

Table SI. Plasma miRNAs median expression levels and associations with clinical characteristics of patients with CRC.

Characteristic	miR-29a/b	P-value	miR-101	P-value	miR-125b	P-value	miR-146a	P-value	miR-155	P-value
Sex		0.860		0.536		0.860		0.044 <sup>a</sup>		0.536
Male	0.788		0.703		1.420		1.244		1.246	
Female	0.506		0.917		1.314		1.115		1.175	
Age at diagnosis		0.666		0.263		0.146		0.994		0.833
<66 years	0.895		0.942		1.558		1.178		1.362	
≥66 years	0.635		0.729		1.190		1.192		1.206	
BMI		>0.999		0.158		0.878		0.233		0.574
<25 kg/m <sup>2</sup>	0.502		1.115		1.380		0.948		0.906	
≥25 kg/m <sup>2</sup>	0.798		0.729		1.409		1.200		1.277	
Hypertension		0.892		0.574		0.644		0.698		0.995
Yes	0.765		0.755		1.171		1.187		1.309	
No	0.788		0.966		1.590		1.169		1.175	
Hyperlipidemia		0.837		0.392		0.118		0.327		0.392
Yes	0.761		0.555		0.853		1.029		0.839	
No	0.776		0.897		1.505		1.200		1.242	
Diabetes mellitus		>0.999		0.912		0.573		>0.999		0.738

Yes	0.981	0.755	0.882	1.157	1.309
No	0.765	0.877	1.420	1.187	1.238
Physical activity	0.837	0.392	0.118	0.327	0.392
<30 min	0.761	0.555	0.853	1.029	0.839
≥30 min	0.776	0.897	1.505	1.200	1.242
History of smoking	0.381	0.031 <sup>a</sup>	0.927	0.573	0.332
Yes	0.541	0.612	1.343	1.151	1.164
No	0.873	1.115	1.409	1.207	1.277
Alcohol consumption	0.775	0.633	0.924	0.143	0.117
Yes	0.765	0.703	1.398	1.244	1.635
No	0.788	0.877	1.420	1.157	1.175

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<sup>a</sup>P<0.05.

Table SII. The associations between median FFPE miRNA levels and clinicopathological characteristics of patients with CRC.

Characteristic	miR-29a/b	P-value	miR-101	P-value	miR-125b	P-value	miR-146a	P-value	miR-155	P-value
Sex		0.967		0.967		0.837		0.711		>0.999
Male	2.608		0.517		1.723		1.922		1.805	
Female	2.747		0.565		1.209		2.795		2.218	
Age at diagnosis		0.536		0.650		>0.999		0.773		0.432
<66 years	2.877		0.479		1.474		2.795		1.789	
≥66 years	2.406		0.552		1.723		1.922		2.098	
Histological grade		0.634		0.210		0.138		0.793		0.712
2	2.608		0.552		1.518		2.364		1.924	
3	2.909		0.441		2.058		3.991		3.029	
Nodal status		0.272		0.020 <sup>a</sup>		0.433		0.545		>0.999
Negative	2.812		0.676		1.897		2.717		1.924	
Positive	1.951		0.488		1.341		1.403		2.218	
Tumor localization		0.127		0.071		0.244		0.282		0.898
Left	1.858		0.676		1.334		1.699		1.924	
Right	2.909		0.482		1.877		3.439		2.135	
KRAS mutation status		0.964		0.298		0.444		0.823		0.257
Yes	1.951		0.479		1.460		2.795		2.520	
No	2.717		0.562		1.855		2.364		1.632	
No. of intratumoral		0.315		0.395		0.725		0.113		0.113

lymphocytes										
1	1.951		0.585		1.877		1.242		1.407	
≥2	2.812		0.494		1.563				2.369	
No. of lymphocytes around tumor		0.842		0.661		0.894		0.661		0.917
1	2.717		0.585		1.877		2.828		1.789	
2	2.529		0.539		1.563		2.508		2.218	
Tumor stroma quantity		0.444		0.186		0.391		0.964		0.444
1	1.692		0.784		1.961		2.573		3.029	
2	2.717		0.488		1.518		2.475		1.924	
Inflammatory infiltrate		0.967		0.902		0.083		0.650		0.384
1	2.687		0.585		1.973		2.155		1.407	
2-3	2.638		0.517		1.467		2.684		2.177	
Composition of inflammatory infiltrate		0.272		0.492		0.414		0.237		0.091
L + P	2.190		0.562		1.925		1.699		1.210	
L + P + G	2.747		0.494		1.518		2.795		2.520	
Necrosis		0.136		0.323		0.719		0.043 <sup>a</sup>		0.277
0-1	2.529		0.585		1.877		1.465		1.514	
2-3	3.263		0.479		1.474		3.982		2.218	
Mucus		0.499		0.622		0.754		0.499		0.034 <sup>a</sup>
0	2.717		0.562		1.723		2.684		2.177	
1-3	1.532		0.482		1.003		1.023		0.3221	

Lympho-vascular invasion		0.129		0.893		0.010 <sup>a</sup>		0.343		0.687
0	2.812		0.575		1.919		2.717		1.924	
1	1.766		0.482		1.003		1.403		2.218	
Lymph nodes with metastasis		0.272		0.166		0.738		0.545		>0.999
Yes	1.951		0.460		1.745		1.403		2.218	
No	2.812		0.676		1.897		2.717		1.924	

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<sup>a</sup>P<0.05.L, lymphocytes; P, plasma cells; G, granulocytes.

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Table SIII. Proteins encoded by genes regulated by at least two studied miRNA.

Symbol	Name
AKT1	RAC-alpha serine/threonine-protein kinase
AKT2	RAC-beta serine/threonine-protein kinase
AKT3	RAC-gamma serine/threonine-protein kinase
ANXA2	Annexin A2
ARID1A	AT-rich interactive domain-containing protein 1A
ARID2	AT-rich interactive domain-containing protein 2
ARID3A	AT-rich interactive domain-containing protein 3A
ARID3B	AT-rich interactive domain-containing protein 3B
BCL10	BCL10 immune signaling adaptor
BCL2	Apoptosis regulator Bcl-2
BCL2L2	Bcl-2-like protein 2
BCL3	B-cell lymphoma 3 protein
BCL6	B-cell lymphoma 6 protein
BCL7A	B-cell CLL/lymphoma 7 protein family member A
BCLAF1	Bcl-2-associated transcription factor 1
CARD10	Caspase recruitment domain-containing protein 10
CARD11	Caspase recruitment domain-containing protein 11
CCDC41	Coiled-coil domain-containing protein 41
CCDC6	Coiled-coil domain-containing protein 6
CCDC82	Coiled-coil domain-containing protein 82
CCND1	G1/S-specific cyclin-D1
CCND2	G1/S-specific cyclin-D2
CD4	T-cell surface glycoprotein CD4
CDC40	Pre-mRNA-processing factor 17
CDC42	Cell division control protein 42 homolog
CDC7	Cell division cycle 7-related protein kinase
CDH5	Cadherin-5
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
CDK4	Cyclin-dependent kinase 4
CDK6	Cyclin-dependent kinase 6
CDKN1A	Cyclin-dependent kinase inhibitor 1

CDKN2A	Cyclin-dependent kinase inhibitor 2A
CDKN3	Cyclin-dependent kinase inhibitor 3
CEACAM6	Carcinoembryonic antigen-related cell adhesion molecule 6
CFH	Complement factor H
COL10A1	Collagen alpha-1(X) chain
COX2	Mitochondrially encoded cytochrome c oxidase ii
CPEB1	Cytoplasmic polyadenylation element-binding protein 1
CPEB3	Cytoplasmic polyadenylation element-binding protein 3
CPEB4	Cytoplasmic polyadenylation element-binding protein 4
CRP	C-reactive protein
CSNK1A1	Casein kinase I isoform alpha
CSNK2A1	Casein kinase II subunit alpha
CXCL10	C-X-C motif chemokine 10
CXCL12	Stromal cell-derived factor 1
DKK1	Dickkopf-related protein 1
DKK3	Dickkopf-related protein 3
DNMT1	DNA (cytosine-5)-methyltransferase 1
DNMT3A	DNA (cytosine-5)-methyltransferase 3A
DNMT3B	DNA (cytosine-5)-methyltransferase 3B
DUSP1	Dual specificity protein phosphatase 1
DUSP6	Dual specificity protein phosphatase 6
E2F2	Transcription factor E2F2
EGFR	Epidermal growth factor receptor
ERBB2	Receptor tyrosine-protein kinase erbB-2
ERBB3	Receptor tyrosine-protein kinase erbB-3
ERBB4	Receptor tyrosine-protein kinase erbB-4
ETS1	Ets proto-oncogene 1
FADD	FAS-associated death domain protein
FBN1	Fibrillin-1
FBN2	Fibrillin-2
FGF7	Fibroblast growth factor 7
FGFR2	Fibroblast growth factor receptor 2
FOXO3	Forkhead box protein O3
FOXP3	Forkhead box protein P3

HBP1	HMG box-containing protein 1
HIF1A	Hypoxia-inducible factor 1-alpha
ICAM1	Intercellular adhesion molecule 1
ICAM2	Intercellular adhesion molecule 2
IGF1	Insulin-like growth factor I
IGF1R	Insulin-like growth factor 1 receptor
IGF2	Insulin-like growth factor II
IL6	Interleukin-6
IL6R	Interleukin-6 receptor subunit alpha
IL8	Interleukin-8
IRAK1	Interleukin-1 receptor-associated kinase 1
IRAK2	Interleukin-1 receptor-associated kinase-like 2
IRAK3	Interleukin-1 receptor-associated kinase 3
IRAK4	Interleukin-1 receptor-associated kinase 4
KLF13	Krueppel-like factor 13
KLF4	Krueppel-like factor 4
KLF6	Krueppel-like factor 6
KRAS	GTPase KRas
LAMC2	Laminin subunit gamma-2
MAP3K10	Mitogen-activated protein kinase kinasekinase 10
MAP3K11	Mitogen-activated protein kinase kinasekinase 11
MAP3K14	Mitogen-activated protein kinase kinasekinase 14
MAPK14	Mitogen-activated protein kinase 14
MCL1	Induced myeloid leukemia cell differentiation protein Mcl-1
MEIS1	Homeobox protein Meis1
MITF	Microphthalmia-associated transcription factor
MMP13	Matrix metalloproteinase-13 (collagenase 3)
MMP16	Matrix metalloproteinase-16
MMP2	Matrix metalloproteinase-2 (gelatinase a)
MMP26	Matrix metalloproteinase-26
MUC1	Mucin-1
MXD1	Max dimerization protein 1
MYC	Myc proto-oncogene protein
MYCN	N-myc proto-oncogene protein



MYD88	Myeloid differentiation primary response protein MyD88
MYLK	Myosin light chain kinase
MYO10	Unconventional myosin-X
MYO1D	Unconventional myosin-Id
MYO6	Unconventional myosin-VI
NFKB1	Nuclear factor NF-kappa-B p105 subunit
NOS1	Nitric oxide synthase, brain
NOS2	Nitric-oxide synthase, inducible
NOS3	Nitric-oxide synthase, endothelial
NOTCH1	Neurogenic locus notch homolog protein 1
NOTCH2	Neurogenic locus notch homolog protein 2
PIK3CD	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform
PIK3R1	Phosphoinositide-3-kinase regulatory subunit alpha/beta/delta
PPP1CA	Serine/threonine-protein phosphatase PP1-alpha catalytic subunit
PPP1R13B	Apoptosis-stimulating of p53 protein 1
PRDM1	PR domain zinc finger protein 1
PTEN	Phosphatase and tensin homolog
PTGS2	Prostaglandin G/H synthase 2
RAC1	Ras-related C3 botulinum toxin substrate 1
RNF11	RING finger protein 11
RNF123	E3 ubiquitin-protein ligase RNF123
ROBO1	Roundabout homolog 1
S100A12	Protein S100-A12
S100B	Protein S100-B
SFRP2	Secreted frizzled-related protein 2
SFRP5	Secreted frizzled-related protein 5
SIRT1	NAD-dependent protein deacetylase sirtuin-1
SIRT7	NAD-dependent protein deacetylase sirtuin-7
SMAD1	Mothers against decapentaplegic homolog 1
SMAD2	Mothers against decapentaplegic homolog 2
SMAD3	Mothers against decapentaplegic homolog 3
SMAD4	Mothers against decapentaplegic homolog 4
SMAD5	Mothers against decapentaplegic homolog 5
SOX1	Transcription factor SOX-1

SOX2	Transcription factor SOX-2
SOX6	Transcription factor SOX-6
SOX9	Transcription factor SOX-9
STAT1	Signal transducer and activator of transcription 1-alpha/beta
STAT3	Signal transducer and activator of transcription 3
TAB2	TGF-beta-activated kinase 1 and MAP3K7-binding protein 2
TBC1D1	TBC1 domain family member 1
TBC1D14	TBC1 domain family member 14
TBC1D8B	TBC1 domain family member 8B
TET1	Methylcytosine dioxygenase TET1
TET2	Methylcytosine dioxygenase TET2
TET3	Methylcytosine dioxygenase TET3
TGFB3	Transforming growth factor beta-3
TGFBR1	TGF-beta receptor type-1
TGFBR2	Transforming growth factor beta receptor 2
TLR2	Toll-like receptor 2
TLR3	Toll-like receptor 3
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor
TNFAIP3	Tumor necrosis factor alpha-induced protein 3
TP53	Cellular tumor antigen p53
TP53INP1	Tumor protein p53-inducible nuclear protein 1
TRAF4	TNF receptor-associated factor 4
TRAF6	TNF receptor-associated factor 6
VEGFA	Vascular endothelial growth factor A
VEGFC	Vascular endothelial growth factor C
VPS18	Vacuolar protein sorting-associated protein 18 homolog
VPS4B	Vacuolar protein sorting-associated protein 4B
VPS51	Vacuolar protein sorting-associated protein 51 homolog
ZNF117	Zinc finger protein 117
ZNF248	Zinc finger protein 248
ZNF254	Zinc finger protein 254
ZNF28	Zinc finger protein 28
ZNF431	Zinc finger protein 431

ZNF493	Zinc finger protein 493
ZNF561	Zinc finger protein 561
ZNF611	Zinc finger protein 611
ZNF652	Zinc finger protein 652
ZNF714	Zinc finger protein 714
ZNF83	Zinc finger protein 83

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