

Table SI. A total of 211 protein markers of T-AMEVs and B-AMEVs.

Protein names	Gene names	emPAI in T-AMEVs	emPAI in B-AMEVs
Alpha-1B-glycoprotein	A1BG	0.9	0.5
Alpha-2-macroglobulin	A2M	0.48	2.12
Angiotensin-converting enzyme	ACE	0.07	0.02
ATP-citrate synthase	ACLY	0.17	0.05
Adenosylhomocysteinase	AHCY	0.7	0.22
Alpha-2-HS-glycoprotein	AHSG	0.27	0.61
Adenylate kinase isoenzyme 1	AK1	0.33	1.05
Serum albumin	ALB	2.69	4.06
Aldehyde dehydrogenase family 16 member A1	ALDH16A1	0.21	0.16
Retinal dehydrogenase 1	ALDH1A1	2.99	0.68
Fructose-bisphosphate aldolase A	ALDOA	2.31	1.4
Fructose-bisphosphate aldolase C	ALDOC	0.38	0.08
Ankyrin-1	ANK1	0.03	0.55
Annexin A1	ANXA1	7.33	0.08
Annexin A7	ANXA7	1.47	0.2
Serum amyloid P-component	APCS	0.64	1.36
Acylamino-acid-releasing enzyme	APEH	0.04	0.12
Apolipoprotein A-I	APOA1	28.62	43.66
Apolipoprotein A-II	APOA2	0.7	6.62
Apolipoprotein A-IV	APOA4	1.87	1.32
Apolipoprotein B-100	APOB	0.03	1.07
Apolipoprotein C-I	APOC1	0.89	1.59
Apolipoprotein C-III	APOC3	0.74	0.6
Apolipoprotein D	APOD	0.34	0.16
Apolipoprotein E	APOE	1.4	2.71
Beta-2-glycoprotein 1	APOH	0.27	0.17
Apolipoprotein L1	APOL1	0.08	0.08
Immunoglobulin lambda-like polypeptide 1	IGLL1	1.25	0.14
Ubiquitin-like modifier-activating enzyme ATG7	ATG7	0.04	0.04
Bifunctional purine biosynthesis protein PURH	ATIC	0.22	0.05
Biliverdin reductase A	BLVRA	0.21	0.1
Flavin reductase	BLVRB	0.52	6.16

Complement C1q subcomponent subunit B	C1QB	0.49	0.12
Complement C1q subcomponent subunit C	C1QC	0.27	0.62
Complement C1r subcomponent	C1R	0.04	0.08
Complement C1s subcomponent	C1S	0.09	0.39
Complement C3	C3	0.92	4.02
Complement C5	C5	0.03	0.21
Complement component C7	C7	0.07	0.14
Complement component C8 beta chain	C8B	0.05	
Complement component C9	C9	0.49	0.1
Carbonic anhydrase 1	CA1	0.12	7.88
Cullin-associated NEDD8-dissociated protein 1	CAND1	0.42	0.05
Calpain-1 catalytic subunit	CAPN1	0.31	0.08
Calpastatin	CAST	0.28	0.04
Catalase	CAT	0.31	3.97
Cell cycle and apoptosis regulator protein 2	CCAR2	0.17	0.05
T-complex protein 1 subunit beta	CCT2	1.42	0.25
T-complex protein 1 subunit delta	CCT4	0.73	0.06
T-complex protein 1 subunit epsilon	CCT5	0.7	0.06
T-complex protein 1 subunit zeta	CCT6A	0.73	0.18
T-complex protein 1 subunit eta	CCT7	0.24	0.17
T-complex protein 1 subunit theta	CCT8	1	0.11
Complement factor H	CFH	0.09	0.34
Complement factor I	CFI	0.05	0.05
Cofilin-1	CFL1	9.11	0.18
Clusterin	CLU	0.83	0.62
COP9 signalosome complex subunit 4	COPS4	0.41	0.07
Ceruloplasmin	CP	0.33	0.93
Casein kinase II subunit alpha	CSNK2A1	1.5	0.07
Deoxyribose-phosphate aldolase	DERA	0.43	0.09
Dynamin-2	DNM2	0.34	0.03
Aspartyl aminopeptidase	DNPEP	1.19	0.27
E3 ubiquitin-protein ligase DTX3L	DTX3L	0.08	0.04
Elongation factor 1-gamma	EEF1G	0.77	0.07
Eukaryotic translation initiation factor 5A	EIF5A	0.43	0.46
Alpha-enolase	ENO1	2.13	0.5
Erythrocyte membrane protein band 4.2	EPB42	0.09	0.28
S-formylglutathione hydrolase	ESD	0.1	0.13
Prothrombin	F2	0.05	0.14

Fibulin-1	FBLN1	0.67	0.04
Filamin-A	FLNA	5.09	0.01
FLOT2_HUMAN	Q14254	1.24	19 (1)
Fibronectin	FN1	0.22	0.22
Fascin	FSCN1	0.59	0.06
Ferritin heavy chain	FTH1	2.71	0.34
Neutral alpha-glucosidase AB	GANAB	1.86	0.03
Glyceraldehyde-3-phosphate dehydrogenase	GAPDH	3.06	1.62
Vitamin D-binding protein	GC	0.42	1.41
Rab GDP dissociation inhibitor beta	GDI2	0.76	0.21
Guanine nucleotide-binding protein subunit beta-1	GNB1	0.09	0.09
Glucose-6-phosphate isomerase	GPI	0.29	0.05
Glutathione peroxidase 1	GPX1	0.32	0.15
Gelsolin	GSN	1.96	0.47
Glutathione S-transferase omega-1	GSTO1	0.4	0.4
Glycophorin	GYPA	0.21	0.21
HCG1745306, isoform CRA_a	HBA2	23.64	1157.55
Hemoglobin subunit beta	HBB	30.19	80.11
Hemoglobin subunit delta	HBD	16.26	43.6
Hemoglobin subunit gamma-1	HBG1	0.46	8.76
Heme-binding protein 1	HEBP1	0.34	0.55
Histidine triad nucleotide-binding protein 1	HINT1	2	0.25
HLA class I histocompatibility antigen, A-23 alpha chain	HLA-A	4.04	0.08
Haptoglobin	HP	0.42	1.65
Hypoxanthine-guanine phosphoribosyltransferase	HPRT1	0.14	0.66
Hemopexin	HPX	0.2	0.63
Histidine-rich glycoprotein	HRG	0.24	0.53
Heat shock protein HSP 90-alpha	HSP90AA1	3.9	0.12
Heat shock 70 kDa protein 4	HSPA4	0.27	0.04
Heat shock cognate 71 kDa protein	HSPA8	2.24	0.64
E3 ubiquitin-protein ligase HUWE1	HUWE1	0.06	0.01
Immunoglobulin heavy constant alpha 1	IGHA1	0.64	0.64
Immunoglobulin heavy constant alpha 2	IGHA2	0.4	0.53
Immunoglobulin heavy constant mu	IGHM	0.38	1.79
Immunoglobulin lambda constant 2	IGLC2	1.2	3.79

Inter-alpha-trypsin inhibitor heavy chain H1	ITIH1	0.03	0.56
Inter-alpha-trypsin inhibitor heavy chain H2	ITIH2	0.13	1.21
Inter-alpha-trypsin inhibitor heavy chain H4	ITIH4	0.17	0.59
Immunoglobulin J chain	JCHAIN	0.18	0.65
Kininogen-1	KNG1	0.14	0.3
Keratin, type II cytoskeletal 1	KRT1	1.64	0.1
Keratin, type I cytoskeletal 14	KRT14	0.64	0.13
Keratin, type II cytoskeletal 75	KRT75	0.17	0.05
L-lactate dehydrogenase A chain	LDHA	1.36	0.29
L-lactate dehydrogenase B chain	LDHB	0.99	2.34
Leucine-rich alpha-2-glycoprotein	LRG1	0.09	0.18
Lumican	LUM	0.78	0.28
Latexin	LXN	0.27	0.27
Microtubule-associated serine/threonine-protein kinase 4	MAST4	0.02	0.01
Malate dehydrogenase, cytoplasmic	MDH1	0.68	0.41
Serine/threonine-protein kinase mTOR	MTOR	0.11	0.01
Myosin-9	MYH9	8.07	0.06
Nucleoside diphosphate kinase A	NME1	1.44	1.93
NSFL1 cofactor p47	NSFL1C	0.27	0.17
Obg-like ATPase 1	OLA1	0.33	0.07
Alpha-1-acid glycoprotein 1	ORM1	1.2	1.2
Ubiquitin thioesterase OTUB1	OTUB1	0.65	0.11
Serine/threonine-protein kinase OSR1	OXS1	0.39	0.06
Platelet-activating factor acetylhydrolase IB subunit gamma	PAFAH1B3	0.13	0.18
Protein/nucleic acid deglycase DJ-1	PARK7	1.53	0.41
Protein-L-isoaspartate(D-aspartate) O-methyltransferase	PCMT1	1.14	0.29
Astrocytic phosphoprotein PEA-15	PEA15	0.23	0.27
ATP-dependent 6-phosphofructokinase, liver type	PFKL	1.2	0.57
ATP-dependent 6-phosphofructokinase, muscle type	PFKM	1.11	0.4
Profilin-1	PFN1	4.02	0.22
Phosphoglycerate mutase 1	PGAM1	3.61	0.39

6-phosphogluconate dehydrogenase	PGD	0.06	0.06
Phosphoglycerate kinase 1	PGK1	1.03	0.89
PITH domain-containing protein 1	PITHD1	0.14	0.14
Phospholipase D3	PLD3	0.06	1.2
Plasminogen	PLG	0.23	0.23
Purine nucleoside phosphorylase	PNP	0.1	1.19
Serum paraoxonase/arylesterase 1	PON1	0.61	0.38
Peptidyl-prolyl cis-trans isomerase A	PPIA	4.48	1.34
Peroxiredoxin-1	PRDX1	3.05	4.08
Peroxiredoxin-2	PRDX2	1.33	3.11
Peroxiredoxin-6	PRDX6	5.52	2.49
Vitamin K-dependent protein S	PROS1	0.09	0.09
Ribose-phosphate pyrophosphokinase 1	PRPS1	0.31	0.57
Proteasome subunit alpha type	PSMA2	0.13	0.27
Proteasome subunit alpha type-3	PSMA3	0.73	0.12
Proteasome subunit alpha type	PSMA4	0.24	0.42
Proteasome subunit alpha type-5	PSMA5	0.61	0.27
Proteasome subunit alpha type	PSMA6	0.4	0.5
Proteasome subunit alpha type-7	PSMA7	0.75	0.12
Proteasome subunit beta type-6	PSMB6	0.28	0.13
26S proteasome regulatory subunit 4	PSMC1	2.01	0.07
26S proteasome non-ATPase regulatory subunit 12	PSMD12	0.82	0.06
Serine/threonine-protein phosphatase 2A activator	PTPA	0.08	0.17
Ras-related protein Rab-10	RAB10	2	0.15
GTP-binding nuclear protein Ran	RAN	1.15	0.43
RNA-binding protein 6	RBM6	0.03	0.03
Protein S100-A4	S100A4	1.13	0.29
Protein S100	S100A6	0.13	1.49
Protein S100-A9	S100A9	2.94	2.94
Methanethiol oxidase	SELENBP1	0.27	1.06
Alpha-1-antitrypsin	SERPINA1	3.47	7.83
Alpha-1-antichymotrypsin	SERPINA3	0.59	1.54
Serpin B6	SERPINB6	0.68	0.08
Antithrombin-III	SERPINC1	0.52	0.62
Heparin cofactor 2	SERPIND1	0.06	0.18
Pigment epithelium-derived factor	SERPINF1	0.07	0.15
Plasma protease C1 inhibitor	SERPING1	0.33	0.8

SH3 domain-binding glutamic acid-rich-like protein 3	SH3BGL3	0.33	0.33
Facilitated glucose transporter member 1	SLC2A1	0.42	0.27
Band 3 anion transport protein	SLC4A1	0.51	1.13
Superoxide dismutase	SOD1	0.77	0.77
Spectrin alpha chain, erythrocytic 1	SPTA1	0.01	0.48
Spectrin beta chain	SPTB	0.04	0.65
Hsc70-interacting protein	ST13	0.85	0.3
Stress-induced-phosphoprotein 1	STIP1	0.58	0.11
Erythrocyte band 7 integral membrane protein	STOM	2.29	0.49
Transgelin-2	TAGLN2	1.64	0.32
Transaldolase	TALDO1	0.4	0.52
T-complex protein 1 subunit alpha	TCP1	0.45	0.05
Serotransferrin	TF	0.76	2.81
Transferrin receptor protein 1	TFRC	0.08	0.08
Thrombospondin-1	THBS1	0.18	0.05
Transketolase	TKT	0.6	0.1
Talin-1	TLN1	2.62	0.02
Tensin-2	TNS2	0.13	0.15
Triosephosphate isomerase	TPI1	1.76	0.36
Tropomyosin 1	TPM1	8.22	0.39
Trafficking protein particle complex subunit 9	TRAPPC9	0.05	0.03
E3 ubiquitin-protein ligase TRIM21	TRIM21	0.12	0.12
GDP-L-fucose synthase	TSTA3	0.19	0.19
Titin	TTN	0.01	0.01
Transthyretin	TTR	0.47	5.85
Thioredoxin	TXN	4.83	0.66
Ubiquitin-like modifier-activating enzyme 1	UBA1	0.87	0.11
Ubiquitin-60S ribosomal protein L40	UBA52	3.18	3.18
Ubiquitin-conjugating enzyme E2 N	UBE2N	1.45	0.43
Ubiquitin-conjugating enzyme E2 variant 1	UBE2V1	0.45	0.45
Ubiquitin carboxyl-terminal hydrolase	USP14	0.25	0.13
Utrophin	UTRN	0.07	0.01
Transitional endoplasmic reticulum ATPase	VCP	1.54	0.59
Vitronectin	VTN	0.59	0.34

von Willebrand factor A domain-containing protein 8	VWA8	0.02	0.02
14-3-3 protein beta/alpha	YWHAB	4.97	0.4
14-3-3 protein epsilon	YWHAE	4.02	0.54
14-3-3 protein zeta/delta	YWHAZ	6.64	0.75

T-AMEV, tissue adenomyosis-derived extracellular vesicle; B-AMEV, blood adenomyosis-derived extracellular vesicle; emPAI: exponentially modified protein abundance index.

Table SIII. Epithelial to mesenchymal transition-associated proteins in T-AMEVs and B-AMEVs.

Protein name	Gene names	emPAI in T-AMEVs	emPAI in B-AMEVs
Histidine triad nucleotide-binding protein 1	HINT1; HINT; PKCI1; PRKCNH1	2.00	0.25
Ubiquitin-60S ribosomal protein L40	UBA52; UBCEP2	3.18	3.18

T-AMEV, tissue adenomyosis-derived extracellular vesicle; B-AMEV, blood adenomyosis-derived extracellular vesicle; emPAI: exponentially modified protein abundance index.

Table SIV. Invasion-associated proteins in T-AMEVs and B-AMEVs.

Protein names	Gene names	emPAI in T-AMEVs	emPAI in B-AMEVs
Fibulin-1	FBLN1; PP213	0.67	0.04
Protein S100-A9	S100A9; CAGB; CFAG; MRP14	2.94	2.94
Plasminogen	PLG	0.23	0.23
Fascin	FSCN1; FAN1; HSN; SNL	0.59	0.06
Heat shock cognate 71 kDa protein	HSPA8; HSC70 HSP73; HSPA10	2.24	0.64
Rho GDP-dissociation inhibitor 1	ARHGDI1; GDIA1	1.25	0.14

T-AMEV, tissue adenomyosis-derived extracellular vesicle; B-AMEV, blood adenomyosis-derived extracellular vesicle; emPAI: exponentially modified protein abundance index.

Table SV. Kyoto Encyclopedia of Genes and Genomes pathway analysis.

Term ID	Term description	Observed gene count	Background gene count	False discovery rate
hsa04979	Cholesterol metabolism	8	48	1.01E-08
hsa00010	Glycolysis / Gluconeogenesis	6	68	3.96E-05
hsa01230	Biosynthesis of amino acids	6	72	3.96E-05
hsa04610	Complement and coagulation cascades	6	78	4.20E-05
hsa00030	Pentose phosphate pathway	4	30	0.00028
hsa01200	Carbon metabolism	6	116	0.00028
hsa05150	Staphylococcus aureus infection	4	51	0.0014
hsa04977	Vitamin digestion and absorption	3	24	0.0027
hsa05133	Pertussis	4	74	0.0041
hsa05020	Prion diseases	3	33	0.0052
hsa05143	African trypanosomiasis	3	34	0.0052
hsa04975	Fat digestion and absorption	3	39	0.0068
hsa05322	Systemic lupus erythematosus	4	94	0.0068
hsa04066	HIF-1 signaling pathway	4	98	0.0073
hsa01100	Metabolic pathways	13	1250	0.0186
hsa05230	Central carbon metabolism in cancer	3	65	0.0205
hsa03320	PPAR signaling pathway	3	72	0.0254
hsa04136	Autophagy	2	30	0.0485

Table SVI. Characteristics of blood samples from women with or without adenomyosis/endometriosis.

Characteristic	Patients with adenomyosis (n=25)	Healthy donors (n=31)	P-value
Age, years	41.84±6.67	42.10±4.49	0.86
Uterine volume, cm ³	409.30±189.17	361.82±190.92	0.35
Age at menarche, years	13.96±1.27	13.65±1.43	0.39
Age at first marriage, years	22.40±2.55	23.03±2.76	0.38
Pregnancy	3.60±1.85	3.29±1.51	0.49
Parity	1.60±1.12	1.65±0.80	0.87