNCTION: May act as a GTPase-activating protein for Rab family protein(s). May play a role in the cell cycle and differentiation of various tissues. Involved in the trafficking and translocation of GLUT4-containing vesicles and insulin-stimulated glucose uptake into cells. {ECO:0000269 PubMed:19740738}.</p>
Mesenteric estrogen-dependent adipogenesis protein	303	<p>FUNCTION: Involved in processes that promote adipocyte differentiation, lipid accumulation, and glucose uptake in mature adipocytes. {ECO:0000269 PubMed:22510272}.</p>
SWI/SNF complex subunit SMARCC2	1213	<p>FUNCTION: Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Component of SWI/SNF chromatin remodeling complexes that carry out key enzymatic activities, changing chromatin structure by altering DNA-histone contacts within a nucleosome in an ATP-dependent manner. Can stimulate the ATPase activity of the catalytic subunit of these complexes. May be required for CoREST dependent repression of neuronal specific gene promoters in non-neuronal cells. Belongs to the</p>

		<p>neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a postmitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (PubMed:17640523). Critical regulator of myeloid differentiation, controlling granulocytopoiesis and the expression of genes involved in neutrophil granule formation (PubMed:28369036).</p> <p>{ECO:0000269 PubMed:17640523, ECO:0000269 PubMed:28369036, ECO:0000269 PubMed:31216030, ECO:0000303 PubMed:22952240, ECO:0000303 PubMed:26601204}.</p>
Protein prune homolog 2	3084	<p>FUNCTION: May play an important role in regulating differentiation, survival and aggressiveness of the tumor cells. {ECO:0000250}.</p>
Ninjurin-1	152	<p>FUNCTION: [Ninjurin-1]: Homophilic transmembrane adhesion molecule involved in various processes such as inflammation, cell death, axonal growth, cell chemotaxis and angiogenesis (PubMed:19557008, PubMed:24347169, PubMed:24917672, PubMed:31526566, PubMed:33472215). Promotes cell adhesion by mediating homophilic interactions via its extracellular N-terminal adhesion motif (N-NAM) (PubMed:24917672, PubMed:30510259). Involved in the progression of the inflammatory stress by promoting cell-to-cell interactions between immune cells and endothelial cells (PubMed:24917672, PubMed:30510259). Involved in leukocyte migration during inflammation by promoting transendothelial migration of macrophages via homotypic binding (PubMed:24917672). Promotes the migration of monocytes across the brain endothelium to central nervous system inflammatory lesions (By similarity). Acts as a regulator of Toll-like receptor 4 (TLR4) signaling triggered by lipopolysaccharide (LPS) during systemic inflammation; directly binds LPS (PubMed:25860173). Acts as a mediator of both programmed and necrotic cell death (PubMed:19557008, PubMed:33472215). Plays a key role in the induction of plasma membrane rupture during programmed and necrotic cell death: oligomerizes in response to death stimuli to mediate plasma membrane rupture (cytolysis), leading to release intracellular molecules</p>

		<p>named damage-associated molecular patterns (DAMPs) that propagate the inflammatory response (PubMed:33472215). Plays a role in nerve regeneration by promoting maturation of Schwann cells (PubMed:31526566). Acts as a regulator of angiogenesis (PubMed:25766274, PubMed:30354207). Promotes the formation of new vessels by mediating the interaction between capillary pericyte cells and endothelial cells (PubMed:25766274, PubMed:30354207). Also mediates vascular functions in penile tissue as well as vascular formation (PubMed:24979788). Promotes osteoclasts development by enhancing the survival of perfusion osteoclasts (PubMed:30700695). Also involved in striated muscle growth and differentiation (PubMed:31091274). Also involved in cell senescence in a p53/TP53 manner, possibly by acting as an indirect regulator of p53/TP53 mRNA translation (PubMed:23690620, PubMed:29073078). {ECO:0000250 UniProtKB:Q92982, ECO:0000269 PubMed:19557008, ECO:0000269 PubMed:23690620, ECO:0000269 PubMed:24347169, ECO:0000269 PubMed:24917672, ECO:0000269 PubMed:24979788, ECO:0000269 PubMed:25766274, ECO:0000269 PubMed:25860173, ECO:0000269 PubMed:29073078, ECO:0000269 PubMed:30354207, ECO:0000269 PubMed:30510259, ECO:0000269 PubMed:30700695, ECO:0000269 PubMed:31091274, ECO:0000269 PubMed:31526566, ECO:0000269 PubMed:33472215}.;</p> <p>FUNCTION: [Secreted ninjurin-1]: Secreted form generated by cleavage, which has chemotactic activity (PubMed:23142597). Acts as an anti-inflammatory mediator by promoting monocyte recruitment, thereby ameliorating atherosclerosis (PubMed:32883094).</p> <p>{ECO:0000269 PubMed:23142597, ECO:0000269 PubMed:32883094}.</p>
cAMP-dependent protein kinase catalytic subunit alpha	351	<p>FUNCTION: Phosphorylates a large number of substrates in the cytoplasm and the nucleus (By similarity). Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5/RPT6, PJA2, RYR2, RORA, SOX9 and VASP (PubMed:10805756, PubMed:19223768). Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis (By similarity). RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts (By similarity). Involved in chondrogenesis by mediating phosphorylation of SOX9 (PubMed:10805756). Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. RYR2 channel activity is potentiated by phosphorylation in</p>

		<p>presence of luminal Ca(2+), leading to reduced amplitude and increased frequency of store overload-induced Ca(2+) release (SOICR) characterized by an increased rate of Ca(2+) release and propagation velocity of spontaneous Ca(2+) waves, despite reduced wave amplitude and resting cytosolic Ca(2+). PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis (By similarity). Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation (PubMed:19223768). May also regulate rapid eye movement (REM) sleep in the pedunculo pontine tegmental (PPT) (By similarity). Phosphorylates APOBEC3G and AICDA. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (By similarity).</p> <p>{ECO:0000250 UniProtKB:P17612, ECO:0000250 UniProtKB:P27791, ECO:0000269 PubMed:10805756, ECO:0000269 PubMed:19223768}.;</p> <p>FUNCTION: [Isoform 2]: Phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation.</p> <p>{ECO:0000269 PubMed:15340140, ECO:0000269 PubMed:19560455}.</p>
Interleukin-4 receptor subunit alpha	810	<p>FUNCTION: Receptor for both interleukin 4 and interleukin 13. Couples to the JAK1/2/3-STAT6 pathway. The IL4 response is involved in promoting Th2 differentiation. The IL4/IL13 responses are involved in regulating IgE production and, chemokine and mucus production at sites of allergic inflammation. In certain cell types, can signal through activation of insulin receptor substrates, IRS1/IRS2.</p>
Protein NEDD1	660	<p>FUNCTION: Required for mitosis progression. Promotes the nucleation of microtubules from the spindle (By similarity). May play an important role during the embryonic development and differentiation of the central nervous system (PubMed:1378265).</p> <p>{ECO:0000250 UniProtKB:Q8NHV4, ECO:0000269 PubMed:1378265}.</p>
Protein phosphatase 3 catalytic subunit alpha	521	<p>FUNCTION: Calcium-dependent, calmodulin-stimulated protein phosphatase which plays an essential role in the transduction of intracellular Ca(2+)-mediated signals (PubMed:7791792, PubMed:26794871). Many of the substrates contain a PxIxIT motif and/or a LxVP motif (By similarity). In response to increased Ca(2+) levels, dephosphorylates and activates phosphatase SSH1 which results in cofilin dephosphorylation (By similarity). In response to increased Ca(2+) levels following mitochondrial depolarization, dephosphorylates DNM1L inducing DNM1L translocation to the mitochondrion (By similarity). Positively regulates the CACNA1B/CAV2.2-mediated Ca(2+) release probability at hippocampal neuronal soma and synaptic terminals</p>

		<p>(By similarity). Dephosphorylates heat shock protein HSPB1 (By similarity). Dephosphorylates and activates transcription factor NFATC1 (By similarity). Dephosphorylates and inactivates transcription factor ELK1 (By similarity). Dephosphorylates DARPP32 (By similarity). May dephosphorylate CRTC2 at 'Ser-171' resulting in CRTC2 dissociation from 14-3-3 proteins (By similarity). Required for postnatal development of the nephrogenic zone and superficial glomeruli in the kidneys, cell cycle homeostasis in the nephrogenic zone, and ultimately normal kidney function (PubMed:15509543). Plays a role in intracellular AQP2 processing and localization to the apical membrane in the kidney, may thereby be required for efficient kidney filtration (PubMed:16735444). Required for secretion of salivary enzymes amylase, peroxidase, lysozyme and sialic acid via formation of secretory vesicles in the submandibular glands (PubMed:21435446). Required for calcineurin activity and homosynaptic depotentiation in the hippocampus (PubMed:10200317). Required for normal differentiation and survival of keratinocytes and therefore required for epidermis superstructure formation (PubMed:19626032). Positively regulates osteoblastic bone formation, via promotion of osteoblast differentiation (PubMed:16286645). Positively regulates osteoclast differentiation, potentially via NFATC1 signaling (PubMed:16968888). May play a role in skeletal muscle fiber type specification, potentially via NFATC1 signaling (PubMed:12773574). Negatively regulates MAP3K14/NIK signaling via inhibition of nuclear translocation of the transcription factors RELA and RELB (PubMed:26029823). Required for antigen-specific T-cell proliferation response (PubMed:8627154). {ECO:0000250 UniProtKB:P48452, ECO:0000250 UniProtKB:P63329, ECO:0000250 UniProtKB:Q08209, ECO:0000269 PubMed:10200317, ECO:0000269 PubMed:12773574, ECO:0000269 PubMed:15509543, ECO:0000269 PubMed:16286645, ECO:0000269 PubMed:16735444, ECO:0000269 PubMed:16968888, ECO:0000269 PubMed:19626032, ECO:0000269 PubMed:21435446, ECO:0000269 PubMed:26029823, ECO:0000269 PubMed:26794871, ECO:0000269 PubMed:7791792, ECO:0000269 PubMed:8627154}.</p>
SLAM family member 5	329	<p>FUNCTION: Self-ligand receptor of the signaling lymphocytic activation molecule (SLAM) family. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and thus are involved in the regulation and interconnection of both innate and adaptive immune response. Activities are controlled by presence or absence of small cytoplasmic adapter proteins, SH2D1A/SAP and/or SH2D1B/EAT-2 (PubMed:20962259). Can mediate natural killer (NK) cell cytotoxicity dependent on SH2D1A and SH2D1B (PubMed:20962259). Increases proliferative responses of activated T-cells and SH2D1A/SAP does not</p>

		<p>seen be required for this process. Homophilic interactions enhance interferon gamma/IFNG secretion in lymphocytes and induce platelet stimulation via a SH2D1A/SAP-dependent pathway. May serve as a marker for hematopoietic progenitor cells (By similarity). Required for a prolonged T-cell:B-cell contact, optimal T follicular helper function, and germinal center formation (PubMed:20153220). In germinal centers involved in maintaining B cell tolerance and in preventing autoimmunity (PubMed:25801429). In mast cells negatively regulates high affinity immunoglobulin epsilon receptor signaling; independent of SH2D1A and SH2D1B but implicating FES and PTPN6/SHP-1 (By similarity). In macrophages enhances LPS-induced MAPK phosphorylation and NF-kappaB activation and modulates LPS-induced cytokine secretion; involving ITSM 2 (PubMed:20628063). Positively regulates macroautophagy in primary dendritic cells via stabilization of IRF8; inhibits TRIM21-mediated proteasomal degradation of IRF8 (By similarity). {ECO:0000250 UniProtKB:Q9UIB8, ECO:0000269 PubMed:16037392, ECO:0000269 PubMed:20153220, ECO:0000269 PubMed:20628063, ECO:0000269 PubMed:20962259, ECO:0000269 PubMed:25801429, ECO:0000305}.</p>
Transmembrane anterior posterior transformation protein 1	564	<p>FUNCTION: Plays a role in primary cilia formation (By similarity). May act as a downstream effector of HOXC8 possibly by transducing or transmitting extracellular information required for axial skeletal patterning during development (By similarity). May be involved in cartilage and bone development (By similarity). May play a role in the differentiation of cranial neural crest cells (By similarity). {ECO:0000250 UniProtKB:A2BIE7, ECO:0000250 UniProtKB:Q6NXT6, ECO:0000269 PubMed:17151244}.</p>
Fibrillin-1	2873	<p>FUNCTION: [Fibrillin-1]: Structural component of the 10-12 nm diameter microfibrils of the extracellular matrix, which conveys both structural and regulatory properties to load-bearing connective tissues. Fibrillin-1-containing microfibrils provide long-term force bearing structural support. In tissues such as the lung, blood vessels and skin, microfibrils form the periphery of the elastic fiber, acting as a scaffold for the deposition of elastin. In addition, microfibrils can occur as elastin-independent networks in tissues such as the ciliary zonule, tendon, cornea and glomerulus where they provide tensile strength and have anchoring roles. Fibrillin-1 also plays a key role in tissue homeostasis through specific interactions with growth factors, such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and latent transforming growth factor-beta-binding proteins (LTBPs), cell-surface integrins and other extracellular matrix protein and proteoglycan components (By similarity). Regulates osteoblast maturation by controlling TGF-beta bioavailability and calibrating TGF-beta and BMP levels, respectively (PubMed:20855508). Negatively</p>

		<p>regulates osteoclastogenesis by binding and sequestering an osteoclast differentiation and activation factor TNFSF11. This leads to disruption of TNFSF11-induced Ca(2+) signaling and impairment of TNFSF11-mediated nuclear translocation and activation of transcription factor NFATC1 which regulates genes important for osteoclast differentiation and function (PubMed:24039232). Mediates cell adhesion via its binding to cell surface receptors integrins ITGA5:ITGB3 and ITGA5:ITGB1. Binds heparin and this interaction plays an important role in the assembly of microfibrils (By similarity).</p> <p>{ECO:0000250 UniProtKB:P35555, ECO:0000269 PubMed:20855508, ECO:0000269 PubMed:24039232}.; FUNCTION: [Asprosin]: Adipokine secreted by white adipose tissue that plays an important regulatory role in the glucose metabolism of liver, muscle and pancreas (PubMed:31230984, PubMed:30997682). Hormone that targets the liver in response to fasting to increase plasma glucose levels (PubMed:31230984). Binds the olfactory receptor Olfr734 at the surface of hepatocytes and promotes hepatocyte glucose release by activating the protein kinase A activity in the liver, resulting in rapid glucose release into the circulation (PubMed:31230984). May act as a regulator of adaptive thermogenesis by inhibiting browning and energy consumption, while increasing lipid deposition in white adipose tissue (PubMed:33705351). Also acts as an orexigenic hormone that increases appetite: crosses the blood brain barrier and exerts effects on the hypothalamus (PubMed:29106398). In the arcuate nucleus of the hypothalamus, asprosin directly activates orexigenic AgRP neurons and indirectly inhibits anorexigenic POMC neurons, resulting in appetite stimulation (PubMed:29106398, PubMed:32337066). Activates orexigenic AgRP neurons via binding to the olfactory receptor Olfr734 (PubMed:32337066). May also play a role in sperm motility in testis via interaction with Olfr734 receptor (PubMed:31798959).</p> <p>{ECO:0000269 PubMed:29106398, ECO:0000269 PubMed:30997682, ECO:0000269 PubMed:31230984, ECO:0000269 PubMed:31798959, ECO:0000269 PubMed:32337066, ECO:0000269 PubMed:33705351}.</p>
Versican core protein	3357	<p>FUNCTION: May play a role in intercellular signaling and in connecting cells with the extracellular matrix. May take part in the regulation of cell motility, growth and differentiation. Binds hyaluronic acid.</p>
All-trans-retinol 13,14-reductase	609	<p>FUNCTION: Catalyzes the saturation of all-trans-retinol to all-trans-13,14-dihydroretinol (PubMed:15358783, PubMed:17253779, PubMed:19139408). Does not exhibit any activity toward all-trans-retinoic acid, nor 9-cis, 11-cis or 13-cis-retinol isomers (PubMed:15358783). May play a role in the metabolism of vitamin A (PubMed:15358783, PubMed:17253779). Independently of retinol conversion, may regulate liver metabolism upstream of MLXIPL/ChREBP (PubMed:28855500). Required for adipocyte</p>

		differentiation in a 3T3-L1 cell culture model (PubMed:19139408). This effect seems not to mimic the in vivo situation in which animals show increased adiposity in the absence of RETSAT (PubMed:19940255). {ECO:0000269 PubMed:15358783, ECO:0000269 PubMed:17253779, ECO:0000269 PubMed:19139408, ECO:0000269 PubMed:19940255, ECO:0000269 PubMed:28855500, ECO:0000305 PubMed:19940255}.
Calcium-transporting ATPase type 2C member 1	918	FUNCTION: ATP-driven pump that supplies the Golgi apparatus with Ca(2+) and Mn(2+) ions, both essential cofactors for processing and trafficking of newly synthesized proteins in the secretory pathway (By similarity). Within a catalytic cycle, acquires Ca(2+) or Mn(2+) ions on the cytoplasmic side of the membrane and delivers them to the luminal side. The transfer of ions across the membrane is coupled to ATP hydrolysis and is associated with a transient phosphorylation that shifts the pump conformation from inward-facing to outward-facing state (By similarity). Plays a primary role in the maintenance of Ca(2+) homeostasis in the trans-Golgi compartment with a functional impact on Golgi and post-Golgi protein sorting as well as a structural impact on cisternae morphology. Responsible for loading the Golgi stores with Ca(2+) ions in keratinocytes, contributing to keratinocyte differentiation and epidermis integrity (By similarity). Participates in Ca(2+) and Mn(2+) ions uptake into the Golgi store of hippocampal neurons and regulates protein trafficking required for neural polarity (PubMed:19793975). May also play a role in the maintenance of Ca(2+) and Mn(2+) homeostasis and signaling in the cytosol while preventing cytotoxicity (By similarity). {ECO:0000250 UniProtKB:P98194, ECO:0000269 PubMed:19793975}.
Exopolyphosphatase PRUNE1	454	FUNCTION: Phosphodiesterase (PDE) that has higher activity toward cAMP than cGMP, as substrate. Plays a role in cell proliferation, migration and differentiation, and acts as a negative regulator of NME1. Plays a role in the regulation of neurogenesis. Involved in the regulation of microtubule polymerization. {ECO:0000250 UniProtKB:Q86TP1}.
Adipocyte plasma membrane-associated protein	415	FUNCTION: Exhibits strong arylesterase activity with beta-naphthyl acetate and phenyl acetate (By similarity). May play a role in adipocyte differentiation. {ECO:0000250}.
Fibroblast growth factor 23	251	FUNCTION: Regulator of phosphate homeostasis (By similarity). Inhibits renal tubular phosphate transport by reducing SLC34A1 levels (By similarity). Acts directly on the parathyroid to decrease PTH secretion (By similarity). Regulator of vitamin-D metabolism (By similarity). Negatively regulates osteoblasts differentiation and matrix mineralization (By similarity). Up-regulates EGR1 expression in the presence of KL. {ECO:0000250, ECO:0000269 PubMed:17086194}.
P2X purinoceptor 4	388	FUNCTION: Receptor for extracellularly released ATP acting as a ligand-gated ion channel that plays multiple role in immunity and central nervous system physiology (PubMed:26456657, PubMed:35119925).

		Plays a key role in initial steps of T-cell activation and Ca(2+) microdomain formation (PubMed:35119925). Participates also in basal T-cell activity without TCR/CD3 stimulation (PubMed:35119925). Promotes the differentiation and activation of Th17 cells via expression of retinoic acid-related orphan receptor C/RORC (By similarity). Upon activation, drives microglia motility via the PI3K/Akt pathway (PubMed:17299767). {ECO:0000250 UniProtKB:Q99571, ECO:0000269 PubMed:17299767, ECO:0000269 PubMed:26456657, ECO:0000269 PubMed:35119925}.
Exostosin-like 3	918	FUNCTION: Glycosyltransferase which regulates the biosynthesis of heparan sulfate (HS). Important for both skeletal development and hematopoiesis, through the formation of HS proteoglycans (HSPGs). Required for the function of REG3A in regulating keratinocyte proliferation and differentiation (By similarity). {ECO:0000250 UniProtKB:O43909}.
Vacuolar protein sorting-associated protein 37B	285	FUNCTION: Component of the ESCRT-I complex, a regulator of vesicular trafficking process. Required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. May be involved in cell growth and differentiation (By similarity). {ECO:0000250}.
Ubiquitin-conjugating enzyme E2 variant 1	147	FUNCTION: Has no ubiquitin ligase activity on its own. The UBE2V1-UBE2N heterodimer catalyzes the synthesis of non-canonical poly-ubiquitin chains that are linked through 'Lys-63'. This type of poly-ubiquitination activates IKK and does not seem to involve protein degradation by the proteasome. Plays a role in the activation of NF-kappa-B mediated by IL1B, TNF, TRAF6 and TRAF2. Mediates transcriptional activation of target genes. Plays a role in the control of progress through the cell cycle and differentiation (By similarity). Plays a role in the error-free DNA repair pathway and contributes to the survival of cells after DNA damage. Promotes TRIM5 capsid-specific restriction activity and the UBE2V1-UBE2N heterodimer acts in concert with TRIM5 to generate 'Lys-63'-linked polyubiquitin chains which activate the MAP3K7/TAK1 complex which in turn results in the induction and expression of NF-kappa-B and MAPK-responsive inflammatory genes (By similarity). Together with RNF135 and UBE2N, catalyzes the viral RNA-dependent 'Lys-63'-linked polyubiquitination of RIG-I/DDX58 to activate the downstream signaling pathway that leads to interferon beta production (By similarity). UBE2V1-UBE2N together with TRAF3IP2 E3 ubiquitin ligase mediate 'Lys-63'-linked polyubiquitination of TRAF6, a component of IL17A-mediated signaling pathway. {ECO:0000250, ECO:0000250 UniProtKB:Q13404, ECO:0000269 PubMed:11406273}.
Ubiquitin carboxyl-terminal hydrolase 25	1055	FUNCTION: Deubiquitinating enzyme that hydrolyzes ubiquitin moieties conjugated to substrates and thus, functions to process newly synthesized Ubiquitin, to recycle ubiquitin molecules or to edit polyubiquitin chains and prevents proteasomal degradation of substrates. Hydrolyzes both

		'Lys-48'- and 'Lys-63'-linked tetraubiquitin chains (By similarity). {ECO:0000250}.; FUNCTION: The muscle-specific isoform (USP25m) may have a role in the regulation of muscular differentiation and function.
Forkhead box protein K1	719	<p>FUNCTION: Transcriptional regulator involved in different processes such as glucose metabolism, aerobic glycolysis, muscle cell differentiation and autophagy (PubMed:25402684, PubMed:29861159, PubMed:30700909). Recognizes and binds the forkhead DNA sequence motif (5'-GTAAACA-3') and can both act as a transcription activator or repressor, depending on the context (PubMed:25402684, PubMed:29861159, PubMed:30700909). Together with FOXK2, acts as a key regulator of metabolic reprogramming towards aerobic glycolysis, a process in which glucose is converted to lactate in the presence of oxygen (PubMed:30700909). Acts by promoting expression of enzymes for glycolysis (such as hexokinase-2 (HK2), phosphofructokinase, pyruvate kinase (PKLR) and lactate dehydrogenase), while suppressing further oxidation of pyruvate in the mitochondria by up-regulating pyruvate dehydrogenase kinases PDK1 and PDK4 (PubMed:30700909). Probably plays a role in gluconeogenesis during overnight fasting, when lactate from white adipose tissue and muscle is the main substrate (PubMed:30700909). Involved in mTORC1-mediated metabolic reprogramming: in response to mTORC1 signaling, translocates into the nucleus and regulates the expression of genes associated with glycolysis and downstream anabolic pathways, such as HIF1A, thereby regulating glucose metabolism (PubMed:29861159). Together with FOXK2, acts as a negative regulator of autophagy in skeletal muscle: in response to starvation, enters the nucleus, binds the promoters of autophagy genes and represses their expression, preventing proteolysis of skeletal muscle proteins (PubMed:25402684). Acts as a transcriptional regulator of the myogenic progenitor cell population in skeletal muscle (PubMed:8007964, PubMed:9271401, PubMed:12446708, PubMed:22956541). Binds to the upstream enhancer region (CCAC box) of myoglobin (MB) gene, regulating the myogenic progenitor cell population (PubMed:8007964, PubMed:9271401). Promotes muscle progenitor cell proliferation by repressing the transcriptional activity of FOXO4, thereby inhibiting myogenic differentiation (PubMed:12446708, PubMed:22956541). Involved in remodeling processes of adult muscles that occur in response to physiological stimuli (PubMed:9271401, PubMed:22956541). Required to correct temporal orchestration of molecular and cellular events necessary for muscle repair (PubMed:10792059). Represses myogenic differentiation by inhibiting MEFC activity (PubMed:22956541). Positively regulates Wnt/beta-catenin signaling by translocating DVL into the nucleus (By similarity). Reduces virus replication, probably by binding the interferon stimulated response element (ISRE) to promote antiviral gene expression</p>

		(By similarity). {ECO:0000250 UniProtKB:P85037, ECO:0000269 PubMed:10792059, ECO:0000269 PubMed:12446708, ECO:0000269 PubMed:22956541, ECO:0000269 PubMed:25402684, ECO:0000269 PubMed:29861159, ECO:0000269 PubMed:30700909, ECO:0000269 PubMed:8007964, ECO:0000269 PubMed:9271401}.
Cleavage and polyadenylation specificity factor subunit 3	684	<p>FUNCTION: Component of the cleavage and polyadenylation specificity factor (CPSF) complex that plays a key role in pre-mRNA 3'-end formation, recognizing the AAUAAA signal sequence and interacting with poly(A) polymerase and other factors to bring about cleavage and poly(A) addition. Has endonuclease activity, and functions as mRNA 3'-end-processing endonuclease. Also involved in the histone 3'-end pre-mRNA processing. U7 snRNP-dependent protein that induces both the 3' endoribonucleolytic cleavage of histone pre-mRNAs and acts as a 5' to 3' exonuclease for degrading the subsequent downstream cleavage product (DCP) of mature histone mRNAs. Cleavage occurs after the 5'-ACCCA-3' sequence in the histone pre-mRNA leaving a 3'hydroxyl group on the upstream fragment containing the stem loop (SL) and 5' phosphate on the downstream cleavage product (DCP) starting with CU nucleotides. The U7-dependent 5' to 3' exonuclease activity is processive and degrades the DCP RNA substrate even after complete removal of the U7-binding site. Binds to the downstream cleavage product (DCP) of histone pre-mRNAs and the cleaved DCP RNA substrate in a U7 snRNP dependent manner. Required for the selective processing of microRNAs (miRNAs) during embryonic stem cell differentiation via its interaction with ISY1 (PubMed:26255770, PubMed:29804889). Required for entering/progressing through S-phase of the cell cycle (By similarity). Required for the biogenesis of all miRNAs from the pri-miR-17-92 primary transcript except miR-92a (PubMed:26255770). Only required for the biogenesis of miR-290 and miR-96 from the pri-miR-290-295 and pri-miR-96-183 primary transcripts, respectively (PubMed:29804889). {ECO:0000250 UniProtKB:Q9UKF6, ECO:0000269 PubMed:16213211, ECO:0000269 PubMed:18955505, ECO:0000269 PubMed:19470752, ECO:0000269 PubMed:26255770, ECO:0000269 PubMed:29804889}.</p>
Mitogen-activated protein kinase 1	358	<p>FUNCTION: Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription</p>

		<p>factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in response to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation. Phosphorylates CDK2AP2 (By similarity). {ECO:0000250 UniProtKB:P28482, ECO:0000250 UniProtKB:P63086, ECO:0000269 PubMed:10753946, ECO:0000269 PubMed:11702783, ECO:0000269 PubMed:12134156, ECO:0000303 PubMed:16393692, ECO:0000303 PubMed:19565474, ECO:0000303 PubMed:21779493}.;</p> <p>FUNCTION: Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity. {ECO:0000250 UniProtKB:P28482}.</p>
RNA-binding protein 15	962	<p>FUNCTION: RNA-binding protein that acts as a key regulator of N6-methyladenosine (m6A) methylation of RNAs, thereby regulating different processes, such as hematopoietic cell homeostasis, alternative splicing of mRNAs and X chromosome inactivation mediated by Xist RNA (PubMed:29535189). Associated component of the WMM complex, a complex that mediates N6-methyladenosine (m6A) methylation of RNAs, a modification that plays a role in the efficiency of mRNA splicing and RNA processing (PubMed:29535189). Plays a key</p>

		<p>role in m6A methylation, possibly by binding target RNAs and recruiting the WMM complex (PubMed:29535189). Involved in random X inactivation mediated by Xist RNA: acts by binding Xist RNA and recruiting the WMM complex, which mediates m6A methylation, leading to target YTHDC1 reader on Xist RNA and promoting transcription repression activity of Xist (By similarity). Required for the development of multiple tissues, such as the maintenance of the homeostasis of long-term hematopoietic stem cells and for megakaryocyte (MK) and B-cell differentiation (PubMed:17283045, PubMed:17376872, PubMed:18981216, PubMed:25468569). Regulates megakaryocyte differentiation by regulating alternative splicing of genes important for megakaryocyte differentiation; probably regulates alternative splicing via m6A regulation (By similarity). Required for placental vascular branching morphogenesis and embryonic development of the heart and spleen (PubMed:18981216). Acts as a regulator of thrombopoietin response in hematopoietic stem cells by regulating alternative splicing of MPL (PubMed:25468569). May also function as an mRNA export factor, stimulating export and expression of RTE-containing mRNAs which are present in many retrotransposons that require to be exported prior to splicing (By similarity). High affinity binding of pre-mRNA to RBM15 may allow targeting of the mRNP to the export helicase DBP5 in a manner that is independent of splicing-mediated NXF1 deposition, resulting in export prior to splicing (By similarity). May be implicated in HOX gene regulation (By similarity).</p> <p>{ECO:0000250 UniProtKB:Q96T37, ECO:0000269 PubMed:17283045, ECO:0000269 PubMed:17376872, ECO:0000269 PubMed:18981216, ECO:0000269 PubMed:25468569, ECO:0000269 PubMed:29535189}.</p>
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BDEs, bile duct epithelial cells; Ger, generation; HOCs, hepatic oval cells; NCBI, National Center for Biotechnology Information.