Supplementary file 1

Ambivalent roles of miRNAs in cancer development via modulating tumor-associated innate immune cells

Bahar Naseri[1#], Amirhossein Mardi[1,2#], Najibeh Shekari[2], Neda Shajari[3,1], Samin Abdolzadeh[1], Hossein Khorramdelazad[4], Amirhossein Hatami-Sadr[1], Milad Taghizadeh Anvar[5], Mohammad Reza Javan[6], Amirhossein Heibatollahi[1], Javad Masoumi[1], Farid Ghorbaninezhad[7*], Behzad Baradaran[1,2*]

[1]Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[3]Cancer Immunology and Immunotherapy Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

[4]Department of Immunology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

[5]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[6]Department of Immunology, Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran

[7]Student Research Committee, Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Table S1. Tumor-derived miRNAs' effects on DCs.

miRNA	Cancer type	Interventions	DC type	Outcomes	References
miR-212-3p	Pancreatic cancer	Transfer of miR-212-3p to DCs via pancreatic cancer-derive exosomes	moDCs	Induction of tolerogenic phenotype in DCs, reduction of MHC II expression	[139]
miR-221	Hepatoma	Co-culture of DCs with mouse hepatoma cell line Hepa1–6	Mouse bone marrow-derived DCs	Inhibition of CD86 and CD40 expression in DCs	[140]
miR-133a	Osteosarcoma	Transfection of miR-133a mimic by lipofectamine2000 reagent	Spleen DCs	Inhibition of the maturation and activation processes of DCs	[141]

miR-155	BC	knocking out the miR-155 gene *in vivo* in mice	Mouse lymph node DCs	Inhibition of the maturation and function of DCs	[144]
miR-17-5p	Gastric cancer	Co-culture of DCs with conditioned medium of GC cells containing miR-17-5p	Mouse bone marrow-derived DCs	Suppression of maturation and endocytosis activity of DCs	[145]
miR-203	Pancreatic cancer	Transfer of miR-203 to DCs via pancreatic cancer-derive exosomes	moDCs	Downregulation of TLR-4 and its downstream cytokines including TNF-α and IL-12 in DCs	[146]
miR-192-5p	Melanoma	Transfection of miR-192-5p with plasmid	Bone-marrow derived DCs	Suppression of the cytotoxic activity of CTLs	[147]
miR-155	Endometrial cancer	Transfection of miR-155 mimic via transfection reagent	Bone-marrow derived DCs	Diminishment of the ability of DCs to secrete IL-12 and polarize Th1 cells	[148]
miR-22	Melanoma	Transfection of miR-22 mimic	Bone-marrow derived DCs	Diminishment of the ability of DCs to secrete IL-6 and polarize Th17 cells	[149]
miR-105	Colon cancer	Increased expression of miR-105 in cancer cells by CXCL1 secreted by DCs	DCs isolated from mice and patients with CRC	Alterations in DC phenotype and anti-cancer cytokine IL-12 secretion	[151]

miR-410-5p	prostate cancer	Transfection of miR-410-5p mimic by lipofectamine reagent, co-culture of DCs with cancer cells	Tumor-draining lymph nodes isolated DCs, human myeloid DCs	Degradation of miR-410-3p and suppression of its function in inhibiting angiogenesis	[152]
miR-31-3p	Lung carcinoma	Hypoxia	Tumor-infiltrating DCs	Elevation of the secretion of VEGF	[153]

Abbreviations: miR: microRNA, DC: dendritic cell, moDC: monocyte-derived DC, BC: breast cancer, TLR: Toll-like receptor, IL: interleukin, TNF-α: tumor necrosis factor-alpha, CXCL1: chemokine C-X-C motif ligand 1, VEGF: vascular endothelial growth factor.

Table S2. Effects of miRNAs on NK cell activity in different cancers.

miRNA	**Model**	**Intervention/ Expression**	**NK cells**	**Outcomes**	**Refs**
miR-338-3p	Human BC cell lines	miR-338-3p overexpression	BC patients-derived NK cells	Elevated NK cells activity via upregulation of granzyme B, CD16, and NKG2D Barricading BC cells' survival	[163]
miR-150-5p	Lung cancer cell line CL1-5	miR-150-5p mimic	NK92 cells	Decreased CD226 expression, lytic ability, IFN-γ production, and elevated IL-10 expression in NK cells Progression of lung cancer by reversing NK cell phenotype	[166]

miR-221-5p and miR-186-5p	Bladder cancer cell line T24	T24 cells-derived exosomes	Human PBMC-derived NK cells	Impairing viability, and suppressing NK cell's cytotoxicity	167
miR-29c	SKOV3 ovarian cancer cells	miR-29c mimic	human $CD56^{+}$ NK cells	Induced antitumor functions of NK cell Reduced B7-H3 expression on tumor cells	169
miR-519a-3p	BC cell lines	miR-519a-3p mimic	NK cells isolated from human PBMCs	Downregulation of the NKG2D ligands ULBP2 and MICA on the surface of tumor cells, and subsequently impairing tumor cell killing by NK cells	170
miR-30c	A549 lung cancer cells	IL-2-induced miR-30c in NK cell-derived exosomes	Lung cancer patients' PBMCs-derived NK cells	Improved the IL-2-treated NK cell's ability to kill lung cancer cells	171
miR-29a, miR-29b, and miR-29c	NB cell line SK-N-BE (2) / mice model	miRNA overexpression and knockdown	NB patients-derived NK cells	miR-29 family enhances the activation of NK cell immune responses through targeting B7-H3 checkpoint	164
miR-18a	Metastatic murine BC cell lines	IDO1-mediated miR-18a over-expression	Murine NK cell line KY-1 and primary NK cells	Impair cytotoxicity of NK cells via downregulating NKG2D	173
miR-15a and miR-15b	Neuroblastoma cell lines	miR-15a and miR-15b mimics	NK cells isolated from human PBMCs	PD-L1 downregulation in cancer cells Increased NK cell-mediated neuroblastoma cytotoxicity	174
hsamiR-301a-3p	NSCLC cell line	Overexpression of	NK cells stimulated by IL-2	Suppressed NK cells' cytotoxicity to NSCLC cells via inhibiting the expression of RUNX3	176

		hsamiR-301a-3p			
miR-130a	NSCLC cell line	miR-130a mimic	NK cells isolated from NSCLC patients/ IL-2-activated NK-92 cells	Promote killing ability of NK cells against NSCLC cells by STAT3 targeting	[177]

Abbreviations: miR: microRNA, BC: breast cancer, NSCLC: non-small cell lung cancer, NB: neuroblastoma, NK cells: natural killer cells, ULBP2: UL16 Binding Protein 2, MICA: MHC class I chain-related protein A, PBMC: peripheral blood mononuclear cell, STAT3: Signal transducer and activator of transcription 3, PD-L1: Programmed death-ligand 1, IDO1: Indoleamine 2,3-dioxygenase-1.

Table S3. Effects of miRNAs on neutrophils in different cancers.

miRNA	**Model**	**Intervention/ Expression**	**Neutrophil**	**Outcomes**	**Ref**
miR-4466	Mouse	Exosomal miR-4466 derived from neutrophils	STAT3-activated N2-neutrophils	Induce lung cancer cell's stemness Promote lung cancer metastasis	[191]
miR-223	GC patients	Exosomal miR-223 derived from $CD66b^+$ neutrophil	$CD66b^+$ neutrophil	Accurate diagnosis of GC	[192]
miR-4780	in silico	miR-4780 was upregulated while hsa-miR-3938 was downregulated	N2 neutrophils	Regulating the invasion and metastasis of CRC cells	[195]

miR-3938		in N2 neutrophils		Diagnosis and prognosis of CRC	
miR-138	Mouse	Ectopic transfection of miR-138	NGAL producing neutrophils	Suppress NGAL expression and cell migration	[196]
miR-146a	in vitro	miR-146a over-expression	Immunosuppressive neutrophils	Inhibit activation of NF-κB and decrease neutrophil infiltration into tumor	[197]
miR301b-3p	in vitro	TANs triggered miR-301b-3p expression	TANs	Promote stem cell characteristics in HCC cells	[198]

Abbreviations: GC: Gastric cancer, CRC: Colorectal cancer, NGAL: neutrophil gelatinase-associated lipocalin, TANs: Tumor-associated neutrophils, HCC: hepatocellular carcinoma.