Role of microRNAs in remodeling the tumor microenvironment (Review)

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Abstract. MicroRNAs (miRNAs) are short non-coding RNAs that are known to regulate gene expression at the post-transcriptional level. miRNA expression is often deregulated in several human cancers, affecting the communication between tumor stroma and tumor cells, among other functions. Understanding the role of miRNAs in the tumor microenvironment is crucial for fully elucidating the molecular mechanisms underlying tumor progression and exploring novel diagnostic biomarkers and therapeutic targets. The present review focused on the role of miRNAs in remodeling the tumor microenvironment, with an emphasis on their impact on tumor growth, metastasis and resistance to treatment, as well as their potential clinical applications.

Contents

1. Introduction

Over the past decade, several studies have demonstrated that cancer initiation and progression are determined not only by cancer cells, but also by the tumor microenvironment (TME) (1-4), which includes fibroblasts, immune cells and endothelial cells, among others (5). Mounting evidence suggests that microRNAs (miRNAs) play a key role in shaping the biology and function of tumor stromal cells (5-8). The deregulation of miRNAs has been associated with almost every aspect of cancer initiation and progression (9-11). In 2006, Volinia *et al* first identified a miRNA signature in human cancers and demonstrated that the predicted targets of these deregulated miRNAs were classic oncogenes or tumor suppressors (12). One of the oncogenic miRNAs identified was miR-21, which was found to be highly expressed in breast and colon cancer, and its overexpression was correlated with poor patient survival. Furthermore, miR-21 was demonstrated to target programmed cell death 4, an apoptosis-inducing protein, thus promoting tumor growth (13,14). Additionally, miR-34a was identified as a downstream target of the p53 tumor suppressor gene (15). With the recent advances in miRNA detection techniques, cancer cell-derived miRNAs have emerged as promising diagnostic biomarkers and therapeutic targets, as has been described in detail elsewhere (16-18).

Recent studies have highlighted the significance of miRNAs in the TME (19-24). Aprelikova *et al* identified 11 miRNAs that were differentially expressed between cancer-associated fibroblasts (CAFs) isolated from human endometrial cancer and normal endometrial fibroblasts (25). Mesenchymal stem cells (MSCs) were previously isolated from gastric cancer (GC) tissues (GC-MSCs) and paired adjacent non-cancerous gastric tissues (GCN-MSCs), and 114 upregulated and 85 downregulated miRNAs were identified in GC-MSCs (26). Liu *et al* compared the miRNA expression profiles of myeloid-derived suppressor cells (MDSCs) from breast cancer-bearing mice and their counterparts from tumor-free mice, and found that 3 miRNAs (miR-494, miR-882 and miR-361) were upregulated, whereas 5 miRNAs (miR-466, let-7e, miR-133b, miR-713 and miR-322) were downregulated in the MDSCs from the tumor-bearing mice. Furthermore, 5 miRNAs were found to be upregulated and 7 miRNAs downregulated in cancer-associated endothelial cells compared with normal endothelial cells (27). The aim of the present review was to summarize the latest advances in understanding the roles of miRNAs in TME remodeling, which ultimately affects tumor progression and may be of value in the clinical setting.

2. Role of miRNAs in regulating TME cells

miRNAs in regulating CAFs. Fibroblasts are one of the major components of the TME. At the primary tumor site, fibroblasts acquire distinct phenotypic characteristics and become CAFs

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through a miRNA-mediated regulation of multiple signaling pathways. CAFs differ from normal fibroblasts (NFs) in their high expression of α-smooth muscle actin and their pro-tumorigenic properties (28). CAFs secrete a wide range of pro-inflammatory molecules, including interleukins, chemokines and extracellular matrix (ECM) components, ultimately promoting tumor growth by modulating tumor-associated inflammation or directing cell-to-cell communication (29). Bronisz *et al* reported that miR-320 expression was significantly reduced when phosphatase and tensin homolog (*PTEN*) on chromosome 10 was ablated, which induced the transition of NFs to CAFs in breast cancer (30). Loss of the *PTEN* gene in stromal fibroblasts results in the activation of an oncogenic secretome. The downregulation of miR-320 and upregulation of one of its direct targets, ETS proto-oncogene 2, transcription factor, are critical events in *PTEN*-deficient stromal fibroblasts that induce the oncogenic secretome, which in turn promotes tumor angiogenesis and tumor cell invasion (30).

In breast cancer, the pro-metastatic miRNA miR-9 was shown to induce a switch in human breast fibroblasts from a normal towards a CAF phenotype, thereby contributing to tumor progression (31). In addition, the downregulation of miR-200s was reported to play an important role in reprogramming NFs into CAFs. miR-200s target friend leukemia virus integration 1 (Fli-1) and transcription factor 12 (TCF12) in the breast cancer microenvironment (32,33). Moreover, decreased miR-205 was shown to convert breast NFs into CAFs by promoting Yes-associated protein 1 (YAP1) expression, which has been proven to be involved in angiogenesis (34).

In ovarian cancer, low expression of miR-214 and high expression of miR-155 are involved in reprogramming quiescent fibroblasts to CAFs. miR-214 directly targets C-C motif ligand 5 (CCL5), which is essential for CAF function. The overexpression of miR-155 in NFs induces fibroblasts to develop CAF-like phenotypes. The disruption of these miRNAs is sufficient to reverse the functions of CAFs, thereby reducing ovarian cancer growth and metastasis (32). Furthermore, miR-155 was shown to convert NFs into CAFs in pancreatic cancer by targeting p53-inducible nuclear protein 1 (35).

In melanoma, melanocytes are specialized in producing pigment vesicles, referred to as melanosomes. Melanosomes have been shown to carry miRNAs, including miR-211, into primary fibroblasts, triggering changes such as increased proliferation, migration and pro-inflammatory gene expression, all of which are known characteristics of CAFs (36).

In lung cancer, downregulation of miR-1 and miR-206, and upregulation of miR-31, may promote the NF-CAF switch by stimulating CCL2/vascular endothelial growth factor A (VEGFA) expression (37). Taken together, these findings underline the importance of miRNAs in driving the conversion of NFs into CAFs in several tumor entities.

Role of miRNAs in regulating tumor-associated MSCs. MSCs are progenitor cells that are known to participate in tumor stroma formation and tumor progression. Bone marrow-derived MSCs (BM-MSCs) can migrate to tumor sites, where they exert tumor-promoting and pro-metastatic effects. We previously demonstrated that miR-155-5p downregulation induced BM-MSCs to acquire the phenotype of GC-MSCs through the activation of nuclear factor-κB p65 (NF-κB p65). In that study, NF-κB p65 and the inhibitor of NF-κB kinase subunit ε were identified as the targets of miR-155-5p (38). miR-214, miR-221 and miR-222 were upregulated in GC-MSCs compared with GCN-MSCs. GC-MSCs significantly promoted the proliferation and migration of GC cells. Targeted inhibition of miR-221 in GC-MSCs was found to inhibit its tumor-promoting effects (26).

Let-7 is downregulated in prostate cancer-associated MSCs, which exhibit a stronger propensity for migration and invasion compared with normal MSCs. Interleukin (IL)-6 was identified as a direct target gene of let-7. The overexpression of let-7 reduces IL-6 expression and represses the metastasis-promoting activity of cancer-associated MSCs (39). miR-146a overexpression leads to increased secretion of chemotactic proteins, including CXCL1, interferon gamma-induced protein 10, CCL5 and IL-6, which are crucial for the growth and migration of multiple myeloma cells. The Notch pathway was also shown to be involved in the miR-146a-induced cytokine and chemokine secretion in MSCs (40). In myeloid neoplasms, miR-7977 in MSCs was found to induce aberrant reduction of hematopoietic growth factors, including Jagged-1, stem cell factor and angiopoietin-1, thereby reducing the hematopoietic-supporting capacity of bone marrow $CD34^+$ cells (41). This evidence indicates that the aberrant expression of miRNAs can promote the evolution of MSCs in the TME, facilitating tumor progression.

Role of miRNAs in regulating tumor-associated macrophages. Tumor progression is intrinsically linked to immune evasion. The activation of certain immune cells drives potent antitumor responses, whereas the suppression of these cells promotes tumor progression and metastasis. Cancer cells can regulate miRNA expression in infiltrating immune cells, thereby suppressing the local antitumor immune response and ultimately leading to tumor progression (42-47). Tumor-associated macrophages (TAMs) have both pro- and anti-tumorigenic properties, depending on whether they belong to the classical M1 or alternative M2 subtype. At the late stage of human cancers, most of the infiltrating macrophages display an M2 phenotype, creating an immunosuppressive microenvironment that favors tumor progression. Increased miR-21-5p delivery by MSC-derived extracellular vesicles was recently reported to promote the polarization of macrophages towards an M2 phenotype (48). miR-125b binds to the 3' untranslated region of tumor necrosis factor-α (TNF-α), inhibiting its production and sustaining an M1 phenotype (49). By contrast, miR-146 directly inhibits the expression of the adaptor protein tumor necrosis factor receptor-associated factor 6 and IL-1 receptor-associated kinase-1 in the NF-κB pathway, thus reducing pro-inflammatory cytokine production and promoting alternative M2 activation (5).

In addition to regulating the polarization and phenotype of TAMs, miRNAs have also been shown to regulate other functionalities of TAMs, including infiltration, immune responses and tumor-promoting effects. Ke *et al* reported that low miR-148b levels in hepatocellular carcinoma (HCC) cells enhanced the expression of colony-stimulating factor-1, promoting TAM infiltration and HCC metastasis (50). Moreover, another crucial miRNA involved in the modulation of immune responses is miR-155, which is persistently

Table I. MicroRNAs in tumor microenvironment remodeling.

MicroRNAs	Cancers	Function	(Refs.)
Regulation of CAFs			
miR-9	Breast cancer	Enhancing the switch to CAF phenotype	(29)
miR-200s	Breast cancer	Inhibiting CAF activation by targeting Fli-1 and TCF12	(31)
miR-205	Breast cancer	Inhibiting the switch to CAFs by regulating YAP1	(34)
miR-155	Ovarian cancer Pancreatic cancer	Promoting conversion of the fibroblasts to a CAF-like phenotype by targeting TP53INP1	(30,32)
miR-214	Ovarian cancer	Inhibiting CAF activation by targeting CCL5	(30)
miR-211	Melanoma	Enhancing the switch to CAF phenotype by targeting IGF2R and leading to MAPK signaling activation	(33)
miR-1, miR-206, miR-31	Lung cancer	Reprograming NF-CAF conversion via affecting CCL2/VEGFA expression	(34)
Regulation of cancer-associated MSCs			
miR-155-5p	Gastric cancer	Inhibiting the conversion of BM-MSCs to GC-MSCs by targeting NF-κB p65	(35)
miR-221	Gastric cancer	Playing a tumor-supporting role	(24)
Let-7	Prostate cancer	Inhibiting the adipogenic differentiation and metastasis-promoting activity of cancer-associated MSCs by targeting IL-6	(36)
miR-146a	Myeloma	Inducing cytokine and chemokine secretion in MSCs	(37)
miR-7977	Myeloid neoplasms	Decreasing hematopoiesis-supporting capacity of bone marrow $CD34^+$ cells.	(38)
Regulation of TAM			
miR-125b	Lymphoma	Enhancing macrophage responsiveness to IFNγ and increasing surface expression of its cognate receptor	(45)
miR-155	Gastric cancer	Suppressing cytokine production in tumor-activated monocytes/macrophages by targeting C/EBPβ	(46)
miR-511-3p	Lung cancer	Inhibiting the tumor-promoting functions of TAMs	(49)
miR-21, miR-29a	Lung cancer	Inducing the secretion of the proinflammatory cytokines TNF-α and IL-6 by TLR8-mediated activation of NF-κB	(50)
miR-21-5p	Lung cancer	Promoting the polarization of M2 macrophages	(48)
miR-148b	Hepatocellular carcinoma	Inhibiting TAM infiltration and HCC metastasis by downregulating the colony stimulating factor-1 expression	(50)
Regulation of T cells			
miR-24-3p	Nasopharyngeal carcinoma	Inducing differentiation of Tregs by targeting FGF11	(53)
miR-214	Lung cancer	Inducing the secretion of IL-10 from Tregs and modulating Treg induction	(52)
miR-21	Breast cancer	Reducing the proliferation of Tregs by targeting the PTEN and Akt pathways	(54)
miR-149-3p	Breast cancer	Enhancing T-cell proliferation and activation	(62)
miR-448	Colon cancer	Suppressing the apoptosis of $CD8^+$ T cells and enhancing $CD8^+$ T-cell response	(63)
Regulation of endothelial cells			
miR-29a/c	Gastric cancer	Suppressing angiogenesis by targeting VEGF in the gastric tumor microenvironment.	(57)
miR-939	Breast cancer	Increasing HUVEC monolayer permeability by targeting vascular endothelial-cadherin.	(58)
miR-143/145	Lung cancer	Stimulating the proliferation of endothelial cells and regulating endothelial cell migration	(60)

Table I. Continued.

MicroRNAs	Cancers	Function	(Refs.)
miR-125b	Glioblastoma	Mediating VEGF-induced angiogenesis by targeting Myc-associated zinc finger protein	(61)
miR-93	Breast cancer	Enhancing endothelial tube formation by increasing blood vessel density	(62)
miR-638	Hepatocellular carcinoma	Suppressing angiogenesis by inhibiting VEGF signaling	(65)
miR-205	Breast cancer	Regulating YAP1-mediated IL-11 and IL-15 expression and secretion in CAFs, which enhance tubule formation	(34)
Regulation of tumor growth			
miR-7	Head and neck cancer	CAF-mediated tumor-promoting effect by targeting RASSF2	(67)
miR-211	Melanoma	CAF-mediated tumor-promoting effect by targeting IGF2R	(33)
miR-125a	Lung cancer	TAM-mediated antitumor activity by targeting FIH1 and IRF4	(48)
miR-638	Hepatocellular carcinoma	Angiogenesis-mediated antitumor activity by targeting VEGF	(65)
miR-143/145	Lung cancer	Endothelial cell-mediated tumor-promoting effect by targeting CAMK1D	(60)
miR-3188	Head and neck cancer	CAF-derived exosomal expression regulating tumor growth	(76)
miR-501-3p	Pancreatic ductal adenocarcinoma	M2 macrophage-derived exosomal miR-501-3p facilitating tumor formation by regulating the TGF-β signaling pathway	(80)
Regulation of tumor metastasis			
miR-126/miR-126*	Breast cancer	Suppressing lung metastasis by inhibiting the recruitment of MSCs and inflammatory monocytes	(74)
miR-9	Breast cancer	CAF-mediated tumor cell migration by reducing E-cadherin	(29)
miR-200s	Breast cancer	CAF-mediated tumor cell invasion and metastasis by targeting Fli-1 and TCF12.	(31)
miRNA-199a	Breast cancer	MSC-mediated tumor initiation and metastasis	(75)
miR-28-5p	Hepatocellular carcinoma	TAM-mediated metastasis by miR-28-5p-IL-34 signaling	(76)
miR-148b		CAF-derived exosomal expression enhances tumor metastasis by targeting DNMT1	(85)
Regulation of drug resistance			
miR-122 (MSCs)	Hepatocellular carcinoma	Increasing the chemosensitivity of HCC cells by negative regulation of CCNG1, ADAM10 and IGF1R	(77)
miR-101 (macrophage)	Hepatocellular carcinoma	Inhibited by sorafenib and enhancing DUSP1, leading to the inhibition of macrophage-induced HCC growth	(78)
miR-21 (macrophage)	Gastric cancer	Reducing the sensitivity of gastric cancer cells to cisplatin through the regulation of PTEN/PI3K/AKT	(79)

downregulated in TAMs (51,52). Soluble factors in HCC can downregulate miR-155 in TAMs. When the expression of miR-155 is restored in macrophages, both direct and indirect antitumor responses are promoted through the enhancement of T-cell function (51). Using a transgenic mouse model, Zhao *et al* demonstrated that miR-125a, a downstream molecule of Notch signaling pathway, could reprogram macrophages in the TME and restore their antitumor potential by targeting certain factors, including factor inhibiting hypoxia-inducible factor-1, interferon regulatory factor 4, and RING1- and YY1-binding protein (53). A recent report indicated that miR-511-3p exerted regulatory effects on

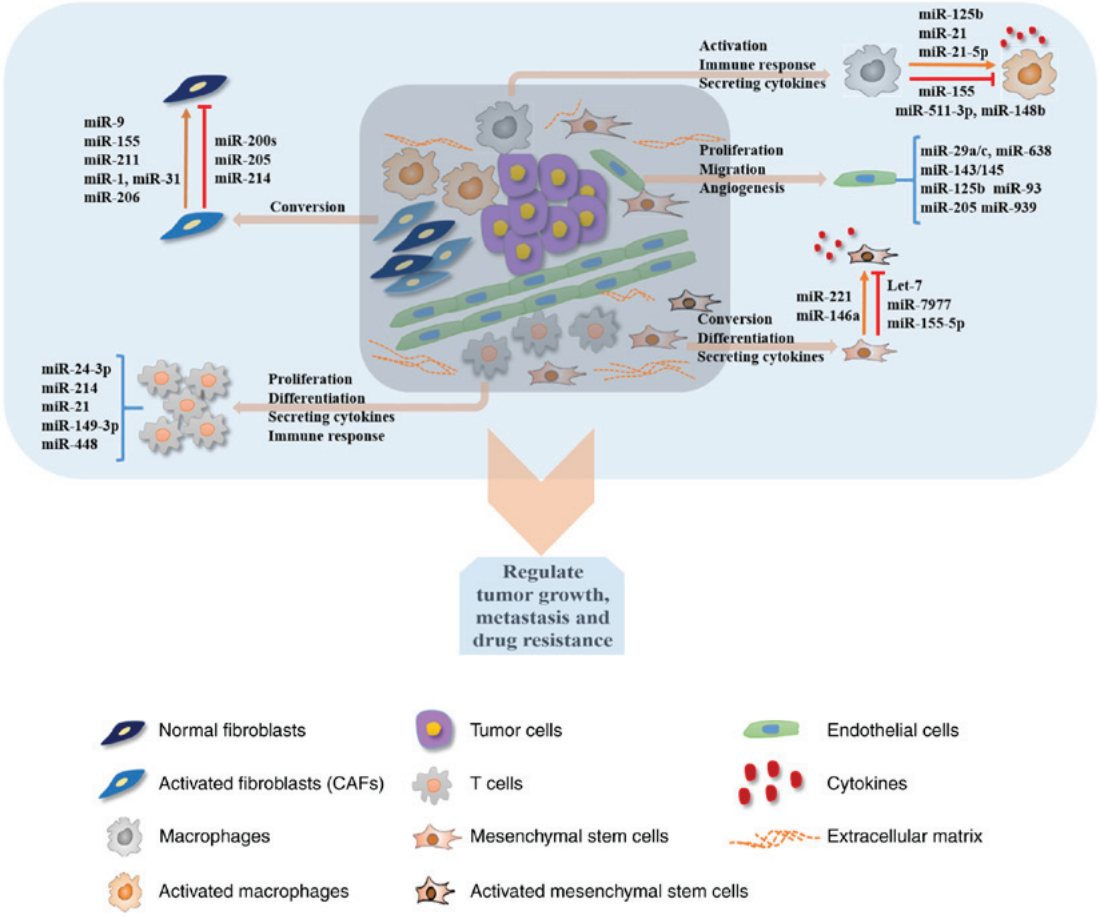

Figure 1. MicroRNAs in tumor microenvironment remodeling. The tumor microenvironment consists of CAFs, immune cells (such as Tregs and TAMs), endothelial cells, MSCs and ECM. The aberrant expression of miRNAs in tumor microenvironment could control cell differentiation, cell activation, and secretion of cytokines and chemokines, which eventually affects the process of tumor progression. CAFs, cancer-associated fibroblasts; Tregs, regulatory T cells; TAMs, tumor-associated macrophages; MSCs, mesenchymal stem cells; ECM, extracellular matrix.

TAMs, and that miR-511-3p overexpression in TAMs inhibited tumor growth *in vivo*, suggesting that miR-511-3p limits the tumor-promoting function of TAMs (54). miR-21 and miR-29a are delivered from cancer cells to macrophages via microvesicles and subsequently bind to intracellular toll-like receptors (TLR7 or TLR8). This miRNA-TLR interaction results in the activation of the NF-κB pathway and increased production of the pro-inflammatory cytokines IL-6 and TNF-α in TAMs, which in turn promotes cancer metastasis (55). Unexpectedly, apoptotic breast cancer cell-derived miR-375, which is released as a non-exosome entity, is taken up by macrophages via the CD36 receptor and enhances the migration and infiltration of macrophages towards tumor spheroids by targeting tensin 3 and paxillin (56). Therefore, the miRNAs of TME play a key role in regulating the phenotype and function of TAMs through several pathways.

Role of miRNAs in regulating T cells. miRNAs play a key role in T-cell maturation, activation and function. The immunosuppressive FOXP3$^+$ regulatory T cells (Tregs) are enriched in tumor tissues and are associated with cancer development and progression (57,58). Exosomal miR-24-3p inhibits T-cell proliferation and Th1 and Th17 differentiation, and promotes Treg development through the repression of fibroblast growth factor 11 (59). Tumor-secreted miR-214 can induce Tregs to secrete higher levels of IL-10 by downregulating *PTEN*, leading to immune suppression and rapid tumor growth. The inhibition of cancer cell-secreted miR-214 has been shown to block Treg induction and tumor growth, suggesting that anti-miR-214 therapy can abolish tumor-induced Treg expansion and suppress tumor growth (58). The silencing of miR-21 has been reported to significantly reduce the proliferation of chemokine receptor 6-positive Tregs by targeting *PTEN* and the subsequently activated Akt pathway, which is crucial for the induction and functional sustainability of CD4$^+$ FOXP3$^+$ Tregs (60). miR-126 silencing was also shown to impair the expression of *FOXP3* and inhibit the expression of functional molecules in Tregs.

Moreover, in a murine mammary cancer model, the silencing of miR-126 in Tregs resulted in enhanced antitumor activity of CD8$^+$ T cells (61). Additionally, miR-149-3p was found to enhance T-cell proliferation and secretion of cytokines, indicative of increased T-cell activation, which may reverse CD8$^+$ T-cell exhaustion and promote CD8$^+$ T-cell-mediated killing of 4T1 mouse breast tumor cells (62). Notably, in human colon cancer, miR-448 could also suppress CD8$^+$ T-cell apoptosis and enhance CD8$^+$ T-cell response by inhibiting indoleamine 2,3-dioxygenase 1 enzyme function (63). These results suggest that miRNAs are key regulators of the functions of T cells in the TME.

Role of miRNAs in regulating endothelial cells. Angiogenesis is crucial for tumor progression and metastasis. Mangala *et al* isolated endothelial cells from high-grade serous ovarian cancer and normal ovarian tissues and identified deregulated miRNAs in cancer-associated endothelial cells (64); they demonstrated that one of the deregulated miRNAs, miR-29a/c, was a regulator of VEGF. The downregulation of miR-29a/c was shown to promote GC progression by increasing VEGF expression (65). In breast cancer, tumor cells can release miR-939 to endothelial cells via exosomes, and miR-939 was shown to suppress the expression of its target gene vascular endothelial-cadherin in endothelial cells, increasing vascular permeability (66). Moreover, miR-205 suppression in other cells of the TME, including CAFs, was reported to enhance tubule formation and sprouting of endothelial cells by regulating YAP1-mediated IL-11 and IL-15 expression and secretion (34). In prostate cancer, miR-218 downregulation was shown to promote tumor angiogenesis through the regulatory-associated protein-independent companion of mammalian target of rapamycin complex 2/VEGFA axis (67). In lung cancer, miR-143/145 markedly promotes tumor growth by stimulating the proliferation of endothelial cells (68). In glioma, the downregulation of miR-125b may inhibit the expression of Myc-associated zinc finger protein, thereby attenuating primary human brain endothelial cell migration and tubule formation *in vitro* (69). The upregulation of miR-93 was reported to enhance tumor growth via integrin-β8-mediated angiogenesis (70), as well as to enhance endothelial tube formation and increase blood vessel density *in vivo* (71). The downregulation of miR-29b was also shown to promote VEGFR signaling in endothelial cells, enhancing angiogenesis (72). Another miRNA involved in angiogenesis is miR-638, which was shown to suppress HCC growth by inhibiting VEGF signaling (73). These findings demonstrate that miRNAs play diverse roles in regulating endothelial cell activity and tumor angiogenesis.

3. Role of TME-derived miRNAs in regulating tumor progression

TME-associated miRNAs in regulating tumor growth. Tumor growth is highly dependent on the communication between tumor cells and cells of the TME. During tumor progression, miRNAs participate in the intricate interactions between tumor cells and tumor stromal cells, such as CAFs, endothelial cells and infiltrating immune cells. For example, fibroblasts provide a stromal framework for tumor cells during early tumor growth (29,74). Recent studies have revealed that the upregulated miR-7 suppresses RAS-association domain family member 2 expression in CAFs, which in turn enhances the proliferation of head and neck cancer cells (75). Wang *et al* also observed that loss of CAF-derived exosomal miR-3188 may affect the proliferation and apoptosis of tumor cells (76). Melanoma cell-derived miR-211 was shown to induce CAF formation by directly targeting insulin-like growth factor 2 and activating mitogen-activated protein kinase signaling, which in turn enhances the growth of melanoma (36). TAMs play pivotal roles in tumor growth (77-79). Yin *et al* reported that M2 macrophage-derived exosomal miR-501-3p facilitated tumor formation *in vivo* via regulating the transforming growth factor (TGF)-β signaling pathway (80). Macrophages transfected with a miR-125a mimic exhibited increased phagocytic activity and repressed lung cancer growth in mice (53).

Additionally, the increased levels of miR-27a inhibited dendritic cell-mediated differentiation of Th1 and Th17 cells and enhanced the growth of melanoma cells (81). The downregulation of miR-638 was demonstrated to promote angiogenesis and HCC growth by targeting VEGF, whereas its overexpression inhibited tumor angiogenesis (73). miR-143/145 in the lung cancer microenvironment markedly promoted tumor growth by targeting calcium/calmodulin-dependent protein kinase 1D, an inhibitory kinase, the overexpression of which prevents the mitotic entry of endothelial cells (68). Thus, TME-associated miRNAs play key roles in tumor growth.

Role of TME-associated miRNAs in regulating tumor metastasis. Metastasis accounts for ~90% of cancer-related deaths (82,83). The metastatic ability of tumor cells is enhanced by their interactions with tumor stromal cells. miRNAs participate in several steps of the metastatic process. In a mouse xenograft model, miR-126/miR-126* independently inhibited the sequential recruitment of MSCs and inflammatory monocytes into the tumor stroma, thus suppressing lung metastasis through the downregulation of stromal cell-derived factor-1 α and CCL2 (84). Tumor-secreted miR-9 may be transferred via exosomes to the recipient NFs, and miR-9, in turn, is secreted by fibroblasts to stimulate breast cancer cell migration through the reduction of E-cadherin (31). Recently, low levels of miR-200s in CAFs were found to increase Fli-1 and TCF12 expression and promote stromal ECM remodeling to drive tumor metastasis through the upregulation of fibronectin and lysyl oxidase in breast cancer (33). Furthermore, low-level CAF-derived exosomal miR-148b may be transferred to endometrial cancer cells and enhance endometrial cancer metastasis by targeting DNA-methyltransferase 1, which is an important regulator of tumor metastasis (85). MSC-induced expression of miRNA-199a was shown to enhance the stem cell properties of breast cancer cells, thereby promoting tumor initiation and metastasis (86). The aberrantly expressed miRNAs in TAMs also play pivotal roles in tumor metastasis. miR-28-5p deficiency was shown to upregulate the expression of IL-34 to recruit TAMs, consequently promoting tumor metastasis (87). M2 macrophage-derived exosomal miR-501-3p was found to facilitate the liver and lung metastasis of pancreatic ductal adenocarcinoma (PDAC) cells (80). In summary, miRNAs in the TME are well-established crucial mediators of tumor metastasis.

Role of TME-associated miRNAs in regulating drug resistance. Resistance to chemotherapy and targeted therapy is a major challenge in clinical practice. Accumulating evidence suggests that miRNAs from the TME may affect drug resistance. In HCC, exosomal miR-122 (122-Exo) from adipose tissue-derived MSCs can be delivered into HCC cells, increasing the chemosensitivity of HCC cells by inhibiting the expression of cyclin G1, a disintegrin and metalloprotease 10, and insulin-like growth factor receptor 1 (IGF1R). Intratumoral injection of 122-Exo significantly increased the antitumor efficacy of sorafenib in HCC *in vivo* (88). Moreover, the chemotherapeutic agent sorafenib can inhibit miR-101

expression and enhance dual-specificity phosphatase 1 expression, leading to the inhibition of macrophage-induced HCC growth (89). In GC, miR-21 was transferred from macrophages to GC cells via exosomes and resulted in a significant reduction in the sensitivity of GC cells to cisplatin chemotherapy *in vitro* and *in vivo*, partially through the regulation of the PTEN/phosphoinositide 3-kinase/AKT signaling pathway (90). The levels of miR-27a/b in the serum were significantly higher in patients with esophageal cancer compared with those in healthy volunteers, and high expression levels of miR-27a/b were shown to induce the transformation of NFs into CAFs through upregulation of TGF-β, leading to chemoresistance in esophageal cancer cells (91). These results suggest that TME-derived miRNAs play a critical role in drug resistance.

4. Clinical applications of tumor-associated miRNAs

*miRNAs as cancer diagnostic biomarkers. miRNA*s have exhibited great potential in cancer diagnosis and prognosis. Circulating miRNAs in body fluids, such as plasma, serum and urine, have high diagnostic potential as cancer biomarkers due to their combination with argonaute protein or high-density lipoprotein, which protects them from degradation by extreme pH, high temperature and RNase. The vast majority of studies conducted thus far have focused on miRNAs in the tumor cells or the TME. Bryant *et al* reported that miR-107 and miR-574-3p were present at higher concentrations in the urine of men with prostate cancer compared with healthy individuals, indicating their potential as non-invasive biomarkers (92). Lee *et al* reported that circulating miR-146b and miR-155 levels were significantly higher in patients with papillary thyroid carcinoma compared with those with benign tumors. The levels of miR-146b and miR-155 were also positively associated with tumor size (93).

Moreover, Yi *et al* identified circulating miR-31-5p as a potentially novel and non-invasive biomarker for the early diagnosis of nasopharyngeal carcinoma (94). Nobuyoshi *et al* observed higher miR-92 levels in patients with colorectal cancer compared with those patients with inflammatory bowel diseases or in healthy volunteers; hence, it may be used as a biomarker to detect colorectal cancer (95). Few studies have explored the diagnostic potential of TME-derived miRNAs. In acute myeloid leukemia (AML), bone marrow stromal cell-derived miRNAs, including miR-150, -155 and -1246, were present in serum exosomes and were able to improve the sensitivity and specificity for detecting residual or recurrent AML, thereby providing a reliable cell-free marker that is unaffected by chemotherapy (96). We also previously demonstrated that miR-221 was highly expressed in MSCs from human GC tissues. The expression of MSC-derived miR-221 was positively associated with the proliferation and migration of GC cells, suggesting that it may be a new potential biomarker for GC diagnosis (26). In breast cancer, the expression of miR-21 in CCR6-expressing Tregs is very high, whereas silencing of miR-21 enhances the expression of *PTEN*, which inhibits the proliferation of Tregs in the tumor tissues and endows $CD8^+$ T cells with effective antitumor functions, indicating a new biomarker for breast cancer prognosis (60). In PDAC, the strong expression of miR-21 in CAFs was found to be associated with decreased overall survival in PDAC patients receiving 5-fluorouracil, but not gemcitabine. Thus, miR-21 may serve as a marker to guide chemotherapy options in PDAC patients (97). However, the number of TME-associated miRNAs identified as cancer biomarkers is currently limited and further research is required.

miRNAs in cancer therapy. According to the literature, miRNA-based antitumor therapy can be broadly divided into two distinct approaches, namely miRNA silencing by anti-miRNAs and miRNA restoration. Cubillos-Ruiz *et al* reported that nanoparticles carrying oligonucleotide duplexes markedly augmented miR-155 activity and transformed tumor-associated dendritic cells from the immunosuppressive phenotype to highly immunostimulatory cells, eliciting potent antitumor responses that eliminate ovarian cancer cells (98). In a mouse breast cancer model, let-7b delivered through a nucleic acid delivery system expeditiously reprogrammed the functions of TAMs and tumor-infiltrating dendritic cells, leading to the inhibition of tumor growth. This strategy may represent a new approach to cancer immunotherapy (99). Additionally, miR-21 depletion in TAMs promoted tumoricidal M1 polarization by upregulating Janus kinase 2 and Signal transducer and activator of transcription 1, and this, combined with programmed cell death protein 1 blockade, may exert synergistic effects and exhibit superior antitumor activity (100).

Moreover, the targeted interference of deregulated miRNAs in cancer-associated endothelial cells was shown to decrease vascular permeability. Pi *et al* reported that the elevated expression of miR-302/367 significantly suppressed tumor growth by restricting sprout angiogenesis and decreasing vascular permeability (101). Schnittert *et al* reported that anti-miR-199a, delivered via peptide-based nanocomplexes, may inhibit human-derived pancreatic stellate cell (hPSC) differentiation into CAFs and repress the size of 3D heterospheroids, which consist of hPSCs and tumor cells (102). In summary, targeting miRNAs has emerged as a novel, promising approach to cancer treatment.

5. Conclusion

The present review summarized the roles of miRNAs in the communication between tumor cells and tumor stromal cells. Deregulated expression of several miRNAs has been observed in both types of cells, clearly highlighting the crucial roles of miRNAs in cancer development and progression (Fig. 1; Table I). Numerous examples in which miRNAs were demonstrated to regulate the critical aspects of TME involved in tumor angiogenesis, tumor cell growth and metastasis were herein summarized. Previous studies elucidated some of the mechanisms by which these small RNAs in the TME considerably affect tumor biology. Undoubtedly, miRNA-related research has great potential for the identification of important biomarkers and for promoting the development of novel cancer therapies. As it has been reported in previous studies, miRNA delivery to tumors is an attractive yet challenging opportunity to improve therapeutic strategies for cancer (103,104). However, more cancer-related pathways must be identified as specific targets of miRNAs, and additional efforts are required to ultimately design an optimal delivery system for miRNAs. Several novel siRNA and miRNA delivery systems are currently under development. However, despite the enormous

potential of microRNAs in cancer diagnosis and anticancer clinical practice, microRNAs are not yet widely applied as cancer biomarkers and therapy targets in the clinical setting, as numerous obstacles must be overcome before their widespread application.

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Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZP and YT made substantial contributions to conception and design and wrote the manuscript. GN and CC critically revised the manuscript for important intellectual content. ZP, YT, GN and CC reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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