Molecular Therapy
Review

Role of exosomal non-coding RNAs from tumor cells and tumor-associated macrophages in the tumor microenvironment

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Exosomes have a crucial role in intercellular communication and mediate interactions between tumor cells and tumor-associated macrophages (TAMs). Exosome-encapsulated non-coding RNAs (ncRNAs) are involved in various physiological processes. Tumor-derived exosomal ncRNAs induce M2 macrophage polarization through signaling pathway activation, signal transduction, and transcriptional and post-transcriptional regulation. Conversely, TAM-derived exosomal ncRNAs promote tumor proliferation, metastasis, angiogenesis, chemoresistance, and immunosuppression. MicroRNAs induce gene silencing by directly targeting mRNAs, whereas lncRNAs and circRNAs act as miRNA sponges to indirectly regulate protein expressions. The role of ncRNAs in tumor-host interactions is ubiquitous. Current research is increasingly focused on the tumor microenvironment. On the basis of the "cancer-immunity cycle" hypothesis, we discuss the effects of exosomal ncRNAs on immune cells to induce T cell exhaustion, overexpression of programmed cell death ligands, and create a tumor immunosuppressive microenvironment. Furthermore, we discuss potential applications and prospects of exosomal ncRNAs as clinical biomarkers and drug delivery systems.

BACKGROUND

Non-coding RNAs (ncRNAs) do not encode proteins but control protein expression and function.[1–3] Several types of ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), affect cell growth, proliferation, and metabolism through multiple mechanisms.[3–5] miRNAs are 20–25 nucleotide ncRNAs that induce gene silencing at the post-transcriptional level by binding to the 3′ untranslated region (3′ UTR) of target mRNAs, thus regulating gene expression and other cellular processes.[6,7]

lncRNAs are longer than 200 nucleotides that are involved in post-transcriptional regulation in the nucleus and cytoplasm.[8,9] lncRNAs modulate the stability, translation, protein stability, and translocation of mRNAs.[9,10] lncRNAs increase target mRNA expressions by sponging miRNAs as competitive endogenous RNAs (ceRNAs), and are secreted either alone or bound to proteins.[11,12] circRNAs are characterized by a covalently closed-loop structure without a 5′ cap and a poly(A) tail.[13,14] These RNAs are implicated in miRNA spongings, protein interactions, and the regulation of nuclear transcription and pre-mRNA splicing.[15,16]

Exosomes are 40–150 nm extracellular vesicles that regulate multiple physiological and pathological processes by mediating intercellular communication.[17,18] The content of exosomes released by donor cells is protected from enzymatic hydrolysis.[19–21] Exosomes have fundamental roles in tumor proliferation, metastasis, and drug resistance.[21–23] Tumoral and immune cells secrete exosomes in the tumor immune microenvironment (TIME).[23,24] Tumor-derived exosomes (TEXs) modulate immunological activities, including macrophage polarization, T cell regulation, and inhibition of natural killer (NK) cell activity.[25–27] TEXs also affect tumor malignancy, suggesting their key role in interactions between tumoral and immune cells.[28–30] The roles of exosomal ncRNAs in tumor development and immunosuppression have attracted increasing attention.[31–33] Exosomes can be used in drug delivery because of their high encapsulation efficiency and the ability to transport anti-cancer drugs, natural agents, nucleic acids, and gene-editing systems such as CRISPR-Cas9.[34–36]

Macrophages are phagocytic immune cells, and their phenotypes are influenced by cytokines and other factors in the TIME.[37] Macrophages can assume a classically activated pro-inflammatory (M1) phenotype and an alternatively activated anti-inflammatory (M2) phenotype.[38] Tumor-associated macrophages (TAMs) have an M1 phenotype in the early stages of cancer.[37] In the later stage, growth factors and anti-inflammatory mediators, such as IL-4, IL-10, and

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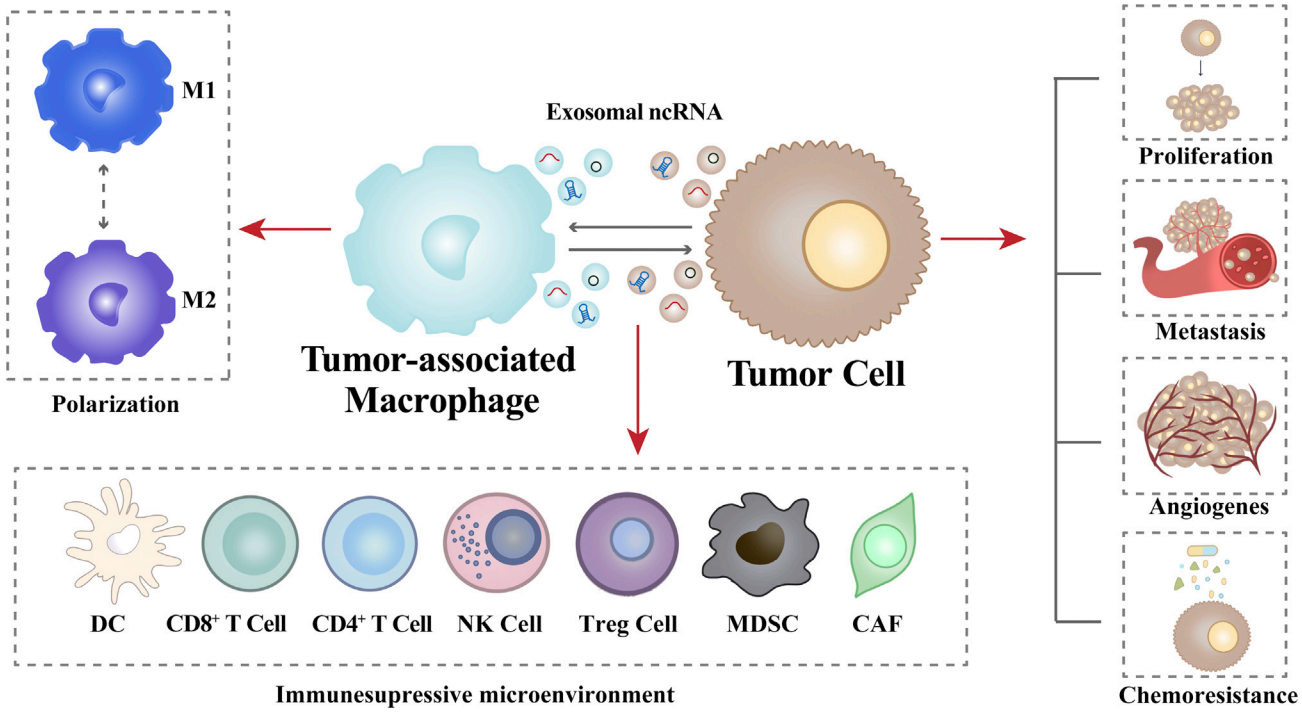

Figure 1. Interactions between tumor cells and TAMs via exosomal non-coding RNAs

Tumor-derived exosomal ncRNAs induce macrophage M1/M2 polarization. Conversely, TAM-derived exosomal ncRNAs promote tumor proliferation, metastasis, angiogenesis, and chemoresistance. Besides, these ncRNAs contribute to an immunosuppressive microenvironment by regulating immune cells.

TGF-β, are expressed in the TIME, inducing M2 polarization.[37] M1-M2 polarization is highly dynamic and reversible.

M2 TAMs produce growth factors and inhibit immune activity in the TIME.[39] TAM infiltration in solid tumors underscores the role of these cells in tumor progression and immunosuppression.[39–41] M2 macrophages can be divided into M2a, M2b, M2c, and M2d.[42] The M2a subgroup is activated by IL-4 and IL-13 and produces CD163, CD206, IL-10, TGF-β, and IL1Ra.[42] The M2b subgroup is stimulated by immune complexes and bacterial lipopolysaccharide to produce CD86, IL-10, IL-6, and TNF-α.[42] The M2c subgroup is induced by glucocorticoids, IL-10, and TGF-β and produces CD163, CD206, IL-10, and TGF-β; in addition, this subgroup is active against apoptotic cells.[42] The M2d subgroup, stimulated by IL-6 and adenosine, secretes anti-inflammatory cytokines (high levels of IL-10 and low levels of IL-12) and vascular endothelial growth factor (VEGF) to promote tumor angiogenesis.[42]

Some signaling pathways regulate macrophage switch.[41,43] Pro-inflammatory cytokines induce malignant behavior, whereas the anti-inflammatory microenvironment promotes tumorigenesis and immune evasion.[41,43] Therefore, macrophage activation is fine-tuned by the TIME. Tumor tissues may contain mixed macrophage populations with a spectrum of activation states. However, in this review, we assumed that TAMs have an M2 phenotype, as described in the literature.[37]

Increased attention has been given to the interactions between tumor cells and TAMs. Tumor cells promote TAM polarization, and polarized TAMs support the malignant phenotype of tumor cells, forming a cycle in which exosomal ncRNAs mediate the communication between tumoral and immune cells (Figure 1). This review discusses the interactions between tumor cells and TAMs during tumor initiation and development, mechanisms controlled by exosomal ncRNAs, the influence of exosomal ncRNAs on the formation of the TIME based on the "cancer-immunity cycle" model, and the potential application of exosomal ncRNAs as diagnostic and prognostic biomarkers and therapeutic targets.

EXOSOMAL ncRNAs ARE IMPORTANT MEDIATORS OF INTERACTIONS BETWEEN TUMOR CELLS AND TAMs IN THE TIME

Tumor-derived exosomal ncRNAs promote macrophage polarization

Signaling pathways and macrophage polarization

Macrophage polarization involves multiple signaling pathways and transcriptional and post-transcriptional regulatory networks.[38] The phosphatidylinositol 3-kinase (PI3K)/AKT and JAK/STAT pathways and key regulatory factors, including the signal transducer and activator of transcription (STAT) family, peroxisome proliferator-activated receptor-γ (PPARγ), and interferon regulatory factors, are implicated in macrophage polarization.[44,45] Tumors can regulate polarization by controlling the function of exosomal ncRNAs and

regulatory factors. For instance, in HPV^+ head and neck squamous cell carcinoma (HNSCC), miR-9 was enriched in TEXs and was transported to macrophages, inducing M1 polarization by downregulating PPARδ.[46] In addition, high levels of miR-451/miR-21 were detected in exosomes from primary human glioblastoma multiforme (GBM) cells and were taken up by TAMs in the brain of mice, decreasing c-Myc mRNA levels. The levels of miR-21 and miR-451 increased in microglia co-cultured with GBM exosomes and heparin reduced this effect.[47] In prostate cancer (PCa), miRNAs let-7a-5p and let7-b, -g, -i were enriched in exosomes and downregulated integrin-β3, causing M2 polarization and PCa cell migration.[48] Exosomal lncRNA TUC339 was highly expressed in hepatocellular carcinoma (HCC) cells and promoted M2 polarization, leading to reduced pro-inflammatory cytokine production, compromised phagocytosis, and decreased co-stimulatory molecule expression in macrophages.[49,50] TUC339 is involved in cytokine receptor signaling pathways and CXCR chemokine receptor binding pathways, which may explain the mechanisms underlying this regulation.[50] miR-21-5p was highly enriched in exosomes from colorectal cancer (CRC) cells.[51] Exosomes from the CRC cell lines SW480, SW620, and LoVo were injected into nude mice and were significantly enriched in liver macrophages. Furthermore, miR-21 in CRC exosomes promoted M1 polarization via TLR7 to produce IL-6, inducing a pro-inflammatory pre-metastatic niche and CRC cell survival and colonization, ultimately leading to liver metastasis.[51]

miRNAs also target metabolic enzymes. For instance, melanoma exosomal miR-125b-5p targeted lysosomal acid lipase A in macrophages, leading to phenotypic switching and increasing M2 macrophage survival.[52]

Several immune factors, including TGF-β, IL-10, and BMP-7, promote M2 polarization via the PI3K/AKT pathway.[45,53,54] Phosphatase and tension homolog deleted on chromosome ten (PTEN) inhibits AKT activity by dephosphorylating PIP3.[45,55] Exosomal miR-21 from bladder cancer cells regulated PI3K/AKT signaling by inhibiting PTEN activation in macrophages and enhanced STAT3 expression, promoting M2 polarization, leading to cancer cell migration and invasion.[56] Exosomal miR-130b-3p, miR-425-5p, and miR-25-3p were transported from CRC cells to macrophages and induced M2 polarization by targeting PTEN and activating the PI3K/AKT pathway. M2 macrophages enhanced epithelial-mesenchymal transition (EMT) and secreted VEGF to promote CRC metastasis.[57,58] circFARSA was upregulated in non-small cell lung cancer (NSCLC) tissues and transported to macrophages by exosomes.[59] Exosomal circFARSA activated PI3K/AKT signaling in macrophages through ubiquitination and degradation of PTEN, promoting M2 polarization.[59] The RNA-binding protein eIF4A3 triggered circFARSA biogenesis and cyclization during M2 polarization, enhancing EMT and metastasis in NSCLC cells.[59]

The JAK/STAT signaling pathway is implicated in macrophage polarization, and STAT1/5 and STAT 3/6 are involved in M1 and M2 polarization, respectively.[60,61] STAT activity is regulated by members of the suppressor of cytokine signaling (SOCS) family.[60] Exosomal miR-29a-3p promoted M2 macrophage polarization in oral squamous cell carcinoma by regulating SOCS1/STAT6 signaling.[62] In a co-culture system, exosomal miR-223 from cervical squamous cell carcinoma (CSCC) induced IL-6 secretion in M1 macrophages, enhancing STAT3 activity and increasing miR-223 expression in CSCC cells, creating a positive feedback loop.[63] Moreover, miR-223 repressed TGFBR3 and HMGCS1 expression in CSCC by targeting their 3′ UTRs, resulting in anchorage-independent growth and tumor growth.[63]

Factors regulating macrophage polarization

Hypoxia stimulates exosome secretion, and hypoxic exosomes from tumor cells trigger M2 macrophage polarization in a HIF1α- and HIF2α-dependent manner.[64,65] Hypoxia induced miR-301a-3p expression in pancreatic cancer (PC) cells and their exosomes and promoted M2 polarization through the PTEN/PI3Kγ signaling pathway.[66,67] In addition, hypoxia stimulated hsa_circ_0048117 expression in exosomes from esophageal squamous cell carcinoma (ESCC) cells, and this circRNA promoted M2 polarization by upregulating TLR4 and sponging miR-140.[68]

The activation or inhibition of the above signaling pathways and regulatory factors is enhanced by hypoxia. For instance, hypoxic tumor exosomes increased oxidative phosphorylation in macrophages via miRNA let-7a, inhibiting the insulin-AKT-mTOR signaling pathway.[69] Mammalian target of rapamycin (mTOR) is a downstream molecule of the PI3K-AKT pathway.[53] Similarly, hypoxic exosomes induced M2 polarization and enhanced the proliferation, migration, and invasion of glioma *in vitro* and *in vivo*.[70] MicroRNA-1246 was highly enriched in hypoxic glioma exosomes and mediated M2 polarization by targeting TERF2IP through the STAT3 and NF-κB pathways.[70]

Different ncRNAs are expressed in tumor exosomes depending on oxygen availability. Under normoxic conditions, miR-222-3p was enriched in macrophage exosomes from epithelial ovarian cancer (EOC) cells and induced M2 polarization via the SOCS3/STAT3 pathway.[71] In contrast, miR-940 was expressed in EOC cells and their exosomes and stimulated M2 macrophage polarization under hypoxic conditions.[72] In addition, under hypoxia, miR-21-3p, miR-125b-5p, and miR-181d-5p in EOC cell exosomes induced M2 polarization by regulating the SOCS4/5/STAT3 pathway.[73] However, the source of exosomes and the mechanisms underlying macrophage polarization by circRNA have not been determined.

EMT is associated with tumor development and chemoresistance.[74] Tumor cells control TAMs via exosomal ncRNAs and promote EMT.[75,76] EMT is accompanied by a large infiltration of M2 macrophages and exosomes in tumor tissues, including HCC, human head and neck cancer, CRC, and NSCLC.[77–82] Whether EMT leads to M2 polarization or M2 macrophages promote EMT remains controversial; notwithstanding, these processes are complementary. HCC exosomal lncRNA DLX6-AS1 regulated M2 macrophage

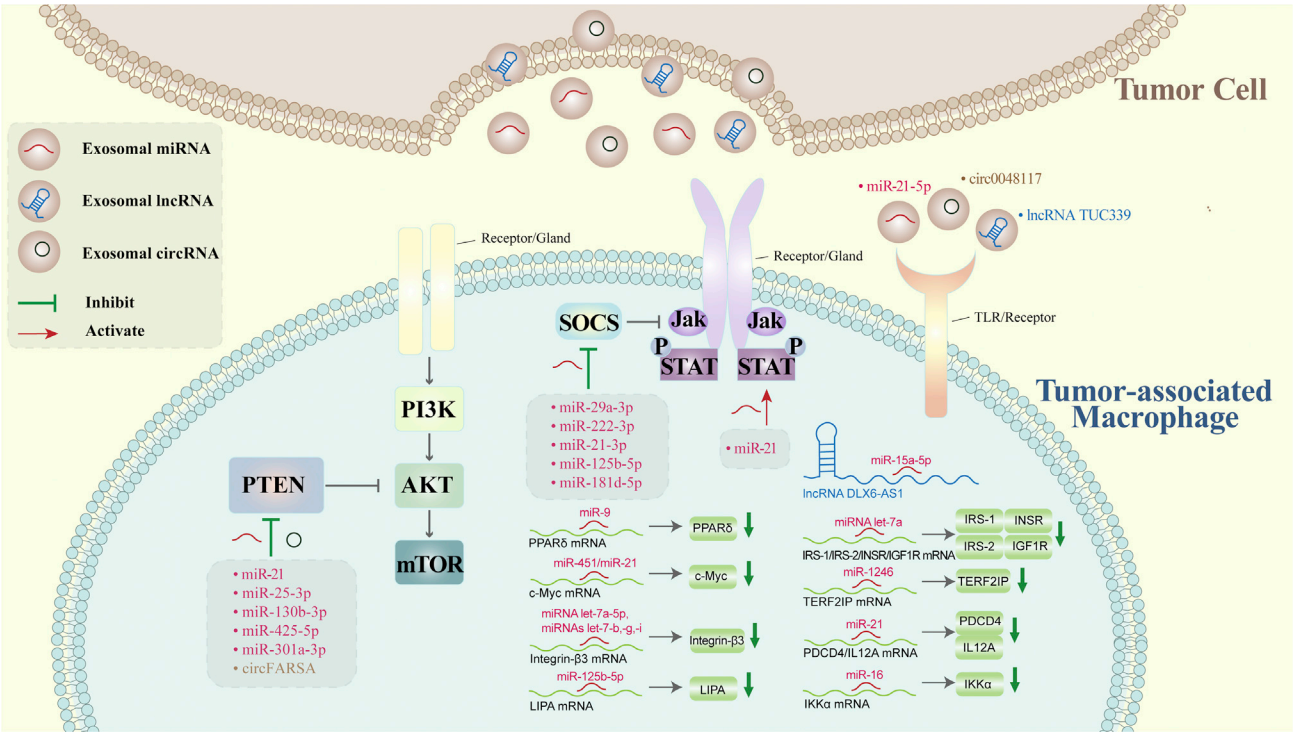

Figure 2. Tumor-derived exosomal non-coding RNAs promote macrophage polarization

Circ0048117, lncRNA TUC339, and miR-21-5p interfere with TLRs or other receptors on the surface of macrophages to induce M2 polarization. miR-21, miR-25-3p, miR-130b-3p, miR-425-5p, hypoxic miR-301a-3p, and circFARSA inhibit PTEN to activate the PI3K/AKT signaling pathway and induce M2 polarization. miR-29a-3p, miR-222-3p, hypoxic miR-21-3p, hypoxic miR-125b-5p, and hypoxic miR-181d-5p promote M2 polarization by suppressing SOCS signaling. miR-21 activates STAT signaling and promotes M2 polarization. miR-9, miR-451/miR-21, miRNA let-7a-5p/let7-b, -g, -i, miR-125b-5p, miRNA let-7a, miR-1246, miR21, and miR-16 downregulate PPARδ, c-Myc, integrin-β3, LIPA, IRS-1/IRS-2/INSR/IGF1R, TERF2IP, PDCD4/IL12A, and IKKα mRNAs, respectively, to induce M1 or M2 polarization. lncRNA DLX6-AS1 competitively binds to miR-15a-5p to induce M2 polarization.

polarization through competitively binding to miR-15a-5p and regulating the miRNA-15a-5p/CXCL17 axis, thereby promoting HCC migration, invasion, EMT, and pulmonary metastasis.[77] The EMT transcription factor Snail activated miR21 transcription and produced miR-21-enriched TEXs. TEXs containing miR-21-, taken up by human monocytes, decreased the expression of M1 markers and increased the expression of M2 markers. In Snail-expressing human head and neck cancer cells, miR-21 knockdown attenuated M2 polarization and inhibited tumor angiogenesis and growth.[78] CRC exosomes containing the lncRNA RPPH1 mediated M2 macrophage polarization, promoting cancer cell proliferation and metastasis.[79,80] Hsa_circ_0074854 was transferred from HCC tissues and exosomes to macrophages and promoted M2 polarization, and hsa_circ_0074854 knockdown suppressed exosome-mediated polarization and HCC migration and invasion.[81] The roles of exosomal lncRNA FGD5-AS1 in NSCLC were similar to those of hsa_circ_0074854 in HCC.[82] Nonetheless, the underlying mechanisms remain unclear.

Epigallocatechin gallate exerts antitumor effects by upregulating miR-16 in tumor cells and their exosomes and inhibiting TAM infiltration and M2 polarization.[83]

The infiltration of M2 macrophages in NSCLC was driven by the Kras mutant and was associated with tumor expansion, Kras-related chemoresistance, and patient survival. Exosome cicHIPK3/PTK2 promoted Kras-driven intratumoral heterogeneity in CD163$^+$ TAMs and lymph node metastasis in mice.[84]

Malignant cells transmit genetic information via exosomal ncRNAs to induce M2 polarization in the TIME (Figure 2; Table 1).

TAM-derived exosomal ncRNAs affect tumor progression

TAM-derived exosomal ncRNAs and tumor cell proliferation

Uncontrolled cell proliferation is an important feature of cancer and is characterized by alterations in the expression and activity of cell-cycle proteins.[85] TAM exosomal ncRNAs regulate the transcription, translation, and function of these proteins.

ncRNAs are transferred from TAM exosomes to tumor cells, regulating cancer cell proliferation and apoptosis.[86] TAMs promote PCa progression via exosome-mediated miR-95 transfer. *In vitro* and *in vivo* experiments showed that miR-95 bound to its target gene, JunB, in PCa cells and further induced tumor proliferation, invasion, and EMT.[87] In addition, miR-21 in TAM exosomes enhanced cell

Table 1. Tumor-derived exosomal ncRNAs promote macrophage polarization

Exosomal ncRNAs		Cancer type	Expression levels in tumor cells and their exosomes	Potential direct target gene(s) of ncRNAs in macrophages	Mechanism	Macrophage polarization	Effect	Ref.
miRNAs	miR-9	HPV^+ HNSCC	high	PPARδ↓	downregulate PPARδ mRNA	M1	increase the radiosensitivity of HPV^+ HNSCC	Tong et al.[46]
	miR-451/miR-21	GBM	high	c-Myc↓	downregulate c-Myc mRNA	M2	/	Van der Vos et al.[47]
	miRNA let-7a-5p miRNAs let7-b, -g, -i	PCa	high	integrin-β3↓	downregulate integrin-β3	M2	tumor migration	Ferguson et al.[48]
	miR-21-5p	CRC	high	/	bind to TLR7	M1	liver metastasis	Shao et al.[51]
	miR-125b-5p	melanoma	high in exosomes	LIPA↓	target LIPA	M2	/	Gerloff et al.[52]
	miR-21	bladder cancer	high	PTEN↓	inhibit PTEN activation and increase STAT3 expression	M2	cancer migration and invasion	Lin et al.[56]
	miR-25-3p miR-130b-3p miR-425-5p	CRC	high	PTEN↓	downregulate PTEN and activate PI3K/AKT signaling	M2	tumor metastasis by enhancing EMT and secreting VEGF	Wang and co-workers[57,58]
	miR-29a-3p	oral squamous cell carcinoma	high	SOCS1↓	regulate SOCS1/STAT6 signaling activity	M2	cancer proliferation and invasion	Cai et al.[62]
	miR-223	CSCC	high	/	/	M1	tumor progression	Zhang et al.[63]
	miR-301a-3p	PC	high under hypoxic conditions	PTEN↓	activate the PTEN/PI3Kγ signaling pathway	M2	cancer migration, invasion, and EMT	Wang and co-workers[66,67]
	miRNA let-7a	/	low in tumor cells and high in exosomes under hypoxic conditions	IRS-1, IRS-2, INSR, and IGF1R↓	enhance oxidative phosphorylation and inhibit the insulin-Akt-mTOR signaling pathway	M2	/	Park et al.[69]
	miR-1246	glioma	high under hypoxic conditions	TERF2IP↓	target TERF2IP to activate STAT3 signaling and inhibit NF-κB signaling	M2	cancer proliferation, migration, and invasion	Qian et al.[70]
	miR-222-3p	EOC	high	SOCS3↓	regulate the SOCS3/STAT3 pathway	M2	cancer proliferation, migration	Ying et al.[71]
	miR-940	EOC	high under hypoxic conditions	/	/	M2	tumor progression	Chen et al.[72]
	miR-21-3p miR-125b-5p miR-181d-5p	EOC	high under hypoxic conditions	SOCS4/5↓	regulate the SOCS4/5/STAT3 pathway	M2	cancer proliferation and migration	Chen et al.[73]
	miR21	head and neck cancer	high	PDCD4 and IL12A↓	downregulate PDCD4 and IL12A	M2	tumor growth and angiogenesis	Hsieh et al.[78]
	miR-16	BC	high after epigallocatechin gallate treatment	IKKα↓	downregulate IKKα and accumulate Iκ-B to suppress NF-κB activity	M2→M1	/	Jang et al.[83]

(*Continued on next page*)

Table 1. *Continued*

Exosomal ncRNAs		Cancer type	Expression levels in tumor cells and their exosomes	Potential direct target gene(s) of ncRNAs in macrophages	Mechanism	Macrophage polarization	Effect	Ref.
lncRNAs	lncRNA TUC339	HCC	high	/	regulate cytokine receptor signaling pathways and CXCR chemokine receptor binding pathways	M2	cancer proliferation and reduce cancer cell adhesion to the extracellular matrix	Kogure and co-workers[49,50]
	lncRNA DLX6-AS1	HCC	high	miR-15a-5p↓	regulate the miRNA-15a-5p/CXCL17 axis	M2	cancer migration, invasion and EMT, including pulmonary metastasis	Wang et al.[77]
	lncRNA RPPH1	CRC	high	/	/	M2	cancer metastasis and proliferation	Liang and co-workers[79,80]
	lncRNA FGD5-AS1	NSCLC	high	/	/	M2	cancer migration and invasion	Lv et al.[82]
circRNAs	circFARSA	NSCLC	high	PTEN↓	increase ubiquitination and degradation of PTEN and activate the PI3K/AKT signaling pathway	M2	EMT and metastasis	Chen et al.[59]
	circ0048117	ESCC	high under hypoxic conditions	miR-140↓	act as a sponge of miR-140 by competing with TLR4	M2	tumor invasion and migration	Lu et al.[68]
	circ0074854	HCC	high	/	/	M2	tumor migration and invasion	Wang et al.[81]
	cicHIPK3 cicPTK2	NSCLC	high	/	/	M2	Kras-associated chemoresistance	Katopodi et al.[84]

proliferation and inhibited apoptosis in gastric cancer (GC) cells by inhibiting PDCD4 expression.[88]

lncRNAs can reverse miRNA-induced gene silencing. For instance, TAM exosomal lncRNA LIFR-AS1 enhanced osteosarcoma cell proliferation by sponging miR-29a and increasing NFIA protein expression.[89]

TAM exosomal ncRNAs alter the proliferative capacity of tumor cells via post-transcriptional regulation. Low levels of cyclin-dependent kinase inhibitor 1B (CDKN1B) were associated with EOC progression and poor prognosis. Exosomal miR-221-3p directly targeted and inhibited CDKN1B expression, favoring EOC proliferation and G1/S progression.[90] miR-142 and miR-223 were effectively transferred from macrophages to HCC cells via exosomes. These RNAs decreased the expression of reporter proteins and endogenous proteins stathmin-1 and insulin-like growth factor-1 receptor and inhibited cancer cell proliferation.[91] miR-125a and miR-125b suppressed HCC cell proliferation by downregulating the cancer stem cell marker CD90.[92]

TAM-derived exosomal ncRNAs and metastasis

Organ-specific metastasis is complex and dynamic and involves tumor-host intercellular interactions.[93,94] TEXs in the circulation can help establish a pre-metastatic niche.[95,96] ncRNAs enter the systemic circulation and travel to distant organs to transmit information via cell receptors, allowing these RNAs to regulate tumor cell proliferation.[51]

Clinical and experimental evidence suggests that TAMs promote cancer cell migration via exosomal signaling.[97,98] Moreover, exosomal ncRNAs are involved in different steps of the metastatic cascade. miR-501-3p was highly expressed in pancreatic ductal adenocarcinoma (PDAC) and TAM exosomes.[99] This RNA promoted PDAC metastasis by downregulating the tumor-suppressor gene TGFBR3, and miR-501-3p inhibition suppressed tumor formation and metastasis *in vivo*.[99]

ncRNAs regulate the expression of proteins involved in invasion or migration. miR-21-5p and miR-155-5p, highly abundant in M2 macrophage exosomes, downregulated the protein expression of BRG1 in CRC cells, promoting cancer cell migration and invasion.[100] Decreased Brg-1 expression is implicated in CRC metastases.[101] lncRNA SBF2-AS1 acted as ceRNA to inhibit miR-122-5p and upregulate X-linked inhibitor of apoptosis protein.[102] The overexpression of exosomal lncRNA SBF2-AS1 promoted PC progression, and the inhibition of this RNA in M2 macrophages attenuated PC tumorigenicity.[102] Similarly, lncRNA AFAP1-AS1 downregulated miR-26a and upregulated its direct target ATF2, increasing esophageal cancer cell migration, invasion, and lung metastasis. Moreover, M2 macrophage exosomes showed higher AFAP1-AS1 and ATF2 expression and lower miR-26a expression than M1 macrophage exosomes.[103]

Androgen receptors (ARs) help regulate HCC initiation and progression.[104] Macrophage exosomal miR-92a-2-5p inhibited AR translation by targeting the 3′ UTR and PHLPP/p-AKT/β-catenin signaling, increasing HCC cell invasion. In addition, a preclinical study showed that miR-92a-2-5p inhibitors suppressed HCC progression.[104]

TAM exosomal miR-223 was upregulated in breast cancer (BC) cells *in vitro* and promoted BC cell invasion through the Mef2c-β-catenin pathway, and miR-223 inhibition decreased the invasiveness of BC cells.[105] Furthermore, macrophage exosomal miR-223 promoted the migration and invasion of GC cells via the PTEN-PI3K/AKT pathway, and RNA silencing reversed this effect. This RNA changed the actin cytoskeleton and upregulated multiple proteins associated with EMT.[106] Exosomes from TWEAK-stimulated macrophages were internalized by EOC cells and suppressed metastasis by inhibiting the EGFR/AKT/ERK1/2 pathway. TWEAK increased miR-7 levels—a tumor-suppressive miRNA—in macrophages, macrophage exosomes, and recipient EOC cells.[107]

Distant metastasis is a complex process in which M1 and M2 facilitate different steps.[51,100] It is essential that tumor cells acquire the ability to migrate and distant organs prepare the environment that favors the metastasis of tumor cells during distant organ metastasis.[108–111] As a first step, cancer cells need to become motile and invasive to enter the bloodstream. miR-21-5p and miR-155-5p in exosomal M2 macrophages from primary tumors regulated the expression of cell migration-related proteins and EMT, endowing tumor cells with invasive activity.[100] Stephen Paget proposed the "seed and soil" hypothesis, expounding that metastasizing cancer cells "seed" only in certain especially suitable tissues, akin to seeding in "fertile soil."[112] Shao et al. found that exosomes carrying miR-21 traveled from the primary tumor portion to the liver and liver macrophages can phenotype pro-inflammatory M1 by miR-21, which prepared a favorable environment for the metastasis of CRC.[51]

TAM-derived exosomal ncRNAs and tumor angiogenesis

Tumor angiogenesis involves several processes and cell types.[113] In the TIME, exosomes derived from mesenchymal, stromal, and endothelial cells play active roles in this process.[114] TAM infiltration in the TIME impacts tumor angiogenesis and epigenetic regulation.[115] Exosomes stimulate the formation of tubular structures, the growth of endothelial cells, and the secretion of VEGF. VEGF and other factors secreted by TAMs during tumor progression promote cancer development.[116] M2 macrophage exosomes increased the expression of migration and angiogenesis-related proteins in PDAC cells and enhanced metastasis *in vivo*.[99] Exosomal miR-501-3p promoted tumor cell migration, invasion, and tube formation.[99] MicroRNA-21 was transferred from glioma to microglia through exosomes. Exogenous miR-21 increased the ability of GBM cells to promote M2 polarization, and miR-21 inhibition reversed this effect.[117,118] This miRNA promoted endothelial angiogenesis through VEGFR2 signaling.[119] miR-21 was involved in the response to anti-angiogenic therapy, and bevacizumab treatment was associated with increased expression of miR-21 in the serum.[120] Moreover, miR-21 silencing increased GBM sensitivity to the anti-angiogenic drug sunitinib.[121] Exosomal miR-130b-3p promoted angiogenesis in GC cells.[122] Mixed lineage leukemia 3 (MLL3), a poor prognostic factor in GC, increased the expression of the gene grainyhead-like 2 (GRHL2).[123] MLL3 inhibited the proliferation, migration, and invasion of GC cells and tube formation in HUEVCs by increasing GRHL2, whereas miR-130b-3p had the opposite effect by inhibiting MLL3 expression.[122] In addition, miR-130b-3p downregulation and GRHL2 upregulation inhibited tumor formation and angiogenesis in GC.[122]

Hypoxia is a crucial regulator of angiogenesis and affects exosome secretion and function and the expression of exosome ncRNAs.[124,125] Tissue inhibitor of metalloproteinases-1 upregulated miR-210 and downregulated the mRNA and protein expression of its downstream targets by activating PI3K/AKT/HIF-1 signaling, increasing angiogenesis and tumor growth *in vivo*.[126] Exosome miR-21 activated STAT3, increasing VEGF levels in recipient cells.[127]

TAM-derived exosomal ncRNAs and tumor chemoresistance

Exosomal ncRNAs increase resistance to antitumor drugs. For instance, M2 macrophage miR-21 increased GC resistance to cisplatin by suppressing apoptosis via PTEN/PI3K/AKT activation.[128] lncRNA CRNDE was upregulated in GC tissues and TAM and promoted cisplatin resistance in GC cells via PTEN ubiquitination. CRNDE silencing in M2 macrophage exosomes increased the sensitivity of these cells to cisplatin, and PTEN knockdown reversed this effect.[129] MicroRNA-21 stimulated temozolomide resistance in GBM by modulating the STAT3/miR-21/PDCD4 signaling pathway. The STAT3 inhibitor pacritinib overcame temozolomide resistance by decreasing miR-21 levels and the number of miR-21-enriched exosomes.[117] The levels of miR-1246 were significantly higher in paclitaxel-resistant ovarian cancer (OC) exosomes than in paclitaxel-sensitive OC exosomes. The Cav1 gene and the multidrug resistance gene were direct targets of miR-1246 and participated in exosome transfer. Cav1 overexpression and miR-1246 mimic treatment sensitized OC cells to paclitaxel.[130,131]

Hypoxia increases macrophage recruitment and promotes exosome production and release, altering drug sensitivity in tumor cells. For instance, miR-223 was enriched in TAM exosomes under hypoxia and was transferred to EOC cells, inducing drug resistance via the PTEN-PI3K/AKT pathway.[132] HIF-1α might be involved in the production of miR-223 in TAM and their exosomes.[132] MicroRNA-365 increased PDAC resistance to gemcitabine by upregulating the triphosphate-nucleotide pool and increasing cytidine deaminase expression, whereas miR-365 antagonists reversed this effect.[133]

TAM exosomal ncRNAs affect every aspect of tumor progression (Figure 3; Table 2).

EXOSOMAL ncRNAs AND THE TIME

The cancer-immunity cycle is the sequence of events that lead to an effective anti-cancer immune response.[134] Tumor-specific antigens released from dead tumor cells are recognized by antigen-presenting cells (APCs), especially dendritic cells (DCs), and further processed to

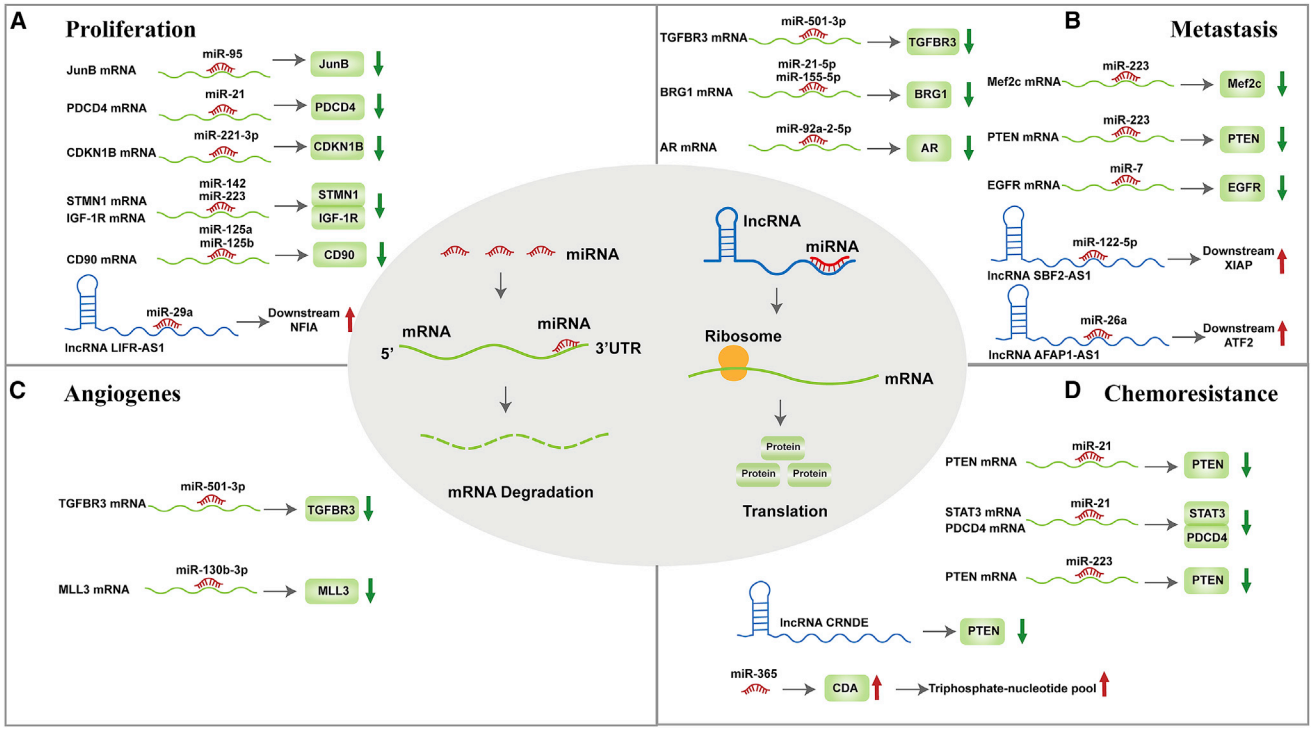

Figure 3. Tumor-associated macrophage-derived exosomal non-coding RNAs affect tumor progression

miRNAs can bind to the 3′ UTR of target mRNAs to induce gene silencing. lncRNAs can sponge miRNAs to increase target mRNA expression. (A) miR-95, miR-21, miR-221-3p, miR-142, miR-223, miR-125a, and miR-125b, promote tumor progression by binding to target mRNAs and downregulating gene expression. lncRNA LIFR-AS1 acts as a miR-29a sponge to upregulate NFIA. (B) miR-501-3p, miR-21-5p, miR-155-5p, miR-92a-2-5p, miR-223, and miR-7 promote tumor cell migration and invasion by targeting the corresponding genes. lncRNA SBF2-AS1 and lncRNA AFAP1-AS1 act as ceRNAs to repress miR-122-5p and miR-26a, respectively, increasing protein expression. (C) miR-501-3p and miR-130b-3p induce tumor angiogenesis by downregulating targeted genes. (D) miR-21, hypoxic miR-223, and lncRNA CRNDE promote chemoresistance by downregulating PTEN. In addition, miR-21 downregulates the STAT3 and PDCD4. miR-365 upregulate cytidine deaminase (CDA) and the triphosphate-nucleotide pool, which is associated with drug resistance in tumors.

form the antigen-peptide-MHC complex. Then, T cell receptors on DCs recognize this complex, whereas B7 molecules on DCs bind to CD28 on T cells, activating these cells. Cytotoxic T lymphocytes (CTLs) infiltrate the tumor and kill cancer cells.

Based on programmed cell death ligand 1 (PD-L1) expression and tumor-infiltrating lymphocytes (TILs), the TIME can be classified as having a "hot" or "cold" phenotype, with distinct pathophysiological characteristics; the former is characterized by the presence of activated lymphocytes and good response to immunotherapy, and the latter is characterized by the lack of T cell infiltrates and poor response to immunotherapy.[135] TILs are reflected by CD8A or cytolytic activity. Immunotherapy aims to stimulate the activity of CTLs and initiate and establish effective and long-term anti-cancer immunity.[136] However, as the tumor progresses, immune editing mediates immune escape through low tumor antigen expression, high PD-L1 expression, and reduced TILs, and hot tumors may transform into cold tumors, leading to poor immune response.[137–139]

Exosomal ncRNAs regulate the functions, interactions, and infiltration of CTLs—DCs, CTLs, NK cells, TAMs, fibroblasts, myeloid-derived suppressor cells (MDSCs), and Treg cells—in the TIME (Figure 4; Table 3).[168–170]

Exosomal ncRNAs regulate DC maturation and function

DCs are APCs that express a wide range of TLRs.[171,172] Upon TLR stimulation, DCs activate T cells and initiate the immune response by upregulating co-stimulatory molecules and pro-inflammatory cytokines.[173] Interference with TLR activation prevents initiating immunity. miR-21 and miR-29a in NSCLC exosomes bound to TLRs, resulting in tumor growth and metastasis.[140] In PCs, the overexpression of miR-203 had a similar effect on TLR4.[141] In addition, miR-203 reduced the expression of TNF-α and IL-12, which were essential for DC maturation and Th1 differentiation, respectively.[141] PC exosomes transferred miR-212-3p to DCs and inhibited the expression of the regulatory factor X-associated protein, decreasing MHC II expression and increasing immune tolerance in DCs.[142] Mature DCs stimulated the activation, proliferation, and differentiation of effector T cells, whereas immature DCs promoted T cell tolerance to tumor antigens.[174] Melanoma exosomes regulated DC maturation.[143] Exosomes blocked DC differentiation from myeloid precursors, producing immature MDSCs that contributed to tumor progression.[144] In

Table 2. Tumor-associated macrophage-derived exosomal ncRNAs affect tumor proliferation, metastasis, angiogenesis, and chemoresistance

Biological function	Exosomal ncRNAs	Expression levels in macrophages and their exosomes	Potential direct target gene(s) of ncRNAs in tumor cells	Mechanism	Cancer type	Ref.
Tumor cell proliferation	miR-95	high	JunB↓	promote tumor progression by binding directly to its downstream target gene JunB to promote PCa cell proliferation, invasion, and EMT	PCa	Guan et al.[87]
	miR-21	high	PDCD4↓	promote tumor progression by targeting the PDCD4 gene and inhibiting PDCD4 expression to prevent apoptosis in GC cells	GC	Wang et al.[88]
	lncRNA LIFR-AS1	high	miR-29a↓	act as a miR-29a sponge to upregulate NFIA, promoting tumor cell proliferation but inhibiting tumor cell invasion and apoptosis	osteosarcoma	Zhang et al.[89]
	miR-221-3p	high	CDKN1B↓	directly target and inhibit CDKN1B expression to promote EOC cell proliferation and G1/S conversion	EOC	Li and Tang[90]
	miR-142 miR-223	high	STMN1 and IGF-1R↓	downregulate the expression of reporter proteins and endogenously expressed stathmin-1 and insulin-like growth factor-1 receptor at the post-transcriptional level to inhibit tumor cell proliferation	HCC	Aucher et al.[91]
	miR-125a miR-125b	underexpressed in exosomes	CD90↑	target CD90 to promote HCC cell proliferation	HCC	Wang et al.[92]
Tumor metastasis	miR-501-3p	high	TGFBR3↓	target TGFBR3 to promote PDAC cell metastasis	PDAC	Yin et al.[99]
	miR-21-5p miR-155-5p	high	BRG1↓	downregulate BRG1 expression by binding to the BRG1 coding sequence to promote CRC cell migration and invasion	CRC	Lan et al.[100]
	lncRNA SBF2-AS1	high	miR-122-5p↓	act as a ceRNA to repress miR-122-5p and upregulate XIAP to promote PC progression	PC	Yin et al.[102]
	lncRNA AFAP1-AS1	high	miR-26a↓	act as a ceRNA to repress miR-26a and upregulate ATF2 to promote esophageal cancer (EC) cell migration and invasion and lung metastasis	EC	Mi et al.[103]
	miR-92a-2-5p	high	AR↓	target the 3′ UTR of AR mRNA and inhibit AR translation to alter PHLPP/p-AKT/β-catenin signaling and promote HCC cell invasion	HCC	Liu et al.[104]
	miR-223	high	Mef2c↓	target the Mef2c-β-catenin pathway to promote BC cell invasion	BC	Yang et al.[105]
	miR-223	high	PTEN↓	target the PTEN-PI3K/AKT pathway, alter the actin cytoskeleton, and upregulate multiple proteins associated with EMT to promote GC cell migration and invasion	GC	Zheng et al.[106]
	miR-7	high after TWEAK treatment	EGFR↓	downregulate the activity of the EGFR/AKT/ERK1/2 pathway to reduce EOC cell metastasis	EOC	Hu et al.[107]

(*Continued on next page*)

Table 2. *Continued*

Biological function	Exosomal ncRNAs	Expression levels in macrophages and their exosomes	Potential direct target gene(s) of ncRNAs in tumor cells	Mechanism	Cancer type	Ref.
Tumor angiogenesis	miR-501-3p	high	TGFBR3↓	target TGFBR3 to promote tube formation	PDAC	Yin et al.[99]
	miR-130b-3p	high	MLL3↓	promote GC progression via miR-130b-3p/MLL3/GRHL2 signaling	GC	Zhang et al.[122]
Tumor chemoresistance	miR-21	high	PTEN↓	activates PI3K/AKT signaling by downregulating PTEN to inhibit GC cell apoptosis and promote DDP resistance	GC	Zheng et al.[128]
	lncRNA CRNDE	high	PTEN↓	facilitate NEDD4-1-mediated PTEN ubiquitination to increase cisplatin resistance in GC cells	GC	Xin et al.[129]
	miR-21	high	STAT3 and PDCD4↓	regulate the STAT3/miR-21/PDCD4 signaling pathway, which is associated with temozolomide resistance in GBM	GBM	Chuang et al.[117]
	miR-223	high	PTEN↓	activate downstream signaling pathways, including PI3K/AKT, through downregulating PTEN to enhance drug resistance in EOC cells under hypoxia	EOC	Zhu et al.[132]
	miR-365	high	CDA↑	upregulate the triphosphate-nucleotide pool and induce the enzyme cytidine deaminase in cancer cells to induce PDAC resistance to gemcitabine	PDAC	Binebaum et al.[133]

summary, TEXs in the TIME inhibit the differentiation and maturation of DCs, thus transforming them from beneficial APCs to negative regulators of the immune response.[175]

Exosomal ncRNAs regulate T cell recruitment, proliferation, and differentiation

T cells are divided into two major groups based on phenotype, surface receptors, and antigen specificity: $CD4^+$ T helper (Th) and $CD8^+$ CLT cells.[176,177] Th cells can be further divided into Th1, Th17, and Tregs.[177]

In addition to inhibiting DC maturation,[178] TEXs control the proliferation, differentiation, and function of T lymphocytes and the expression of immune function genes in these cells.[179] miR146a in HCC exosomes promoted M2 polarization and impaired T cell function.[39] In addition, exosomes decreased the release of antitumor immune factors, such as IFN-γ, IL-2, and IL-17, from $CD4^+$ and/or $CD8^+$ T cells.[145] In advanced lung cancer, miR-23a was upregulated in tumor-infiltrating $CD8^+$ T cells and suppressed $CD8^+$ T cell function by downregulating its target gene BLIMP-1.[146] In HCC, TGF-β inhibited $CD8^+$ T cell function by suppressing miR-34a, enhancing Treg recruitment to the TIME.[147]

TEXs are associated with the proliferation and apoptosis of T cells. Exosomal miR-24-3p inhibited T cell proliferation and Th1 and Th17 differentiation and induced Treg differentiation by targeting FGF11 in nasopharyngeal carcinoma.[148] Hypoxia increased the level and activity of miR-24-3p.[148] Hypoxia-induced miR-210-inhibited Th17 differentiation in T cells by targeting HIF1α.[149] PC exosomes induced endoplasmic reticulum-mediated apoptosis of T lymphocytes by activating p38 mitogen-activated protein kinase (MAPK), ultimately leading to immunosuppression.[150]

TAMs contribute to immune escape and immunosuppression by affecting T lymphocyte infiltration in the TIME. M2 macrophage exosomes promoted immune escape by shuttling miR-21 and decreasing PEG3 mRNA expression in a mouse model of glioma.[151] In addition, exosomal miR-21 enhanced tumor volume and reduced the percentage of $CD8^+$ T cells in glioma tissues.[151] miR-21 depletion inhibited glioma growth, migration, and invasion, enhanced apoptosis, upregulated IFN-γ levels, and increased $CD8^+$ T proliferation and cytotoxicity.[151]

ncRNAs mediate the upregulation of immune checkpoints. HCC exosomal lncRNA PCED1B-AS1 enhanced the expression and function of programmed cell death ligands (PD-Ls) in HCC cells via sponging hsa-miR-194-5p and induced immunosuppression by inhibiting recipient T cells and macrophages.[152]

NK cells are a T cell subpopulation with cytotoxic activity and the ability to produce antitumor cytokines, such as IL-4, IFN-γ, Fas ligand, IL-13, and perforin.[180,181] TGF-β inhibits the cytotoxic activity of these cells by upregulating miR-183 and decreasing the protein levels of DNAX-activating protein 12, a signaling adaptor for NK cell function and a key factor in TGF-β-mediated immunosuppression.[153] In addition, glioma cell-derived miR-92a significantly decreased the

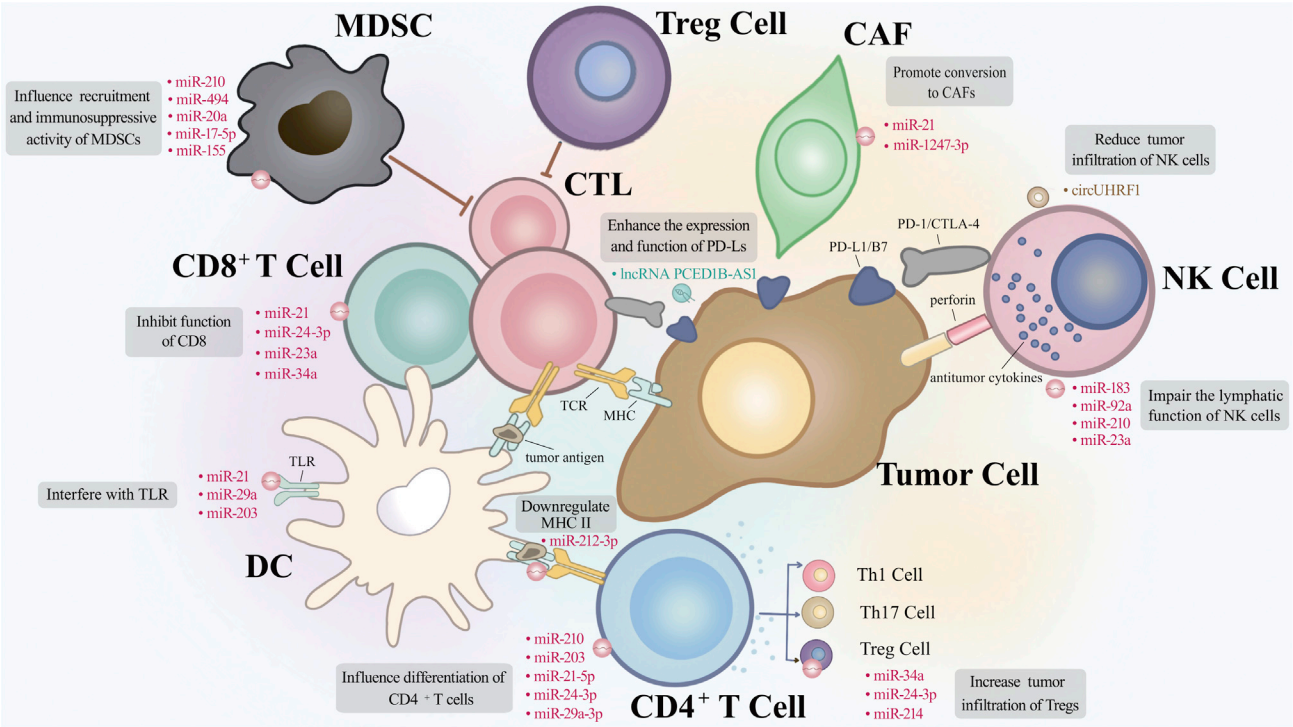

Figure 4. Exosomal non-coding RNAs of tumor cells or TAMs remodel the tumor immune microenvironment

Dendritic cells (DCs) process tumor antigens and form the antigen-peptide-MHC complex, which activates T lymphocytes. $CD4^+$ T cells can differentiate into Th1, Th17, and Treg cells. Activated $CD8^+$ T cells generate cytotoxic T lymphocytes (CTLs) that kill tumor cells. NK cells kill tumor cells by producing antitumor cytokines, such as IL-4, IFN-γ, FasL, IL-13, and perforin. Myeloid-derived suppressor cells (MDSCs) and Tregs have immunosuppressive activity. miR-21, miR-29a, and miR-203 bind to TLRs on the surface of DCs and inhibit DC maturation. miR-212-3p downregulates MHC II on DCs. miR-21 and miR-24-3p decrease $CD8^+$ T cell proliferation, whereas miR-23a, miR-34a, and miR-21 suppress $CD8^+$ T cell function. miR-29a-3p, miR-21-5p, miR-24-3p, hypoxic miR-210, and miR-203 affect $CD4^+$ T cell differentiation. miR-183, miR-92a, hypoxic miR-210, and hypoxic miR-23a reduce NK cell cytotoxicity. miR-210, miR-494, miR-20a, miR-17-5p, and miR-155 affect the recruitment and function of MDSCs. miR-34a, miR-24-3p, and miR-214 promote Treg recruitment and expansion. lncRNA PCED1B-AS1 suppresses T cell function via enhancing the expression and function of programmed cell death ligands in tumor cells. miR-1247-3p and miR-21 promote conversion from normal fibroblasts to CAFs.

expression of antitumor cytokines in NK cells and increased the ability of NK cells to suppress cytotoxic $CD8^+$ T cell activity.[154] HCC-derived circUHRF1 inhibited the secretion of IFN-γ and TNF-α by NK cells and caused NK cell dysfunction by inhibiting miR-449c-5p and upregulating its target gene TIM-3. High levels of plasma exosomal circUHRF1 decreased the NK cell ratio and NK cell infiltration.[155] TEXs decreased NK cell cytotoxicity under hypoxic conditions via miR-210 and miR-23a.[156,157] As a primary regulator of the hypoxic tumor response, miR-210 controlled antigen-specific immune response,[156] whereas miR-23a directly targeted CD107a expression.[157] These data demonstrate the vital role of exosomal ncRNAs in mediating T cell exhaustion and creating an immunosuppressive microenvironment.

Exosomal ncRNAs regulate immunosuppressive cell recruitment and function

Other immune cells in the TIME influence the cytotoxicity of CTLs and NK cells.[182,183] M1 macrophages enhance the antitumor effects of cytotoxic cells, whereas M2 macrophages, MDSCs, and Treg cells have the opposite effect.[182,183] Exosomal ncRNAs stimulate these immunosuppressive cells in the TIME, indirectly influencing the function of CTLs and NK cells.

Treg cells are a major subgroup of immunosuppressive leukocytes. $CD25^+$ $CD4^+$ Tregs produce immunosuppressive cytokines and express co-stimulatory molecules that inhibit tumor-specific CTL function.[182] The frequency of Tregs is increased during tumorigenesis and is positively correlated with compromised immune response.[182,184,185] The Treg/Th17 ratio was correlated with histological grade and was significantly increased in EOC.[158] miR-29a-3p and miR-21-5p were enriched in TAM exosomes.[158] These two miRNAs directly inhibited STAT3 in transfected $CD4^+$ T cells but caused an imbalance in the Treg/Th17 ratio and synergistically suppressed STAT3.[158] These results indicate that exosomes mediate the crosstalk between TAMs and T cells to create an immunosuppressive microenvironment.[158] miR-214 induced Treg expansion in $CD4^+$ T cells by targeting PTEN, causing immunosuppression and tumor growth.[159]

MDSCs are immature myeloid cells that suppress adaptive and innate immunity in the TIME and are a major driver of tumor immune

Table 3. Exosomal ncRNAs of tumor cells or TAMs remodel the tumor immune microenvironment

Exosomal ncRNAs	Immune cells	Mechanism	Effect	Cancer type	Ref.
miR-21 miR-29a	DCs	bind to TLRs to induce primary inflammation	tumor growth and metastasis	NSCLC	Fabbri et al.[140]
miR-203	DCs	bind to TLR4 to induce primary inflammation and reduce the expression of cytokines such as TNF-α and IL-12	inhibit DC maturation and Th1 differentiation to reduce cellular immunity	PC	Zhou et al.[141]
miR-212-3p	DCs	suppress RFXAP to induce MHC II downregulation	enhance immune tolerance in DCs	PC	Ding et al.[142]
Exosomes	DCs	/	regulate DC maturation	melanoma	Maus et al.[143]
Exosomes	DCs	/	inhibit DC differentiation and stimulate MDSC differentiation to promote tumor progression	/	Condamine and Gabrilovich[144]
miR146a	T cells	/	stimulate M2 polarization and inhibit anti-HCC T cell activity	HCC	Yin et al.[39]
Exosomes	T cells	/	Decrease the release of antitumor factors such as IFN-γ, IL-2, and IL-17 from $CD4^+$ and $CD8^+$ T cells	nasopharyngeal carcinoma	Ye et al.[145]
miR-23a	T cells	downregulate the target gene BLIMP-1	suppress $CD8^+$ T cell function	advanced lung cancer	Lin et al.[146]
miR-34a	T cells	suppress TGF-β	inhibit $CD8^+$ T cell function and recruit Tregs to the TIME	HCC	Yang et al.[147]
miR-24-3p	T cells	target FGF11	stimulate Tregs and inhibit T cell proliferation and Th1 and Th17 differentiation;	nasopharyngeal carcinoma	Ye et al.[148]
Hypoxia miR-210	T cells	target HIF1α	promote Th17 differentiation of T cells and promote tumor immune escape	/	Wang et al.[149]
Exosomes	T cells	uptake by T lymphocytes to activate p38 MAPK	induce ER stress-mediated apoptosis of T lymphocytes and lead to immunosuppression	PC	Shen et al.[150]
miR-21 (TAM)	T cells	regulate PEG3	decrease $CD8^+$ T cell proliferation and cytotoxic activity to accelerate immune escape and cancer cell growth, migration, and invasion; inhibit apoptosis to enhance tumor volume decrease	glioma	Yang et al.[151]
lncRNA PCED1B-AS1	T cells	sponge hsa-miR-194-5p and enhance the expression and function of PD-Ls in HCC cells	suppress recipient T cells and macrophages to induce immunosuppression in HCC	HCC	Fan et al.[152]
miR-183	NK cells	induced by TGF-β, target and inhibit DAP12	impair the lymphatic function of NK cells and trigger TGF-β-mediated immunosuppression	/	Donatelli et al.[153]
miR-92a	NK cells	reduce the expression of antitumor cytokines (perforin, FasL, and IFN-γ) by NK cells	induce NK cells to decrease cytotoxic $CD8^+$ T cell activity	glioma	Tang et al.[154]
circUHRF1	NK cells	degrade miR-449c-5p and upregulate TIM-3 to inhibit IFN-γ and TNF-α secretion in NK cells	reduce the NK cell ratio and tumor infiltration	HCC	Zhang et al.[155]
Hypoxic miR-210	NK cells	control antigen-specific immune responses and tumor hypoxia	reduce NK cell cytotoxicity and function	/	Norman et al.[156]
Hypoxic miR-23a	NK cells	directly target the expression of CD107a as an immunosuppressive factor	reduce NK cell cytotoxicity and function	/	Berchem et al.[157]
miR-29a-3p miR-21-5p (TAM)	Tregs	directly inhibit STAT3 in $CD4^+$ T cells and induce imbalance in the Treg/Th17 ratio to have a synergistic effect on STAT3 dinhibition	increase the Treg/Th17 ratio and create an immunosuppressive microenvironment	EOC	Zhou et al.[158]
miR-214	Tregs	decrease PTEN secretion	promote Treg expansion to enhance immunosuppression and tumor growth	/	Yin et al.[159]

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Table 3. *Continued*

Exosomal ncRNAs	Immune cells	Mechanism	Effect	Cancer type	Ref.
miR-210 miR-494	MDSCs	target IL-16 and CXCL12 (miR-210) and PTEN (miR-494), respectively	enhance MDSC recruitment and immunosuppressive activity	/	Liu and co-workers[160,161]
miR-20a miR-17-5p	MDSCs	repressed by hypoxia	inhibit MDSC immunosuppressive activity	/	Truettner and co-workers[162–164]
miR-155	MDSCs	repressed by tumor-derived exosomes	enhance MDSC recruitment and immunosuppressive activity	/	Wang et al.[165]
miR-1247-3p	CAFs	convert HSC to CAFs via activation of PTEN/PDK1/AKT signaling	secret pro-inflammatory cytokines to promote HCC progression	HCC	Fang et al.[166]
miR-21	CAFs	convert HSC to CAFs via activation of PTEN/PDK1/AKT signaling	secret angiogenic cytokines to promote HCC progression	HCC	Zhou et al.[167]

escape.[186] The accumulation of MDSCs and activation of suppressive cells require inflammatory factors regulated by immune-related miRNAs.[187] Tumor exosomal miR-210 and miR-494 were upregulated in rodent models.[160,161] Targeting CXCL12, PTEN, and IL-16 via miR-210, miR-494, and miR-210/miR-494, respectively, increased the recruitment and suppressive activity of MDSCs.[160,161] In addition, miR-20a and miR-17-5p were downregulated in MDSCs under hypoxic conditions, and their overexpression reduced the suppressive activity of MDSCs.[162–164] MicroRNA-155 deficiency increased the recruitment of MDSCs to the TIME and enhanced their immunosuppressive and pro-angiogenic function.[165]

Exosomal ncRNAs regulate the function of cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) represent the majority of stromal cells in the TIME.[188] In the lung metastatic niche, metastasis-prone HCC cells had advantages in converting normal fibroblasts to CAFs via secreting exosomal miR-1247-3p that targeted B4GALT3 in fibroblasts and activated β1-integrin-NF-κB signaling.[166] Similarly, HCC-derived exosomal miR-21 could convert normal hepatocyte stellate cells (HSCs) to CAFs through activating PTEN/PDK1/AKT signaling in HSCs.[167] Activated CAFs further promoted HCC progression by secreting angiogenic cytokines, including VEGF, MMP, and TGF-β.[167] CAF-derived exosomal ncRNAs are associated with immunosuppression. For example, the levels of miR-92 were higher in CAF exosomes of BC patients than in healthy controls.[189] CAF exosomes upregulated PD-L1 in BC cells, decreasing T cell proliferation and increasing apoptosis.[189] Hypoxia induced CAFs to release exosomal circEIF3K but inhibited miR-214, which downregulated PD-L1 expression in CRC. As a result, PD-L1 expression was upregulated in CRC under hypoxia.[190]

In summary, exosomes and their ncRNAs mediate tumor immune escape and the interaction between cancer cells and TAM in the TIME.

CLINICAL APPLICATIONS OF EXOSOMAL ncRNAs AND EXOSOMES

Exosomes and their ncRNAs are found in virtually all body fluids and thus can be used as non-invasive diagnostic biomarkers in cancer.[191] Exosomes are suitable for delivering small interfering RNAs (siRNAs), antitumor agents, and CRISPR-Cas9 systems, decreasing antigenicity and drug toxicity.[34,192–194]

Exosomal ncRNAs as promising diagnostic and prognostic biomarkers

Exosomal ncRNAs are highly enriched in biological fluids and can be used for liquid biopsies, improving diagnostic specificity and sensitivity.[191] In addition, improving exosome membrane structure can increase miRNA stability.[191]

circSATB2 was implicated in NSCLC progression and thus can be potentially used as a diagnostic marker for this cancer type.[195] Exosomal circ0048117 regulated ESCC progression, and higher serum exosomal circ0048117 was positively and significantly correlated with TNM stage.[68] Exosomal circSHKBP1 is a promising biomarker for GC diagnosis and prognosis and a therapeutic target since this RNA was detected in the blood and promoted GC progression.[196] CRC exosomal miR-203 promoted the expression of M2 markers *in vitro*.[197] MicroRNA-203-transfected CRC mouse cells developed more liver metastases than the control group.[197] Circulating exosomal miR-203 levels were correlated with metastasis, and low miR-203 expression in tumor tissue was a poor prognostic factor in CRC.[197] Bioinformatics analysis showed that the high expression of lncRNA GAS5 and miR-221 in tissue, plasma, and exosomes was of diagnostic value in CRC and was a prognostic factor for CRC.[198] A prognostic model targeting the STAT3-miR-223-HMGCS1/TGFBR3 axis predicted survival in HCC patients.[199] The exosomal lncRNAs RP11-538D16.2 and CTD-2116N20.1 are associated with poor prognosis in CRC.[199] The level of exosomal RPPH1 in the plasma was high in treatment-naive CRC patients but low after tumor resection.[79,80] Exosomal RPPH1 had a higher diagnostic value than CEA and CA199 in CRC.[79,80]

Exosomes and ncRNAs as potential therapeutic targets

Exosomes and their ncRNAs play essential roles in physiological and pathological processes. Exosomes are being developed for drug delivery in cancer therapy.[34,200] Exosome encapsulation enables the effective transfer of unstable molecules to target cells to participate

in antitumor and immunomodulatory processes, increasing drug concentration and decreasing drug toxicity.[201,202] Compared with synthetic carriers, such as liposomes and nanoparticles (NPs), exosomes have better biocompatibility, lower immunogenicity, wider distribution, and chemical stability in biological fluids, allowing targeted delivery to the blood-brain barrier and preventing phagocytosis by mononuclear macrophages.[200,201] Exosomes enter recipient cells by endocytosis, enhancing drug internalization.[200,201] Exosomes have a strong homing property and can target specific tissues and cells, increasing the cytotoxicity of therapeutic agents.[200,201] Milk exosomes have been developed for paclitaxel delivery and comply with good manufacturing practices.[203] The inhibition of the CD47-SIRPα interaction by engineered exosomes promoted T cell infiltration in syngeneic mouse models of cancer.[204] It has been proposed that CAR T cell-derived exosomes are more efficient and less toxic than CAR T therapy.[205] Exosomes can potentially be used as cancer vaccines.[206] miRNAs and siRNA can be delivered to recipient cells via exosomes to help regulate the expression of relevant genes, particularly oncogenes, which are potential targets for tumor therapy.[207,208] Exogenous siRNAs target human monocytes and lymphocytes and have been used to silence the MAPK1 gene.[209] Engineered mesenchymal stromal cell exosomes carrying KRASG12D siRNA are currently in phase I clinical trials for patients with metastatic PC and KRASG12D mutations (NCT03608631). Clinical trials on therapeutic exosomes have been well organized previously.[200,210,211]

Although these advantages make exosomes promising therapeutic targets, some limitations, such as off-targeting, low loading efficiency, fast clearance *in vivo*, and the lack of standardized production and preparation, need to be resolved before clinical application.

Exosomes are surface-functionalized with ligands to prevent off-targeting and achieve targeted drug delivery.[200,212] Common modification methods include chemical ligation of targeted peptides, genetic engineering of progenitor cells and exosomal membranes, magnetic NPs, and electrostatic interactions. Nonetheless, exosome engineering has some limitations.[200,212] First, changing the exosome surface structure is challenging. Second, genetically modifying parental cells reduces transfection efficiency and the biological activity of membrane proteins. Third, chemically modified viral proteins may have adverse health effects. Fourth, cationic nanomaterials may cause cytotoxicity and have low loading efficiency when used in electrostatic interactions.

Achieving the efficient, cost-effective, large-scale production of therapeutic exosomes determines whether they can be used in clinical practice. Exosome production is divided into two stages: large-scale cell culture and exosome isolation and processing. In addition, several characterization indexes are needed to assess whether the extracted components are exosomes. Exosomes are characterized based on morphology, size, and protein markers. The most commonly used isolation methods are ultracentrifugation, particle size separation, polymer precipitation, and immunoaffinity capture. However, several methods need to be combined to achieve the desired yield, purity, integrity, price, and other relevant characteristics. Combining different methods can improve purification efficiency and allow cost-effective large-scale production. However, the effectiveness of these strategies has not been determined. Recent advances in therapeutic exosome production are detailed in two reviews.[210,212,213]

Tumor-suppressive miRNAs are expressed at low levels in tumors and inhibit cancer development. The recovery of these miRNAs using miRNA mimics is a promising therapeutic strategy. A proof-of-concept study evaluated the effectiveness of these mimics as an miRNA-replacement therapy in a preclinical animal model.[214,215] Antisense oligonucleotides, miRNA sponges, ribonucleases, small molecules, and the CRISPR-Cas9 system can suppress oncomiRs.[216–220]

Despite recent achievements in the study of immune checkpoint inhibitors (ICIs), immunotherapeutic agents have limitations on response rates, toxicity, and resistance.[221] Exosomal ncRNAs impact the efficacy of immunotherapy. For instance, endoplasmic reticulum stress promoted the release of exosomes from HCC, and miR-23a-3p-loaded exosomes were phagocytosed by macrophages and activated the PI3K/AKT pathway through inhibiting PTEN. As a result, macrophages were polarized to M2, increasing the expression of PD-L1 and impairing T cell function. The blockade of HCC-macrophage interactions by miR-23a-3p inhibitors may be a novel strategy to treat HCC progression.[222] In addition, HCC exosome-educated macrophages suppressed the expression of IFN-γ and TNF-α and upregulated the expression of inhibitory receptors, such as PD-1 and CTLA-4 in T cells.[39] HCC exosomal lncRNA PCED1B-AS1 regulated the expression of PD-L1 and PD-2 in HCC, affecting the efficacy of ICIs.[152] Serum exosome PCED1B-AS1 correlated with the expression of PD-Ls in HCC and predicted the efficacy of immunotherapy.[152] PCED1B-AS1 inhibitors can potentially improve immunotherapy. HCC exosomal circUHRF1 reduced NK infiltration in tumors and inhibited the secretion of IFN-γ and TNF-α by NK cells. In addition, circUHRF1 upregulated TIM-3 expression by inhibiting miR-449c-5p, thereby reducing NK cell function. More importantly, circUHRF1 might be involved in immunosuppression by inducing NK cell dysfunction in HCC, leading to anti-PD1 therapy resistance.[155] Blocking circUHRF1 may restore the function of NK cells and improve the efficacy of immunotherapy. Exosomes from drug-resistant BC cells increased the levels of TGF-β1 and the expression of PD-L1, inducing resistance to antitumor agents such as trastuzumab.[223] These results suggest that the exosome-mediated transfer of ncRNAs to monocytes contributes to cancer-associated immune escape.[224]

As an important part of the TIME, macrophages are becoming a new target for antitumor immunity. Current cancer immunotherapies targeting macrophages can inhibit macrophage recruitment, deplete TAMs, reprogram TAMs, and block the CD47-SIRPα pathway.[225,226] First, targeting the colony-stimulating factor 1 (CSF-1)/CSF-1R axis, C-C chemokine ligand 5 (CCL5)/CCR5 axis, CCL2/CCR2 axis, or VEGF effectively decreased TAM recruitment in preclinical and

clinical studies.[227] The delivery of a CCR2 siRNA to monocytes using cationic NPs in peripheral blood, bone marrow, and spleen inhibited monocyte recruitment and reduced TAM infiltration, leading to TIME remodeling.[228] Similarly, M2 TAM dual-targeted NPs loaded with anti-CSF-1R siRNA decreased macrophage infiltration in melanoma and tumor size and improved overall survival in mice.[229]

Hyaluronic acid (HA) NPs loaded miRNA-125b promoted M1 polarization and enhanced antitumor efficacy.[230] miRNA mimics are being used in preclinical trials to reprogram TAMs. MicroRNA-125b/wt-p53 plasmids encapsulated in CD44/EGFR-targeted HA NPs triggered M1 polarization and inhibited tumor growth in a mouse model of lung cancer.[231] Similarly, the targeted delivery of miR-99b to mice with HCC or subcutaneous Lewis lung cancer induced M1 polarization by targeting κB-Ras2 and mTOR, enhancing immune surveillance and preventing tumor growth.[232]

CD47 is a transmembrane protein expressed in all cell types, particularly immature red blood cells and cancer cells.[233] CD47 overexpression is linked with decreased phagocytosis/apoptosis by TAMs and poor prognosis in tumors.[234] Therefore, blocking the CD47-SIRPα pathway can potentially restore the antitumor effect of TAMs. CD47 could be downregulated by antiD47 siRNA.[235,236] Exosomes containing SIRPα variants significantly enhanced tumor phagocytosis and induced an effective antitumor T cell response.[204] Anti-SIRPα therapy targeting myeloid cells has fewer side effects than anti-CD47 therapy, especially in red blood cells, making it a promising strategy to block the CD47-SIRPα pathway.[237] In addition, inhibiting this pathway induces macrophage repolarization.[238,239]

DISCUSSION

Exosomal ncRNAs usually represent the ncRNA landscape of the mother cell. However, many ncRNAs are differentially expressed between cells and exosomes. In this respect, miR-21 and miR-451 were highly expressed in GBM.[47] The relative expression level of miR-21 did not differ significantly between GBM cells and exosomes; however, the level of miR-451 was 1,000–10,000 times higher in exosomes.[47] Similarly, 117 ultraconserved RNAs (ucRNAs) were upregulated, 68 miRNAs were downregulated, and 24 ucRNAs were detected exclusively in exosomes.[49] The transport of ncRNAs via exosomes is selective, although the underlying mechanisms are unclear. lncRNA LIFR-AS1, a miR-29a sponge, was transferred from macrophages to tumor cells by exosomes. lncRNA LIFR-AS1 was highly expressed and miR-29a was lowly expressed in osteosarcoma tissues. The expression of miR-29a in macrophages was significantly upregulated by lncRNA LIFR-AS1 knockdown, but not in exosomes. This indicated that the two ncRNAs were not co-transported in exosomes, which may be related to selective inclusion of exosomes.[89]

In addition, the miRNA landscape of exosomes varies depending on the tumor type.[48] Viral infection can also affect miRNA expression in tumor cells and exosomes. MicroRNA-9 was highly expressed in HPV^+ HNSCC cells but not in HPV^- HNSCC cells.[46]

Hypoxia promoted the secretion of exosomes in tumor cells,[66–68] and increased miRNA levels in TEXs.[72] Under hypoxia, the expression of total let-7a miRNA in tumor cells decreased to approximately 30% of that in normal hypoxia controls, while the content of let-7a in exosomes increased to approximately 25 times.[69] This reflected the enhanced enrichment ability of exosomes under hypoxia.

The functions of miRNAs in recipient cells depend on the characteristics of exosomes, uptake mechanism, the amount of miRNA transferred to recipient cells in the cytoplasm, and the level of endogenous target mRNAs.[47]

PROSPECTS AND CONCLUSIONS

Macrophages are one of the most abundant cell types in the TIME and are closely associated with tumor development. The heterogeneity in macrophage activity may have significant diagnostic and therapeutic implications in cancer. Exosomes mediate interactions between tumoral cells and TAMs via ncRNAs.

Immune escape is a hallmark of tumors and disrupts the cancer-immunity cycle, leading to T cell depletion and long-term immunosuppression.

Exosomal ncRNAs are used by cancer cells to evade immune surveillance and can serve as diagnostic markers given their abundance in tumor tissues and peripheral circulation. Nonetheless, their specificity and sensitivity in solid tumors must be further assessed.

Antagonists can be used to reverse the effects of exosomes and their ncRNAs; nonetheless, the development of effective and clinically applicable antagonists is challenging.

Targeting signaling pathways and designing drugs that can reverse macrophage phenotype and tumor drug resistance have tremendous implications in oncotherapy. However, large follow-up studies and clinical validation are needed.

Moreover, miRNAs and siRNAs transferred to recipient cells via exosomes can abrogate the expression of target genes, limiting tumor progression.[34] Notwithstanding, establishing standard production practices, improving purity, yield, and targeting, and achieving cost-effective large-scale production are necessary before these nanovesicles advance to clinical trial.

Macrophage-targeting therapies are emerging immunotherapies. More preclinical studies are needed to improve the targeting of these treatments. The exact efficacy and immune-related adverse effects need to be fully evaluated before clinical studies can be conducted.

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AUTHOR CONTRIBUTIONS

L.Z. and Y.S. designed the study. Z.X., Y.C., and L.M. collected the related papers and drafted the manuscript. Z.X., Y.C., and L.M. contributed equally to the manuscript. Y.C., J.L., Y.G., T.Y., and L.Z. revised the manuscript. All authors have read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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