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microRNA-mediated regulation of the tumor microenvironment

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The tumor microenvironment includes cells such as fibroblasts, immune cells, endothelial cells, as well as extracellular matrix (ECM), proteases, and cytokines. Together, these components participate in a complex crosstalk with neoplastic tumor cells that affects growth, angiogenesis, and metastasis. MicroRNAs (miRNAs) are small, non-coding RNAs involved in post-transcriptional regulation of gene expression and have recently emerged as important players involved in regulating multiple aspects of cancer biology and the tumor microenvironment. Differential miRNA expression in both the epithelial and stromal compartments of tumors compared with normal tissue suggests that miRNAs are important drivers of tumorigenesis and metastasis. This review article summarizes our current understanding of the diverse roles of miRNAs involved in tumor microenvironment regulation and underscores the importance of miRNAs within multiple cell types that contribute to the hallmarks of cancer.

Introduction

It is increasingly recognized that the tumor microenvironment, which includes cells such as macrophages, dendritic cells, T cells, endothelial cells, pericytes, and fibroblasts, as well as extracellular matrix (ECM) components, proteases, and cytokines, plays an important role during tumor evolution and metastasis.[1,2] Although these stromal cells are not themselves malignantly transformed, they are often induced by tumor cells to promote tumorigenesis, and they co-evolve with tumor epithelial cells to foster angiogenesis, growth, and invasion.[3,4] These microenvironmental changes are observed in nearly all tumor types, including cancers of the breast, prostate, pancreas, liver, brain, skin, and ovary, and contribute to both early and late stages of tumor progression. The alterations in the microenvironment are also critical in the development of metastases. Indeed, upon arriving at a distant metastatic site, tumor cells are exposed to a foreign microenvironment very different from their origin and must set up a new home conducive to their growth in order to colonize successfully and survive.[5] Recent evidence suggests that changes to the ECM in potential metastatic sites involve recruiting bone marrow-derived immune and inflammatory cells even before metastatic cells take hold.[6-9] Because of their contributions to tumorigenesis, microenvironmental cells and the ECM and proteolytic components of tumors have emerged as new therapeutic targets for treating primary and metastatic cancer.

The crosstalk between cancer cells and the environment has been intensely investigated over the last decade. Secreted proteins such as cytokines, chemokines, and growth factors can signal in a paracrine or endocrine manner. Recently, tumor-derived exosomes, which contain various proteins and RNAs, have also been shown to be involved in cell–cell communication.[6,10,11] In addition, tumor cells and tumor-associated macrophages (TAMs) release proteases such as matrix metalloproteinases (MMPs) and cathepsins, which release bioactive growth factors sequestered in the ECM and mediate tumor responsiveness to chemotherapy.[12,13] Many ECM components such as collagen, fibronectin, and tenascin are also produced and secreted by tumor cells and fibroblasts. Because production of these molecules is itself a regulated process, identifying these regulatory mechanisms has been of great interest.

MicroRNAs (miRNAs) are small non-coding RNA molecules that negatively regulate gene expression at the post-transcriptional level and have recently been implicated in fine-tuning various aspects of tumor development.[14,15] (Excellent reviews on the biogenesis of miRNAs have appeared elsewhere[14,15] and will not be discussed further here.) Increasing evidence demonstrates that miRNA expression is dysregulated in numerous cancer types, and that miRNA expression profiles are capable of classifying human tumors, which can be correlated with clinical outcomes in cancer patients.[16,17] In this article, we describe examples of the diverse functions of miRNAs in regulating multiple aspects of the complex tumor microenvironment and highlight the role of one particular master orchestrator, the miR-29 family.

Results

microRNAs that regulate cancer-associated fibroblasts

Fibroblasts are one of the principal constituents of the tissue microenvironment. During normal wound healing, fibroblasts change their phenotype to become reactive. Reactive fibroblasts, also known as a myofibroblasts, share properties with both fibroblasts and smooth muscle cells, and are also found in tumors, where they are referred to as cancer-associated fibroblasts (CAFs). CAFs differ from normal fibroblasts by their high expression of α-smooth muscle actin (SMA) and their pro-tumorigenic properties.[1,18,19] They secrete a repertoire of pro-inflammatory molecules including interleukins (e.g., IL-6), chemokines (e.g., CXCL12/SDF-1α), vascular endothelial, and platelet-derived growth

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factors (e.g., VEGF and PDGFs), matrix metalloproteinases (MMPs), and ECM components (e.g., tenascin C, fibronectin, and collagen type I).[20] These factors recruit other cell types to the primary tumor and to future sites of metastatic colonization[5] and actively participate in remodeling the surrounding microenvironment to facilitate growth, invasion, and metastasis.

The precise mechanisms by which CAFs are generated are poorly understood, but current evidence suggests that they are generated locally by inducing normal fibroblasts to take on CAF properties via tumor-derived paracrine signals. Interestingly, when CAFs are isolated from tumors and cultured in vitro, their phenotype is sustainable over multiple passages.[18,19] Recently, it was shown that miRNAs regulate the CAF phenotype in ovarian cancer.[21] MicroRNA expression profiling of primary CAFs and adjacent normal fibroblasts isolated from ovarian cancer patients, as well as of induced human CAFs generated by co-culturing normal fibroblasts with tumor cells, has identified 3 differentially expressed miRNAs (miR-31, miR-214, and miR-155). Perturbation of these miRNAs is sufficient to convert normal fibroblasts into induced CAFs that promote ovarian cancer growth, invasion, and migration. Conversely, CAFs can be retro-converted into "normal" fibroblasts by reverse perturbation. miR-214 targets *CCL5* and loss of miR-214 increases CCL5 production, leading to increased tumor growth and migration, which can be blocked by an anti-CCL5 antibody. The exact mechanism of CCL5 in ovarian cancer remains unclear, but CCL5 can upregulate *Mmp9* transcription, promote invasion and migration, and maintain an immunosuppressive environment by recruiting myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment.[22-24] In addition, miR-31 has been identified as the most downregulated miRNA in endometrial cancer CAFs,[25] suggesting that this miRNA plays crucial roles in fibroblasts of diverse cancer types. miR-31 directly targets the homeobox gene *SATB2*, which is significantly upregulated in CAFs and plays a role in chromatin remodeling. Re-expression of miR-31 in endometrial CAFs impairs their ability to stimulate cell migration and invasion without affecting cell proliferation.

In prostate cancer, miR-15a and miR-16 are downregulated in the stroma.[26] These tumor-suppressive miRNAs are located in a chromosomal region frequently deleted in cancer.[27] Restoring miR-15a/miR-16 expression in prostate CAFs decelerates tumor growth, at least in part by regulating fibroblast growth factor (FGF) signaling via *Fgf2* and *Fgfr1*. Other targets of miR-15a/miR-16 include cell cycle and anti-apoptotic genes (*Ccnd1*, *Wnt3A*, and *Bcl2*).[27] In addition, prostate tumors mixed with CAFs that express miR-15a/miR-16 have decreased blood vessel density, suggesting that miRNAs expressed in fibroblasts affect endothelial cell recruitment within tumors. Other recently discovered miRNAs within fibroblasts include miR-148, which targets 2 WNT family members, *WNT1* and *WNT10B*, that stimulate migration in endometrial cancer cell lines.[28]

Interestingly, perturbation of fibroblast homeostasis by deleting *Pten* in mammary stromal fibroblasts accelerates the initiation, progression, and malignant transformation of mammary epithelial tumors.[29] Loss of *Pten* is associated with extensive ECM remodeling, immune infiltration, and angiogenesis.[29,30] Interestingly, deletion of *Pten* alters the repertoire of miRNAs expressed in fibroblasts and results in the downregulation of miR-320. Re-expressing miR-320 in *Pten*-null fibroblasts within tumors suppresses tumor proliferation and blood vessel density. Mechanistically, miR-320 targets *ETS2* (v-ets erythroblastosis virus E26 oncogene homolog 2), which is upregulated upon *Pten* loss and induces an oncogenic secretome that promotes tumor angiogenesis and invasion. The miR-320 secretome signature distinguishes normal vs. tumor stroma in human breast cancer and correlates with patient outcomes. Taken together, these studies illustrate that miRNA dysregulation within CAFs significantly affects the tumor microenvironment and cancer progression.

microRNAs that regulate angiogenesis, endothelial cells, and the hypoxic response

Tumors must recruit new blood vessels to meet the high metabolic and nutritional demands during tumor growth. In embryogenesis, the development of the vasculature involves the birth of new endothelial cells and their assembly into tubes (known as vasculogenesis), as well as sprouting from pre-existing vessels (known as angiogenesis). During tumor progression, cancer cells mainly utilize angiogenesis to sustain delivery of oxygen and nutrients and removal of carbon dioxide and other waste. Secreted growth factors released by tumor and other microenvironmental cells, including members of the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) families, regulate angiogenesis. These growth factors bind to the membrane-bound receptors tyrosine kinases VEGFR1 (also known as Flt-1) and VEGFR2 (also known as Flk-1 or KDR), and transmit signals through kinase-dependent signaling cascades, which ultimately result in gene expression changes that affect the growth, migration, morphology, and function of endothelial cells to form new blood vessels.

Recently, miRNAs have been shown to regulate tumor angiogenesis. One such miRNA is miR-126, which is silenced in many human cancers. Loss of miR-126 is associated with reduced metastasis-free survival in recurrent breast cancer patients.[31] Mechanistically, miR-126 regulates endothelial cell recruitment to metastatic breast cancer cells by inhibiting several previously uncharacterized pro-angiogenic genes including IGFBP2, PITPNC1, and MERTK.[32] In addition, miR-126 levels inversely correlate with microvessel density in lung cancer,[33] suggesting that miR-126 is an important regulator of angiogenesis in multiple tumor types. Interestingly, during normal zebrafish development, miR-126 also regulates vascular integrity by repressing Sprouty-related protein 1 (SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK2R2), 2 proteins that negatively regulate VEGF signaling, which increases PI3 kinase and MAP kinase signaling.[34] Knockdown of miR-126 results in loss of vascular integrity and hemorrhage during embryonic development, indicating that miR-126 is critical in promoting VEGF signaling to maintain endothelial cell survival. Therefore, the cellular and developmental context dictates the role miR-126 plays in promoting angiogenesis during normal endothelial cell development and inhibiting angiogenesis in breast cancer cells, which will be important in designing anti-angiogenesis therapies.

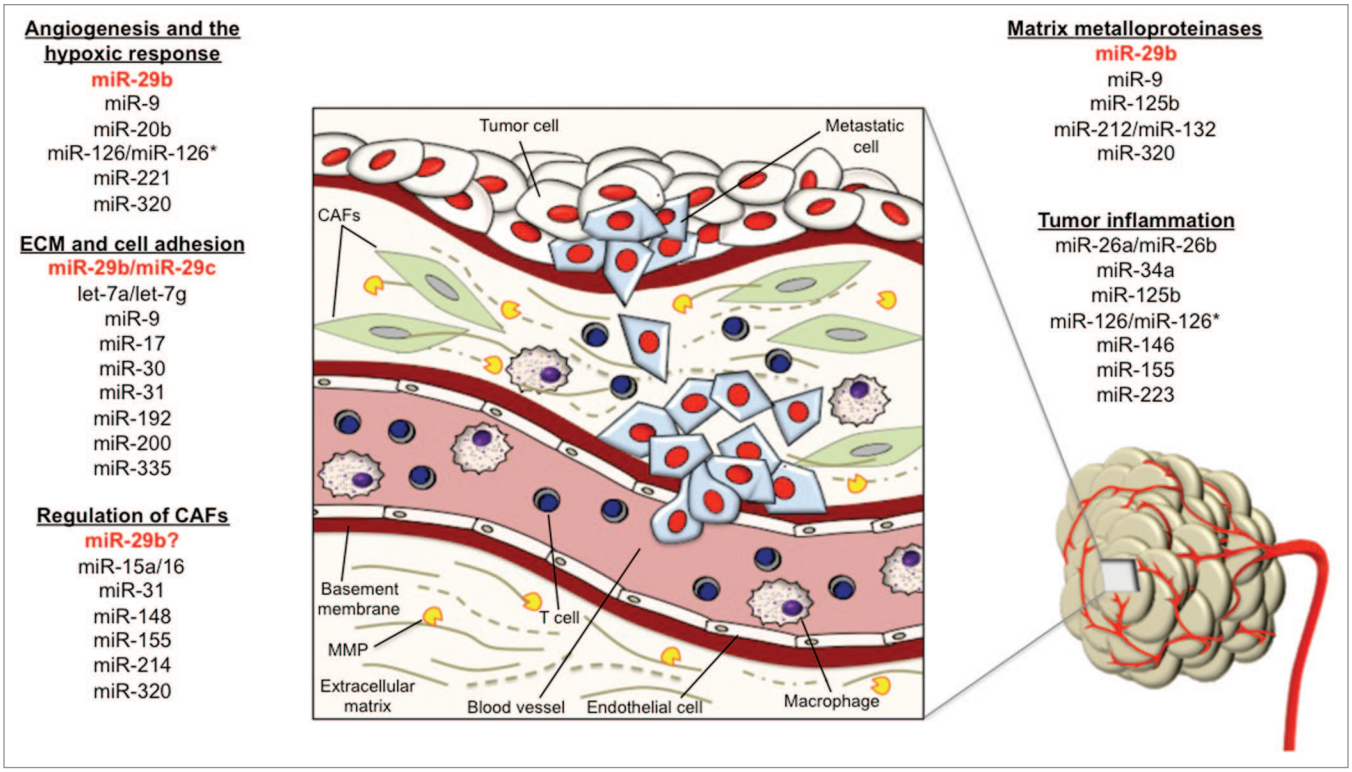

Figure 1. microRNA-mediated control of the tumor microenvironment. The tumor microenvironment is shown, which is composed of cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), endothelial cells, and immune cells (such as T cells and macrophages). Cytokines produced by various cell types recruit other bone-marrow derived and immune cells into the vicinity. Matrix metalloproteinases (MMPs) cleave the ECM and also release sequestered growth factors. Many cell types within the microenvironment and biological processes that contribute to tumor growth (such as angiogenesis, the hypoxic response, and collagen remodeling) are subject to miRNA regulation.

Another miRNA involved in angiogenesis is miR-9, which is enriched in MYC-amplified human tumors. Interestingly, miR-9 not only promotes epithelial-to-mesenchymal transition (EMT) by repressing E-cadherin, priming cells to lose cell adhesive properties, but also stimulates angiogenesis through activation of β-catenin signaling.[35] Increased β-catenin signaling upregulates VEGF. Overexpression of miR-9 in non-metastatic breast tumor cells enables these cells to form lung micrometastases in mice, while inhibiting miR-9 in highly malignant cells inhibits metastasis formation.

Upstream of VEGF, hypoxia is a potent inducer of angiogenesis through hypoxia-inducible factor 1α (HIF1α). Recently, a signature of hypoxia-inducible miRNAs has been identified.[36] Interestingly, many hypoxia-induced microRNAs are also overexpressed in human cancers,[37] suggesting that induction of these miRNAs might enhance tumor survival, proliferation, and vascularization or alter the response to chemotherapy. For example, HIF1α regulates *VEGF* expression by binding to the *VEGF* promoter in MCF7 breast cancer cells in hypoxic conditions. However, this binding is blocked when miR-20b is present, suggesting that HIF1α-mediated induction of VEGF occurs in a miR-20b-dependent manner.[38] Mechanistically, miR-20b regulates HIF1α and VEGF expression by directly binding to the 3¢UTR of *Hif1a* and *Vegfa*. Conversely, inhibition of miR-20b increases HIF-1α and VEGF in normoxic tumor cells. Interestingly, overexpression of HIF-1α in normoxic tumor cells downregulates miR-20b expression, suggesting a feedback mechanism to fine-tune the response to hypoxia.[39]

Finally, additional miRNAs involved in endothelial cell biology have been identified through deep sequencing and functional screening in model organisms. For example, in zebrafish, miR-221 is specifically induced in endothelial cells at the time of sprouting and regulates endothelial cell tip behavior by repressing *cyclin-dependent kinase inhibitor 1b* (*cdkn1b*) and *phosphoinositide-3-kinase regulatory subunit 1* (*pik3r1*). These results identify *miR-221* as an important mediator through which endothelial tip cell migration and proliferation are controlled during normal angiogenesis.[40] Taken together, these studies demonstrate the diverse roles miRNAs play in regulating tumor-derived angiogenic factors like VEGF and multiple signaling pathways within endothelial cells, as well as the tumor response to hypoxia.

microRNAs that regulate the inflammatory milieu

Inflammation is a potent contributor to cancer progression, as many cancers arise from sites of infection and chronic inflammation.[41] Inflammatory cells, which include cells such as tumor-associated macrophages (TAMs), neutrophils, dendritic cells, natural killer (NK) cells, B and T cells, have been shown to play both pro- and antitumorigenic roles.[42,43] In addition, tumor cells have co-opted many of the same signaling molecules (e.g., selectins, chemokines, and interleukins) for invasion, migration, and metastasis.

Table 1. Examples of microRNAs that regulate the tumor microenvironment

miRNA	Targets	Tumor microenvironment function
let-7a/let-7g	COL1A2, ITGA3, RAS, GAB2, FN1,	- Cell adhesion and ECM
miR-9	CDH1, MMP14, REST, CoREST	- Angiogenesis, endothelial cells, and hypoxia - MMPs - Cell adhesion and ECM
miR-15a/16	FGF2, FGFR1, CCND1, WNT3a, BCL2	- Regulation of CAFs
miR-17	FN1, FNDC3A, IL8	- Cell adhesion and ECM
miR-20b	HIF1α, VEGF	- Angiogenesis, endothelial cells, and hypoxia
miR-29b/miR-29c	ANGPTL4, COL1A1, other collagens (including type II, IV, V, VII, VIII), ELN, FBN1, IGF1, ITGA6, ITGB1, LOX, LOXL2, LOXL4, MMP2, MMP9, PDGFA, PDGFB, PDGFC, PDGFRA, PDGFRB	- Regulation of CAFs (?) - Angiogenesis, endothelial cells, and hypoxia - MMPs - Cell adhesion and ECM
miR-30	ITGB3	- Cell adhesion and ECM
miR-31	SATB2, RhoA, ITGA5, E-selectin	- Regulation of CAFs - Cell adhesion and ECM
miR-34a	CCL22, SIRT1	- Inflammation
miR-101	MKP-1, MYCN	- Inflammation
miR-125b	TNFα, IRF4, MMP13	- Inflammation - MMPs
miR-126/miR-126*	IGFBP2, PITPNC1, MERTK, SPRED1	- Angiogenesis, endothelial cells, and hypoxia
miR-132/miR-212	MMP9	- MMPs
miR-146	TRAF6, IRAK1	- Inflammation
miR-148	WNT1, WNT10B	- Regulation of CAFs
miR-155	SOCS1, BCL6, SHIP-1, c-Maf, PU.1, IL13R, TP53INP1	- Regulation of CAFs - Inflammation
miR-214	CCL5, ITGA3	- Regulation of CAFs - Cell adhesion and ECM
miR-221	CDKN1B, PIK3R1, ICAM-1	- Angiogenesis, endothelial cells, and hypoxia - Cell adhesion and ECM
miR-320	ETS2, MMP9, EMILIN2	- Regulation of CAFs - Angiogenesis, endothelial cells, and hypoxia - MMPs
miR-335	SOX4, TNC	- Cell adhesion and ECM

Many of these cells are derived from the bone marrow, particularly the myeloid lineage, and are recruited by cancer cells to enhance their survival, growth, invasion, and dissemination.[44] One of the major inflammatory cell types within the tumor microenvironment is the TAM, which has been implicated in pro- and antitumorigenic roles depending on whether they are the classical M1 or the alternative M2 subtype.[43,45] Recently, several miRNAs have been implicated in modulating macrophage activation and function in response to Toll-like receptors (TLRs), tumor necrosis factor (TNF), and various interleukin stimuli (e.g., IL4, IL10).[46] For example, in response to TLR ligands, NFκB signaling promotes expression of miR-155.[47] To enhance the classical pro-inflammatory response, miR-155 targets suppressor of cytokine signaling (SOCS) 1, B-cell lymphoma-6 protein (BCL6), and the IL-13 receptor, which promote alternative activation.[48,49] In addition, macrophages that express miR-125b are highly responsive to interferon (IFN) γ and potently activate T cell responses. miR-125b binds to the *Tnfa* 3′ UTR, inhibits TNFα production, and sustains a M1 phenotype by targeting IFN regulatory factor 4 (IRF4).[50] On the other hand, miR-146 directly inhibits adaptors TRAF6 and IRAK1 in the NFκB pathway, thus attenuating pro-inflammatory cytokine production and promoting alternative M2 activation. TAMs also produce miRNA-containing microvesicles that fuse with acceptor cells. In vitro studies demonstrate that the invasive properties of breast cancer cells can be modulated by microvesicle-mediated transfer of miR-223, which downregulates *MEF2C* expression in cancer cells, leading to increased β-catenin nuclear localization and, ultimately, cell invasion.[51] These studies point to miRNAs playing a critical role in regulating M1 and M2 polarization, and hence macrophage responses that promote or inhibit tumor growth.

miRNAs also control the development and function of NK cells, which are involved in tumor surveillance and mediate cytotoxic killing of tumor cells. For example, mice with a targeted deletion of *miR-150* have an impaired, cell lineage-intrinsic defect in their ability to generate mature NK cells,[52] while *miR-155* overexpression in transgenic mice causes an expansion and constitutive activation of NK cells, resulting in more potent antitumor activity in vitro and improved survival of lymphoma-bearing mice in vivo.[53] This is partly explained by the diminished expression of the inositol phosphatase *SHIP1*, which is regulated by miR-155. Other profiling studies in NK/T-cell lymphomas demonstrate several downregulated miRNAs, including miR-101 and miR-26a/b, which function in part by regulating NK cell growth.[54]

Other immune cells present within the tumor microenvironment include monocytes, which are part of the innate immune system that responds quickly to inflammatory signals and replenishes the resident macrophage and dendritic cell populations in tissues. In addition to promoting a role in angiogenesis, miR-126 and its complementary counterpart miR-126* also inhibit breast cancer metastasis by repressing recruitment of mesenchymal stem cells (identified by Sca1+CD44+CD45-Lin- cells) and inflammatory monocytes (identified by CD11+Gr1+CD115+ cells) in xenografted tumors.[55] miR-126 and miR-126* directly and independently inhibit *Sdf-1a* expression through 2 unique binding sites in the *Sdf-1a* 3′ UTR, resulting in the suppression of mesenchymal stem cell migration, which indirectly inhibits expression of chemokine C–C motif ligand 2 (*Ccl2*). Interestingly, expression of miR-126 and miR-126* does not affect the F4/80+ macrophage population in tumors. This pair of miRNAs is downregulated in cancer by increased promoter methylation of the host gene, *Egfl7*, thus illustrating how changes in gene methylation within tumor cells can affect the microenvironment via a miRNA-mediated mechanism.

Finally, T cells, which include Th1, Th2, and Th17 as well as T regulatory cells (Tregs), have also been shown to be pro- and antitumor, depending on the T cell subtype and polarization. For example, Th2 cells promote invasion and metastasis through an IL-4-mediated mechanism,[56] while Tregs promote immune tolerance, thus allowing cancer cells to evade the immune system. Tregs also supply a source of RANKL, which initiates downstream NFκB signaling, to promote metastasis.[57] In hepatocellular carcinoma, the pro-inflammatory microenvironment caused by hepatitis infection induces transforming growth factor-β (TGFβ), which suppresses expression of miR-34a.[58] Decreased miR-34a increases one of its targets, CCL22, thereby enhancing the recruitment of immune-suppressive Tregs into the microenvironment. This study points to miR-34a as a critical downstream target of TGFβ that influences immune cell recruitment, and suggests that increasing miR-34a expression, perhaps by promoting known inducers such as p53,[59] will suppress the influx of Tregs and other CCL2-mediated microenvironmental changes.

microRNAs that regulate matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that are involved in ECM degradation, the generation of novel ECM fragments with pro-tumor activities, the conversion of growth factors from inactive to active forms, and the release of growth factors sequestered within the ECM. Moreover, MMPs have been shown to be involved in metastatic niche formation and orchestrating the inflammatory response in cancer. In addition to their proteolytic functions, recent evidence suggests that MMPs also have important non-proteolytic functions that affect processes such as cell migration.[60] MMP activity is regulated at various levels, including gene expression, compartmentalization, conversion from its inactive zymogen to its active form, and by interactions with specific inhibitors such as tissue inhibitors of metalloproteinases (TIMPs).[60] A number of miRNAs have been implicated in the regulation of MMPs. For example, miR-320 in fibroblasts inhibits *Mmp9* through 2 mechanisms involving the direct interaction with the *Mmp9* 3′ UTR and indirect regulation of *Ets2*.[30] Other miRNAs, such as miR-125b and miR-9, suppress cancer cell proliferation and invasion of by targeting MMP13 and MMP14, respectively.[61,62] In addition, the miR-212/miR-132 family regulates the outgrowth of mammary ducts during normal development by directly targeting *Mmp9*. Interestingly, transplantation experiments demonstrated that miR-212/miR-132 is required in the stromal and not the epithelial compartment. Genetic deletion of *miR-212/miR-132* in mice alters collagen deposition and leads to hyperactivation of TGFβ signaling.[63] Recent reports have suggested that *miR-132* is downregulated in prostate cancer, breast ductal carcinoma in situ, and pancreatic cancer, suggesting that miR-132 and miR-212 are important in multiple cancer types,[64-66] though the exact mechanism of action in these cancers remains to be investigated.

microRNAs that regulate cell adhesion, integrins, and components of the ECM

In addition to regulating proteases, growth factors, and cytokines, miRNAs directly affect ECM composition such as collagen, laminin, and fibronectin, as well as integrins, which cells use to interact with the ECM. Numerous collagens, which are frequently overexpressed in breast tumors, provide not only structure in the mammary gland, but also actively contribute to tumor initiation and migration. Indeed, mammographic density, which reflects the composition of collagen, fat, and epithelial cells within the breast, is strongly associated with breast cancer risk, with collagen-dense breasts associated, and with increased risk of malignancy.[67] Tumor cells exposed to an ECM high in type I collagen form invasive projections in vitro and large, invasive tumors when xenografted in mice.[68,69] Interestingly, collagen type I is a downstream target of let-7a and let-7g,[70,71] and a feedback mechanism allows collagen to regulate let-7 expression in pancreatic cancer cells as well.[72] In addition, the lysyl oxidase (LOX) and its family of proteins, which modify collagen cross-linking, are also regulated by miRNAs (see below). These enzymes promote tumorigenesis and metastasis and are important therapeutic targets in cancer and fibrotic disorders.[73-76]

The laminins, which form the basement membrane and are breached during tumor progression, are regulated by miRNAs such as miR-29c (see below for a complete discussion about the miR-29 family).[77] Other miRNAs, such as miR-17, target fibronectin and the fibronectin type-III domain containing 3A (FNDC3A) both in vitro and in transgenic mice. Overexpression of miR-17 decreases cell adhesion, migration, and proliferation,

and miR-17 transgenic mice show overall growth retardation and reduced hematopoietic cell lineages.[78] miR-17 abundance is reduced in highly invasive breast cancer cell lines and node-positive breast cancer, as well as in human prostate cancer specimens.[79] In breast cancer, miR-17 is anti-metastatic by directly repressing *IL-8* through its 3′ UTR, which inhibits migration and invasion.[80] However, whether miR-17 exerts any antitumor activity by regulating fibronectin remains to be determined.

miRNA expression profiling has also identified miR-335 as one of the most significantly downregulated miRNAs in parental vs. metastatic-enriched cell lines. miR-335 is lost in breast cancers that relapse, and re-expression of miR-335 decreases both lung and bone metastasis in a mouse model.[31] Interestingly, miR-335 not only controls the expression of transcription factors involved in progenitor cell development such as *SOX4*, but also tenascin C (*TNC*), an extracellular matrix protein that promotes stem cell niches. This affects the aggressiveness of lung metastases by enhancing survival and growth through increased WNT and Notch signaling.[81]

Integrins, which are receptors used for cell–ECM communication, are also subject to miRNA regulation. For example, miR-31 represses radixin, RhoA, and integrin α5 (ITGA5), which impairs local invasion, extravasation, and colonization.[82] Inhibition of metastasis is mediated in part by targeting ITGA5, which diminishes AKT signaling and triggers apoptosis in a BIM-dependent manner.[83] Meanwhile, miR-183, whose expression is inversely correlated with lung cancer metastatic capacity,[84] and miR-124, which is downregulated in oral squamous cell cancer, inhibit invasion and motility by targeting integrin β1 (ITGB1), in addition to affecting cytoskeletal dynamics and migration.[85,86] Furthermore, miR-338 and miR-451 also target ITGB1, while miR-30 and let-7a inhibit ITGA3.[87] Loss of integrin expression can also be oncogenic, as miR-93 overexpression in glioblastoma promotes tumor growth and angiogenesis by targeting ITGB8.[88] Finally, a cohort of miRNAs, including miR-9, miR-192, miR-200, miR-221, and miR-222, regulate cell adhesion molecules such as E-cadherin and ICAM-1.[35,89] These studies demonstrate that miRNAs regulate integrin signaling and cell adhesion, in addition to many major components of the ECM.

miR-29 as a master orchestrator of the tumor microenvironment

We recently showed that the transcription factor GATA3, which is expressed in good-prognostic luminal type breast cancers, promotes expression of miR-29b, an miRNA that negatively regulates a network of pro-metastatic microenvironmental genes.[90] The miR-29 family consists of 3 members that share the same seed sequence (miR-29a, miR-29b, and miR-29c) and are downregulated in numerous cancer types, including leukemia, breast cancer, lung cancer, liver cancer, rhabdomyosarcoma, cholangiocarcinoma, and melanoma.[90-96] Their decreased expression correlates with poor prognosis.[97] We found that by targeting genes such as *ANGPTL4*, *PDGF*s, and *VEGFA*, miR-29b regulates multiple factors involved in angiogenesis and vascular permeability within lung capillaries.[90] Interestingly, miR-29b has direct binding sites in multiple PDGF family members, including *PDGFA*, *PDGFB*, and *PDGFC*, as well as their receptors, *PDGFRA* and *PDGFRB*, demonstrating the exquisite ability of miR-29b to exert control over an entire family of genes. As a result, miR-29b-expressing breast tumors are less vascularized, which, in turn, decreases lung metastasis. Indeed, miR-29b overexpression in mammary[90] and hepatocellular carcinoma[98] reduces microvessel density. The anti-metastatic effects of miR-29b can be reversed with *VEGFA* re-expression, suggesting that it is a critical target of miR-29b. In addition, miR-29b also regulates trophoblastic angiogenesis by targeting *VEGFA* in models of pre-eclampsia,[99] suggesting that miR-29b regulates angiogenesis in diverse cellular contexts.

Interestingly, multiple collagen genes also contain miR-29 binding sites in their 3′ UTRs, including collagen type I, type II, type IV, type V, type VII, and type VIII, many of which have been experimentally validated as miR-29 targets.[77,100] Again, this shows that miR-29 is capable of regulating entire gene families. miR-29b suppresses collagen expression in a number of different experimental systems, including renal and cardiac fibrosis, systemic sclerosis, as well as osteoclast differentiation, demonstrating that this is a common mechanism used by cells to control collagen expression.[100-104] In some collagen genes, there are multiple miR-29b binding sites in the 3′ UTR, as in the case of *COL1A1*, which has 3 sites. An integrated miRNA and mRNA ananglysis of 101 primary breast cancers revealed that miR-29c expression is inversely correlated with cell adhesion and ECM gene expression.[105] In addition, miR-29 also targets *fibrillin-1* (*FBN1*) and *laminin* γ1, 2 other proteins that are important constituents of the ECM, although their function in cancer remains poorly understood.[77,103]

In addition to ECM composition, ECM organization is also tightly regulated, and aberrations occur during cancer progression.[106] Recent evidence suggests that cells sense the stiffness of their microenvironment, mediated in part by lysyl oxidase (LOX) and LOX-like enzymes. In addition, LOX also recruits CD11b+ myeloid bone marrow-derived cells into tumors by crosslinking collagen type IV.[107] Interestingly, *LOX*, *LOXL2*, and *LOXL4* all have miR-29b binding sites in their 3′ UTRs, and in the case of *LOX* and *LOXL2*, multiple binding sites (3 and 2 sites, respectively). By regulating *LOX*, *LOXL2*, and *LOXL4*, miR-29b exerts coordinated control over collagen crosslinking and tissue stiffness,[90] properties that contribute to metastasis.[108,109] We found that overexpression of miR-29b reduces *Lox*, *Loxl2*, and *Loxl4* expression, thus decreasing fibrillar collagen in xenografted breast tumors.[90] In addition, miR-29 expression reduces *LOX* in hepatic stellate cells.[110] Together, these studies point to the pivotal role the miR-29 family has in regulating collagen crosslinking and the ECM microenvironment, which ultimately affects tumor invasiveness and metastasis.

Several MMPs also have miR-29b binding sites, including *MMP2* and *MMP9*, which we and others have demonstrated are regulated by miR-29b in multiple tumor types, including breast,[90] prostate,[111] and liver.[98] Re-expression of *Mmp9* in miR-29b-expressing breast cancer cells attenuates the ability of miR-29b to inhibit metastasis, suggesting that *Mmp9* is an important downstream target. Interestingly, loss of miR-29b-mediated suppression of *MMP2* promotes colorectal metastasis to the liver.[112]

These studies illustrate that *MMP* expression is subject to miR-29b control in cancer.

In addition to these microenvironmental genes, we also found that integrins α6 and β1 (also known as CD49f/*ITGA6* and CD29/*ITGB1*, respectively) are miR-29b targets.[90] These integrins not only serve as receptors that mediate signaling between the ECM, the cytoskeleton and gene transcription, but also as markers for the stem cell population within the mammary gland.[113] Recent work suggests that these integrins, particularly CD49f, play an active role in maintaining the stemness of mammary stem cells.[114,115] Other differentiation related factors targeted by miR-29b include *KLF4*.[116] Therefore, in addition to regulating integrin-mediated cell adhesion and ECM signaling, miR-29b also regulates cell differentiation and progenitor-like properties. Indeed, miR-29b promotes luminal differentiation and gene expression, while loss of miR-29b results in a de-differentiation/mesenchymal phenotype. In accordance, miR-29b expression is enriched in luminal type breast cancer compared with basal type cancers and inversely correlates with metastatic potential.[90]

Taken together, these studies add to the growing body of evidence demonstrating that the miR-29 family is a master orchestrator of the tumor microenvironment. Impressively, a single miRNA family regulates a network of genes involved in modulating the tumor microenvironment, including angiogenesis, vascular permeability, ECM composition, organization and stiffness, proteolysis, and cell adhesion. Of note, the miR-29 family targets multiple members within a gene family (e.g., PDGFs, LOX/LOXLs, and collagens) to finely tune microenvironmental properties. In accordance with the pleiotropic effects of miRNAs, miR-29b also plays a role in regulating epithelial plasticity and is well-positioned to function as a rheostat for cellular differentiation. Because GATA3 is required for the specification of luminal epithelial cells in the mammary gland and is lost in breast cancer,[117-119] our work also reinforces the concept that microenvironmental control is critical during cell differentiation. Interestingly, other proteases, such as members of the disintegrin and metalloproteinase domain-containing proteins with thrombospondin motifs 2, 5, 6, 7, 9, 10, 17, 18, and 19 (ADAMTS), as well the proto-cadherin family (PCDHA1–13), which are hypothesized to be involved in cell–cell adhesion, are predicted targets of miR-29b. With the exception of ADAMTS7,[120] these targets have not been validated, and their functions in cancer remain to be investigated. Finally, whether miR-29b might play anti-metastatic roles in other cell types within the microenvironment, such as fibroblasts or endothelial cells, remains to be determined experimentally. Interestingly, many of the miR-29b targets that we identified are commonly expressed in CAFs to promote tumor growth and metastasis. Thus, it will be interesting to explore whether expressing miR-29b in CAFs or endothelial cells might also have a potent anti-tumor or anti-metastatic effect.

Conclusions

Emerging work on miRNAs demonstrates the importance of miRNAs in controlling and regulating homeostasis within the tumor microenvironment. We have highlighted a few examples where miRNAs regulate critical aspects of the microenvironment, including cancer-associated fibroblasts, angiogenesis and the hypoxic response, inflammation, MMPs, ECM composition, and ECM organization (**Fig. 1**; **Table 1**). Interestingly, miRNAs such as miR-29b are poised to orchestrate multiple properties within the tumor microenvironment by coordinating the expression of major gene families. Our work on miR-29b points to the importance of controlling networks to suppress complex processes such as metastasis. Additional work on miRNAs will continue to elucidate how these small RNAs exert big effects on tumor biology, and will likely offer crucial insights and therapeutic opportunities, so that we can better control cancer and metastatic disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interests were disclosed.

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