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REVIEW ARTICLE

Tracking miRNAs' Footprints in Tumor–Microenvironment Interactions: Insights and Implications for Targeted Cancer Therapy

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In the past decades, cancer medicine studies have mainly focused on tumor cell biology as the main promoter of solid tumor progression. However, tumor biology does not explain the intertwinement and ambiguity of the tumors' territory. Recently, the approach of understanding cancer has shifted from investigating the biology of tumor cells to studying the microenvironment surrounding them. MicroRNAs (miRNAs), which play a role in exploiting indigenous stromal cells and are components that cooperate and produce a favorable microenvironment for progressive tumor formation, have been implicated in numerous processes essential for tumor initiation and growth. Understanding the mechanisms underlying interactions between tumor cells and their adjacent environment holds many promises for the future of cancer-targeted therapies. Herein, we provide a step-by-step account of miRNA involvement in tumor–microenvironment interactions as the micromediators of tumor cell and stroma communications. We also focus on the clinical challenges in using miRNAs tof overcome therapy resistance mechanisms and tumor heterogeneity bias in cancer therapy.

INTRODUCTION

Powerful technologies such as next-generation sequencing have discovered increasingly fascinating data about RNA. However, among all the newly discovered noncoding RNAs, microRNAs (miRNAs) are the most compelling in terms of their biological aspects and clinical implications.

MiRNAs are small regulatory noncoding RNAs that are involved in many critical cellular processes. As significant post-transcriptional regulators of eukaryotic gene expression, miRNAs are versatile elements involved in diverse key cellular processes that support tissue homeostasis. Their impaired expression is associated with a number of pathologies, notably cancer. In the recent years, an abundance of miRNA studies has provided discoveries that have modified the face of medical science and translational biology. The most impressive facet of these discoveries has been the promising implications miRNAs have for the field of cancer research and treatment, where miRNAs represent potential therapeutic tools. Tumor-suppressor and oncogenic miRNAs have been found to be related to a number of processes governing tumorigenesis, including cellular differentiation and tumor cells' lineage formation, proliferation, growth, and apoptosis, and recently, they are known as secreted hormones (Zhang et al., 2007). These secretary miRNAs have been used for a variety of diagnostic and prognostic implications. Recent investigations have also focused on the role of miRNAs in controlling the tumor microenvironment—the cellular contexts in which tumor cells grow, progress, and metastasize (Bronisz et al., 2011). In this review, we aim to

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explain the role of miRNAs as micromodulators of tumor microenvironment. Given the pivotal role played by miRNAs in the microcommunications between tumor cells and their adjacent stroma, we focus on the potential approaches using miRNA as target for cancer therapy.

MiRNAs AND THE TUMOR MICROENVIRONMENT

Solid tumors are dynamic microecosystems whose cells are surrounded by a fibrillar matrix in connective tissue. This matrix is mainly composed of nonparenchymal cells, including fibroblasts, endothelial cells, mesenchymal cells, inflammatory cells, and immune cells, and the components of the extracellular matrix (ECM), such as collagen type I, tenascin, and fibronectin, which act in concert to establish and maintain carcinogenesis (Soon and Kiaris, 2013).

Tumor stroma is a "battle field" with intertwined connections that contribute to oncogenesis, regulate tumor growth, and delineate metastasis. The pivotal players of tumor stroma are fibroblasts, endothelial cells, and immune cells, which fuel cancer progression. Many tumor stromal cells are bone marrow-derived cells that cohabit with the resident tissue cells. In the tumor niche, cohabiting cells interact with their neighbors and/or distal tissues via signaling molecules, such as interleukins and growth factors through direct cell-to-cell contact, exocrine signaling, and paracrine signaling (Swartz et al., 2012).

Another way that cells in the tumor microenvironment communicate is through miRNAs. The subcellular localization and tissue distribution patterns of miRNA expression in solid tumors provide a window into the inner workings of those tumors (Kent et al., 2014). The variation in these miRNA patterns indicates that miRNA expression is cell type-dependent, and thus, miRNAs play different roles in neoplastic cells and the tumor microenvironment.

The heterogenic character of tumors and differential pattern of miRNA expression in various tissues highlight the error-prone nature of the current miRNA-related or associated studies. When we refer to a miRNA-specific function as oncogenic or tumor-suppressive activity or compare the miRNA expression profile between tumor and normal tissues, the levels of stromal components and the distribution pattern of miRNAs in each of the analyzed specimens should be considered (Nouraee et al., 2013).

This section provides an overview of the steps of tumorigenesis and some examples of stromal miRNAs involved in the tumorigenesis process. A more detailed list of such miRNAs is provided in Table 1. In addition, a schematic view of the role of miRNAs in different steps of tumorigenesis is shown in Figure 1.

MiRNAs, Carcinogenesis initiation, and tumor progression

Calin and Croce (2006) were the first to report a relationship between miRNAs and cancer initiation and progression. Since then, an enormous body of molecular research in the field of cancer has been allocated to miRNAs and their potential application in cancer screening, in determining prognosis, and as therapy.

The epigenetic activation of an oncogenic miRNA, the suppression of a tumor-suppressor miRNA, or the misexpression of such miRNAs due to mutations in the molecules involved in their biogenesis are usually detected in the initial processes of neoplastic transformation. At the beginning, normal stroma resists tumorigenesis, but newly transformed cancer cells support their survival and progression by exploiting stromal components. miRNAs regulate the "gatekeepers" of cancer initiation and progression. For example, miR-135a and b overexpression in colon cancer targets the adenomatous polyposis coli gene (*APC*; Nagel et al., 2008), and overexpressed miR-373 targets CD44 markers in breast cancer (Huang et al., 2008; Yan et al., 2011), and these have been linked to the activating of the signaling pathways involved in early cellular transformations and tumor initiation. In addition, Ryu et al. (2010) proposed that miR-155 overexpression is an early event in the multistep progression of pancreatic adenocarcinoma and found miR-21 abnormalities in lesions at advanced stages.

One important early step of tumorigenesis is cells overcoming apoptosis. Several apoptosis regulators, such as programmed cell death 4 (PDCD4), an apoptosis inhibitor that suppresses cell proliferation and tumor initiation and invasion, are controlled by miRNAs. For example, at increased levels, the well-known oncomir miR-21 reduces PDCD4 levels and promotes transformation and intravasation (Asangani et al., 2008; Lu et al., 2008). Our previous finding that miR-21 expression is confined to the stromal compartments of esophageal cancer pinpoints the communicative role of this miRNA (Nouraee et al., 2013). Nishida et al. (2012) also showed that the miR-17-92 and miR-106b-25

TABLE 1. MiRNAs Involved in Different Stages of Cancer Progression

Cancer progression stage	MiRNA	Cancer type	Validated gene targets	Mechanism of action	Effect on carcinogenesis[a]	Reference
Neoplasm formation (tumor initiation)	miR-31	Breast cancer	*C11orf30* (*EMSY*)	Silences *BRCA2* and binds to the promoter region of miR-31	+	Vire et al. (2014)
	miR-34	Lung adenocarcinoma	*MET*, *BCL2*, *HDAC1*, and *SIRT1*	Blocks proliferation and tumor initiation	−	Kasinski and Slack (2012)
	miR-135 family	Colorectal cancer	*APC*	Activates WNT signaling and initiates tumorigenesis	+	Nagel et al. (2008)
	miR-92	Colorectal cancer	*E2F1*	Cell proliferation and neoplastic formation	+	Schetter and Harris (2011)
Angiogenesis	miR-210	Brain tissue (ischemic stroke repair)	*VEGFA*, *EFNA3*, and *NPTX1*	Increase VEGF levels (initiation of microvascularization); tubulogenesis	+	Zeng et al. (2014)
	miR-221 and miR-222	HUVECs	*KIT*, *IFI27* (*P27*)	Vessel permeabilization; downregulation of VEGF; and inhibition of endothelial cell migration and angiogenesis	−	Litz and Krystal (2006); Poliseno et al. (2006)
	miR-10b	Breast cancer; HMEC-1 cell line	*HOXD10*	Responds to VEGF stimulation; miR-10b overexpression leads to HMEC-1 migration, tube formation, and angiogenesis	+	Shen et al. (2011); Plummer et al. (2013)
	miR-17–92 cluster		*TIMP1*, *VEGF*, *HIF1A*, and *E2F1*	Proangiogenic factors; they cause endothelial cell sprouting and tube formation	+	Taguchi et al. (2008)
	miR-23/27/24 cluster	Choroidal neovascularization; HUVECs	*SPRY2* and *SEMA6A*	*SEMA6A* blocks VEGF receptor phosphorylation; *SPRY2* represses RAS/RAF/ERK signaling and endothelial cell sprouting	+	Urbich et al. (2011); Zhou et al. (2011)
	miR-320	MMFs	*ETS2*, *KDR* (*VEGFR2*), *IGF1*, and *IGF1R*	Regulated by *PTEN*, reprograms tumor microenvironment and blocks proliferation of endothelial cells	−	Bronisz et al. (2011)

TABLE 1. (Continued)

Cancer progression stage	MiRNA	Cancer type	Validated gene targets	Mechanism of action	Effect on carcinogenesis[a]	Reference
	miR-34 family	HCC	*CCND1*, *CDK4/6*, *MAP2K1* (*MEK1*), *MET* (*HGFR*), *E2F3*, and *CREBBP*	Involved in the TP53 pathway, endothelial senescence	−	Li et al. (2009)
Tumor inflammation	miR-155	Breast cancer and acute monocytic leukemia	*INPP5D* (*SHIP1*) and *TP53INP1*	Induced by LPS, IFN-β, and TLR ligands, activates TNF-α and IL6, causes myeloproliferation, and induces PIK3/AKT pathways	+	Tili et al. (2007); Hu et al. (2014)
	miR-146a	Hematopoietic stem cells	*TRAF6* and *IRAK1*	Induced by proinflammatory cytokines, IL1B, TNF-α, or NF-κB, and inhibits IL1R signaling	+	Taganov et al. (2006)
	miR-21	Majority of solid tumors	*PDCD4*, *TPM1*, *PTEN*, *BTG2*, and *IL12*	Induced by IL6 and EGFR pathway and involved in macrophage inflammatory response	+	Loffler et al. (2007); Schetter et al. (2009)
Hypoxia	miR-200b	HMECs	*ETS1*	Hypoxia-sensitive and induces angiogenesis	−	Chan et al. (2011)
	miR-210, miR-155, and miR-373	Head and neck cancer and pancreatic cancer	*EFNA3*, *HIF1A*, *HOXA1*, and *CA9* (*CAIX*)	HRMs, induced and regulated by HIF1	+	Huang et al. (2009, 2010); Bruning et al. (2011)
	miR-17–92 cluster	Lung cancer	*HIF1A*	Reduced owing to hypoxia	−	Taguchi et al. (2008)
	miR-20b	Breast cancer	*HIF1A* and *VEGFA*	Fine-tunes HIF1A and VEGF and adapts tumor cells to different oxygen concentrations	−	Lei et al. (2009)
	miR-15b/16, miR-21, and miR-372/373		Tumor suppressor *RECK*	miR-372/373 induced by HIF1A; miR-21 upregulated by RAS/ERK signaling; all promote malignant behavior	+	Loayza-Puch et al. (2010)
TAMs	miR-511-3p		*ROCK2*	Genetically reprograms TAMs; inhibits tumor growth, and alters tumor blood vessel morphology	−	Squadrito et al. (2012)

TABLE 1. (Continued)

Cancer progression stage	MiRNA	Cancer type	Validated gene targets	Mechanism of action	Effect on carcinogenesis[a]	Reference
	Let-7c		*CEBPD*	Regulates the bactericidal and phagocytic activities of macrophages, which leads to macrophage polarization	+	Banerjee et al. (2013)
	miR-19a-3p	RAW264.7 macrophages	*FRA1* proto-oncogene	Induces VEGF and STAT3, inhibits macrophage polarization, and impairs the migration and invasion of breast tumors	−	Yang et al. (2014a)
EMT, cancer stem cells' properties and metastasis	miR-200a/b/c and miR-141	Breast cancer	*ZEB1* and *ZEB2*	Blocks EMT, as *ZEB1* and *ZEB2* are repressors of E-cadherin	−	Korpal et al. (2008)
	miR-31	Breast cancer	*RHOA*, *RDX*, and *ITGA5*	Induces apoptosis and reduces invasion and migration	−	Valastyan et al. (2010)
	miR-10b	Breast cancer	*HOXD10*	A "metastamir" that induces migration and invasion	+	Ma et al. (2007)
	miR-21	Colorectal cancer and glioblastoma	*PDCD4*, *TIMP3*, and *RECK*	Increases intravasation and induces metastasis	+	Asangani et al. (2008); Papagiannakopoulos et al. (2008)

HUVECs, human umbilical vein endothelial cells; HMEC, human mammary epithelial cell; MMFs, mouse mammary stromal fibroblasts; HCC, hepatocellular carcinoma; LPS, lipopolysaccharide; IFN-β, interferon beta; TLR, Toll-like receptor; TNF-α, tumor necrosis factor alpha; IL, interleukin; NF-κB, nuclear factor kappa B; EGFR, epidermal growth factor receptor; HRMs, hypoxia-regulated miRNAs; TAMs, tumor-associated macrophages; VEGF, vascular endothelial growth factor; STAT3, signal transducer and activator of transcription 3; EMT, epithelial–mesenchymal transition.
[a]Promotive (+) or inhibitory (−) effects on the tumorigenesis processes.

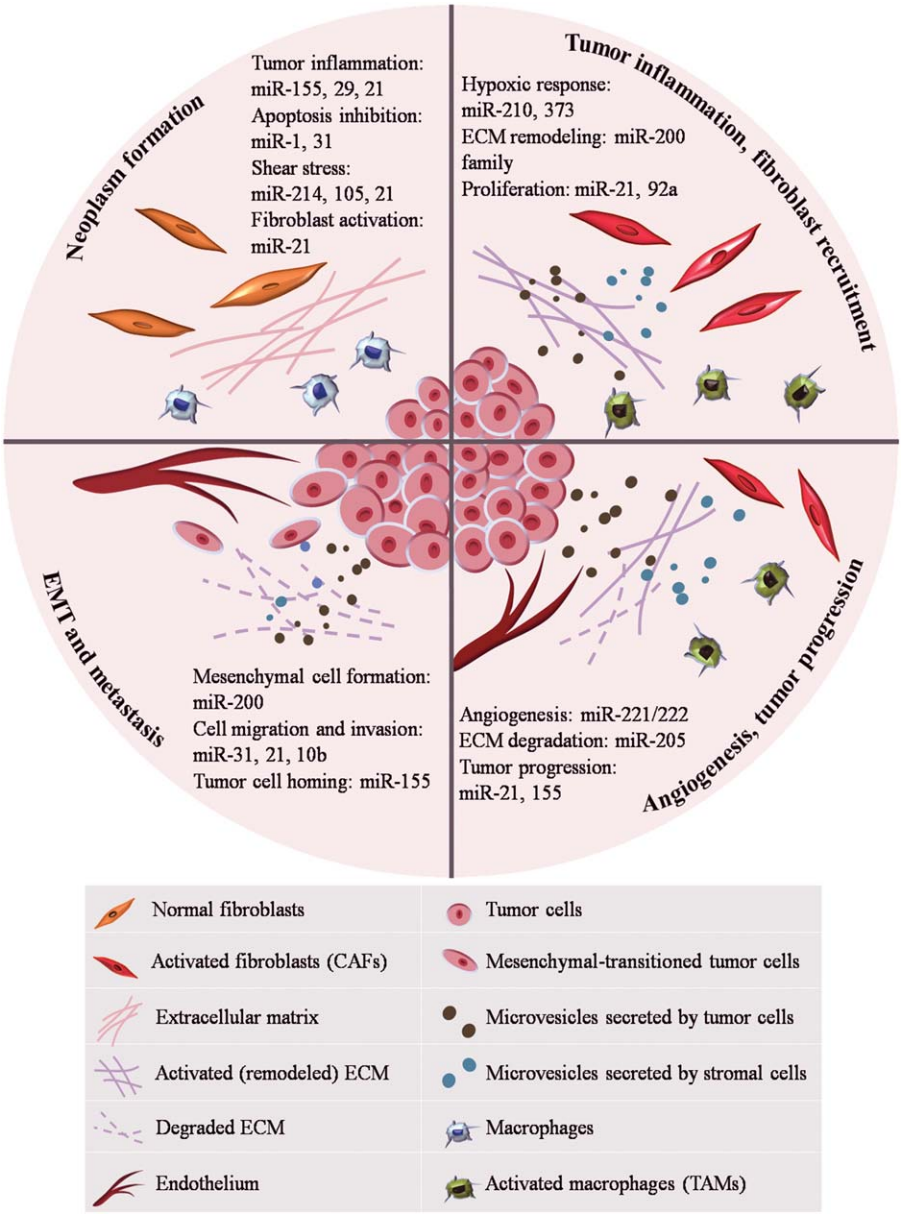

Figure 1. Schematic view of main tumor microenvironment phenomena. miRNAs involved in different steps of tumor progression and tumor–stroma interactions are shown. ECM, extracellular matrix; EMT, epithelial–mesenchymal transition. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

clusters in colorectal cancer stromal tissues are upregulated when compared with those in normal stroma. The upregulation of miR-92 in colon cancers and these cancers' secretion of the miRNA into the peripheral blood make miR-92 a suitable diagnostic marker during the early stages of the disease (Schetter and Harris, 2011).

TP53-dependent apoptosis is one of the primary mechanisms activated in response to cellular stress, such as that caused by neoplasm formation. The interaction of miR-605 and miR-29 family members has been found to activate this process (Park et al., 2009; Xiao et al., 2011). By targeting cell cycle-controlling genes, such as the cell division cycle 42 gene (*CDC42*), and by upregulating TP53, miR-29 family members (including miR-29a, b, and c) induce TP53-dependent apoptosis. These miRNAs are usually downregulated in progressive tumors.

Because they can be used to help physicians distinguish between the initial steps of plasticity and the later stages of cancer progression,

miRNAs in tumor cells as well as those in blood and urine samples may be useful as diagnostic biomarkers (Paranjape et al., 2009; Hanke et al., 2010; Aushev et al., 2013; Godfrey et al., 2013). Profiling experiments have demonstrated several miRNA deregulation patterns during the early steps of carcinogenesis (Chen et al., 2013).

miRNAs have been linked to the differentiation of cancer stem cells, which are involved in the initiation, self-renewal, and survival of tumors. One well-known mechanism in this regard is epithelial–mesenchymal transition (EMT), in which the normal cells adjacent to cancer cells take on mesenchymal traits, thus entering a cancer stem cell-like state. Known as a mechanism of tubular destruction, EMT promotes tumor metastasis and the clonal expansion of premalignant cells (Tellez et al., 2011). Different miRNAs are known to be critical regulators of each of the cellular and molecular processes that eventually led to the transdifferentiation of tumor stromal cells. Following alterations in cellular junctions and polarity and the indoctrination of the surrounding stroma, cancer cells are free to expand and invade other tissues; this enhances the potential of malignancy. Members of the miR-200 family have been shown to regulate EMT and inversely correlate with the EMT markers such as zinc finger E-box binding homeobox protein 1 (*ZEB1*) and *ZEB2*. A fundamental signal in the stromal conversions is transforming growth factor β that, in crosstalk with Hedgehog signaling, upregulates *ZEB1* and *ZEB2* by controlling the expression levels of miR-141, miR-205, miR-429, and miR-200 family members (Gregory et al., 2008). Cancer-secreted miR-105 has been shown to destroy the tight junctions of the vascular endothelial barrier and to promote breast cancer metastasis (Zhou et al., 2014). miR-148a has also been proven to be a negative regulator of EMT, and its downregulation is associated with tumor progression, which suggests that this miRNA is a candidate for cancer therapy (Korpal et al., 2008; Renthal et al., 2010; Banyard et al., 2013; Zhang et al., 2014).

MiRNAs IN ANGIOGENESIS

Endothelial cells, which line blood vessels and form the blood and lymphatic circulatory systems, are ubiquitous within tumors and modulate a variety of pathophysiological processes. Angiogenesis is an early stage in carcinogenesis that is induced by macrophages, Tie2-expressing monocytes, neutrophils, mast cells, and progenitor cells working in concert. This process includes paracrine secretion of growth factors (mainly vascular endothelial growth factor [VEGF] A), cytokines, and proteases such as matrix metalloproteinases (Joyce and Pollard, 2009).

Angiogenesis starts with oxygen deficiency, or hypoxia, that alters gene expression and causes an immunosuppressive niche that allows malignant cells to escape from host immune surveillance. Then, an orchestrated series of processes promoting (such as the proliferation of endothelial cells and the migration of immune cells and fibroblasts) and suppressing (such as apoptosis and growth arrest) events take place. These processes require the activation of a variety of molecular and cellular pathways.

Angiogenesis is a crucial component of metastasis, and common miRNAs are implicated in both processes. Hypoxia, an initiative element in angiogenesis, perturbs the miRNAs expression in the tumor stroma and leads to the consequent activation of signaling pathways. One well-studied hypoxia-related gene is the transcription factor hypoxia-inducible factor 1 gene (Shen et al., 2013). Since Kulshreshtha et al. (2007) first reported miRNA involvement in hypoxia, there has been a wealth of discoveries regarding miRNA–stroma interactions. However, the precise role of miRNA involvement in angiogenesis and the hypoxia-regulated microenvironment remains unknown.

A number of miRNAs has been implicated in angiogenesis. Upregulation of miR-210, a master hypoxia-regulated miRNA, has been shown with a variety of hypoxia-inducible factors. miR-210 contributes to angiogenesis through the NOTCH signaling pathway (Huang et al., 2010; Lou et al., 2012) and has been widely investigated for the treatment of ischemic heart disease (Hu et al., 2010). Overexpression of miR-210 has been found to result in angiogenesis and neurogenesis, which are important phenomena in brain tissue regeneration and repair after injury (Zeng et al., 2014). miR-27a and b have been found to promote angiogenesis by targeting semaphorin 6A, an angiogenesis inhibitor that controls the repulsion of the neighboring endothelial cells (Urbich et al., 2011). miR-126, which is exclusively expressed in the endothelial lineage and hematopoietic progenitor cells, is referred to as an "angiomir" owing to its contribution to angiogenesis (Ivey et al., 2008; Wang et al., 2008; Jakob et al., 2012). miR-221 and miR-222 have been found to inhibit endothelial cell migration and tube formation by silencing *KIT*

expression, an important marker of cardiac stem cells (Suarez et al., 2007; Wu et al., 2009; Yan et al., 2011). Grange et al. (2011) discovered that microvesicles released from human renal cancer stem cells shuttled RNAs and miRNA cargoes, including miR-19b, miR-29c, and miR-151, to trigger angiogenesis and facilitate the formation of premetastatic lung lesions. Other miRNAs reported to be responsible for angiogenesis regulation and neovascularization include miR-155 and miR-21 (Liu et al., 2011; Donnem et al., 2012), miR-126 (Png et al., 2011), the miR-17-92 cluster (Dews et al., 2006), and the miR-23/24/27 cluster (Zhou et al., 2011). The studies addressing the relationship between miRNAs and angiogenesis provide a wealth of information concerning the paramount importance of these regulatory molecules to the evolvement of blood vessels. Therefore, it becomes possible to develop anticancer strategies that target the stromal components sending angiogenic signals to the endothelial cells.

MiRNAs AND TUMOR INFLAMMATION

One hallmark of all solid tumors is an established immunosuppressive tumor microenvironment that requires neovasculature and infiltrating myeloid cells. Myeloid cells support tumor cells by promoting angiogenesis, inducing resistance to hormones and antiangiogenic therapies, and avoiding host immune surveillance; each of these actions causes chronic inflammation through different mechanisms (Jain, 2005; Schmid and Varner, 2010). A variety of inflammatory cells, including myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory natural killer cells, inhabits the inflammatory microenvironment and facilitates the transformed cells' progression toward malignancy (Klampfer, 2011). Moreover, proinflammatory mediators, the metabolic byproducts of cancer cells, help to establish the inflammatory milieu (Tili and Michaille, 2011). Cytokines such as interleukin 17a, tumor necrosis factor alpha (TNF-α), and interleukin 6, as well as their related transcription factors, including nuclear factor kappa B (NF-κB) and signal transducers and activators of transcription proteins, are the key regulators of chronic inflammation and tumor-surveillance mechanisms. They also induce angiogenesis and tumor immunity, two key mechanisms of tumor development. These molecules are the main modeling tools of the tumor microenvironment (Madhusudan et al., 2005; Karin, 2006; Balkwill, 2009; Grivennikov and Karin, 2011; Hayata et al., 2013).

Tumor-associated macrophages, which participate in the shuttling of miRNA between cells, are implicated in pervasive tumor growth. They are usually activated by anti-inflammatory components, including interleukin 4 and NF-κB, or by microbial agents such as lipopolysaccharides; their activation is known as macrophage polarization. As the most plastic cells of the hematopoietic system with diverse functions, tumor-associated macrophages are also involved in microcommunications in the proinflammatory tumor microenvironment through exosome secretion.

Several miRNAs have been linked to the aforementioned transitions in the tumor stroma. By triggering the innate immune response and providing an inflammatory environment, miR-155 is considered to be a prominent proinflammatory miRNA that accommodates carcinogenesis and tumor progression (Tili et al., 2009, 2011; Trotta et al., 2012). miR-21 is a global oncomir that is implicated in the crosstalk between inflammation and cancer cells in a variety of tumors. miR-21, which is activated by signal transducer and activator of transcription protein 3, interleukin 6, and Toll-like receptor signaling, targets phosphatase and tensin homolog and triggers a negative feedback loop in interferon-induced apoptosis (Folini et al., 2010; Iliopoulos et al., 2010; Yang et al., 2010). There are also anti-inflammatory miRNAs, such as miR-125b, which targets the cytokine TNF-α to inhibit inflammation (Tili et al., 2007), miR-663, which downregulates miR-155 (Tili et al., 2010), and miR-29 family members. The downregulation of such anti-inflammatory miRNAs plays a pivotal role in cancer progression (Schmitt et al., 2013).

MiRNAs, THE EXTRACELLULAR MATRIX, AND CANCER-ASSOCIATED FIBROBLASTS

Because they are the main promoters of malignancy, cancer-associated fibroblasts (CAFs), also known as tumor-associated fibroblasts, have been the focus of recent studies. CAFs, the most abundant cell population in the tumor niche, are involved in angiogenesis and inflammation, two fundamental processes in tumor progression. In normal connective tissues, fibroblasts perform a critical role in sustaining tissue homeostasis, ECM architecture, and tissue development by secreting fibrillar ECM constituents and producing ECM proteases such as matrix metalloproteinases. They

also affect neighboring epithelium by secreting growth factors. In neoplastic conditions, fibroblasts confront tumor cells by producing inflammatory signals and recruiting the host immune system. However, when these actions are circumvented by tumor cells through the secretion of growth factors, signal molecules, and, as discovered recently, miRNAs, fibroblasts transform to an active state, which is characterized by the cells' elevated proliferation and paracrine/endocrine secretion of ECM components, growth factors (including epidermal growth factor, hepatocyte growth factor, VEGF, and transforming growth factor beta [TGF-β]), cytokines, and chemokines. In this scenario, microvesicles and exosomes transport cellular information and prepare the tumor microenvironment for cancer progression (Castellana et al., 2009; Atay and Godwin, 2014; Roma-Rodrigues et al., 2014), and some mechanisms have been implicated in the sorting of miRNAs into exosomes for this purpose (Gibbings et al., 2009; Villarroya-Beltri et al., 2013).

The perturbation of miRNA expression and their subsequent introduction into the stroma is an early event in neoplasia. Downregulation of miR-31 and miR-214 and upregulation of miR-155 in ovarian cancer (Mitra et al., 2012), overexpression of miR-21 in esophageal squamous cell carcinoma (Nouraee et al., 2013), ovarian and cervical cancers (Yao et al., 2011), myeloma (Loffler et al., 2007), and miR-320 overexpression in breast carcinoma (Bronisz et al., 2011) have been implicated in the reprogramming of myofibroblasts and induction of CAF formation. In addition, Li et al. (2013) demonstrated miR-21 involvement in TGF-β-induced CAF formation through inhibiting Smad7 mRNA that in turn blocks the activation of TGF-β receptor (Li et al., 2013). Such miRNAs target key signaling molecules, including phosphatase and tensin homolog (a target of miR-21), v-ets erythroblastosis virus E26 oncogene homolog 2 (*ETS2*, a target of miR-320), chemokines (e.g., C—C motif ligand 5, a target of miR-214), and SMAD7 signaling pathways, to initiate the oncogenic mechanisms. The key mechanisms through which miR-21 contributes to the activation of CAFs are shown in Figure 2.

Stromal cells may also play a role in cell–cell communications during fibroblast-to-CAF transition by releasing miRNA signals into the microenvironment. Normal fibroblasts can trigger tumorigenesis-promoting mechanisms by causing perturbations in key pathways; examples include perturbations in phosphatase and tensin homolog signaling by miR-30 upregulation in breast cancer

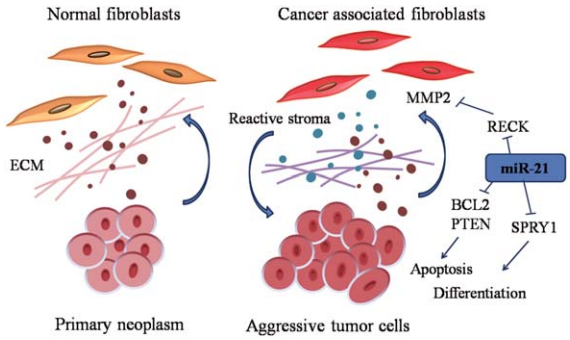

Figure 2. Involvement of miR-21, a well-known oncomir, in tumor–microenvironment interactions and reactive stroma. miR-21 is one component of tumor cell-secreted exosomes. In fibroblasts, miR-21 is induced by transforming growth factor β, angiotensin II, and the shear stress produced by the tumor cells. This activation happens through the induction of the signal transducer and activator of transcription 3 and activator protein 1 signaling pathways. Tumor cells induce stromal fibroblasts to become cancer-associated fibroblasts, which introduce miR-21 and other components into the tumor stroma. By targeting *RECK*, miR-21 induces *MMP2* in the stromal compartments and blocks apoptosis in the tumor cells by targeting proapoptotic signals that include *PTEN* and *BCL2*. Moreover, by downregulating *SPRY1* expression, miR-21 induces tumor cell proliferation and reduces their differentiation. ECM, extracellular matrix. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and perturbations in WNT signaling by miR-148a downregulation in endometrial cancers (Bronisz et al., 2011; Aprelikova et al., 2013). A list of some miRNAs that are deregulated in CAFs when compared with normal fibroblasts in a variety of human cancers is given in Table 2.

CAFs reactivate through the lateral transfer of miRNAs, which transforms fibroblasts into myofibroblast-like cells that express tissue-specific CAF markers that include α-smooth-muscle actin, CD248, and fibroblast activation protein. Alternative sources of CAFs at the neoplasia site likely include bone marrow precursor cells from the circulating blood and epithelial cancer cells originating from the EMT process. The CAF phenotype has been correlated with tumors' progression, recurrence, and metastatic potential (Ayala et al., 2003; Kalluri and Zeisberg, 2006; Maia et al., 2011; Kharaziha et al., 2012). Recognizing tissue-specific CAF markers, the mechanisms underlying their reactivation, and the miRNA signals in these processes could lead to identifying promising targets for anticancer therapy.

MiRNAs' ROLE IN TUMOR REPOPULATION KINETICS

As the tumor develops, its cells are influenced by different external mechanical stresses. The most important of these stresses are biophysical forces, including the fluid shear stress caused by

TABLE 2. Cancer-Associated Fibroblast (CAF)-Specific MiRNAs Deregulated in Human Cancers

miRNA	Cancer type	Specimen analyzed	Clinical correlation	Reference
miR-106b	Gastric	Primary cell culture from tumor tissues	Overexpression is associated with poor prognosis and tumor progression	Yang et al. (2014b)
miR-31 and miR-214	Ovarian	Primary cell culture from tumor tissues	Downregulation is associated with reprogramming of normal fibroblasts into CAFs	Mitra et al. (2012)
miR-155	Ovarian	Primary cell culture from tumor tissues	Upregulation is associated with reprogramming of normal fibroblasts into CAFs	Mitra et al. (2012)
miR-15 and miR-16	Prostate	Patient samples	Downregulation promotes tumor growth and progression by increasing FGF2 and FGFR1, which act on both stromal and tumor cells to enhance cancer progression	Musumeci et al. (2011)
miR-148a and miR-31	Endometrial	Patient samples (laser capture microdissection)	Downregulation results in tumor cell migration and invasion	Aprelikova et al. (2010, 2013)

FGF, fibroblast growth factor 2; FGFR1, FGF receptor 1.

blood flow, interstitial flow in the tumor microenvironment, and lymphatic flow, and the biochemical stresses induced by the metabolic activities of the tumor cells, such as hypoxia or low pH. Fluid mechanics augments the activity of focal adhesion kinase in tumor cells, and this might contribute to the upregulation of miR-151 (the miRNA with *FAK* as its host gene) or downregulation of miR-7 (Luedde, 2010; Michor et al., 2011; Wu et al., 2011; Swartz and Lund, 2012). In its avascular stage, owing to the deprivation of oxygen and nutrients and the reduced diffusion of macromolecules, the tumor fails to grow larger than a specific size; this ignites the secretion of signals to promote angiogenesis, which not only provides the requirements for growth but also facilitates the cancer's systemic expanse. Fitting the demands of the tumor cells, the concentration of proangiogenic miRNA signals such as miR-214 (van Balkom et al., 2013) must exceed that of antiangiogenic miRNAs such as miR-16 (Lee et al., 2013) in the secretory exosomes to activate endothelial cells, which reform the microenvironment in favor of tumor evolution. Tadokoro et al. (2013) reported that miR-210-enriched exosomes secreted from hypoxic leukemia cells are of great importance in reprogramming endothelial cells and promoting angiogenesis. Magnified stresses within or outside the tumor gradually cause the cancer cells to undergo EMT and, by deforming their cell–cell or cell–matrix interfaces, disseminate. The resultant force causes the activation of migration- and invasion-regulating genes, which leads to tumor metastasis. The proximal stromal cells and CAFs react to these stresses by secreting a variety of signals that promote tumor growth metastasis.

Several miRNAs have been linked to the formation of this premetastatic milieu by activating protease, enhancing proliferation and angiogenesis, reforming cell adhesion, and secreting chemokine ligands. On the other hand, metastatic tissue, by secreting specific signals predominantly through miRNAs, prepares distal premetastatic tissues to foster the intravasated tumor cells. Thus, the cooperation of the normal host cells is necessary for cancer cell progression (Kosaka et al., 2013; Rana et al., 2013; Valencia et al., 2014). The secretion of several miRNAs has been shown to play a fundamental role in cancer metastasis; examples include miR-199a-5p/3p in melanoma (Pencheva et al., 2012), miR-105, which targets tight junction proteins in breast cancer (Zhou et al., 2014), and miR-155 in hepatocarcinoma (Yan et al., 2013). These miRNAs are of importance in targeted cancer therapies.

CLINICAL IMPLICATIONS: TARGETING THE TUMOR MICROENVIRONMENT

The Promise of miRNA-Based Therapy

Previous studies have investigated therapies targeting components in the tumor microenvironment. Such approaches include using anti-inflammatory drugs (Yang et al., 2014c) and

antiangiogenic agents such as anti-VEGF antibodies (Ferrara et al., 2004; Whyte et al., 2010). Besides, small molecules that inhibit the VEGF receptor and the platelet-derived growth factor receptor have been indicated to bridle tumor progression and prolong patient survival when used in combination with chemotherapies. These agents have been approved by the US Food and Drug Administration (Ratner, 2004; Bergers and Hanahan, 2008; Ellis and Hicklin, 2008; Ivy et al., 2009; Huang et al., 2012). miRNA-based targeting of the tumor microenvironment is a novel strategy that requires further improvement. miRNAs are one of the most attractive therapeutic agents being rapidly translated to the clinic in the past decade. Several companies have made efforts to bring these tiny molecules to market, including Mirna Therapeutics that was the first to introduce a liposome-formulated mimic of miR-34 to treat hepatocellular carcinoma. Several other studies have paved the way for future potential use of miRNAs in cancer therapy.

Despite improvements in targeted cancer therapies, overcoming the obstacles to these approaches remains challenging. The chief among these obstacles are tumor heterogeneity, which requires multimodal treatments, and the immunosuppressive tumor stroma, which diminishes the effectiveness of cancer immunotherapy. The strategies to overcome such obstacles might include combining chemotherapy and radiotherapy with antiangiogenic or vaccine therapy. In an effort to normalize the tumor territory and to preserve the normal tissue homeostasis, researchers are investigating novel gene and drug delivery techniques and finding effective molecular targets for targeted therapy. In addition, the new methods proposed to achieve efficient and targeted delivery of drugs without stimulating the immune response, efficient distribution of drugs in the tumor, increased stability of drugs in the systemic blood and tissues, recognition of tumor-specific markers to avoid normal tissue damage, and efficient drug uptake by tumor cells are also of great interest.

MiRNAs, owing to their small size, high stability, and sequence conservation, have changed the face of molecularly targeted medicine. miRNA-based therapies are mainly based on two approaches to reinstate miRNA expression: (1) overexpression of tumor suppressor miRNAs and (2) downregulation of oncomirs. Several strategies can be used to overcome miRNA deficiency and to normalize the regulation of their targets in a cancer-related pathway, from using synthetic miRNA mimics to replace tumor suppressor miRNAs by using miRNA-overexpressing vectors that express the pre-miRNA transcript. miRNA antagonists include antisense-mediated miRNA inhibitors, including antisense oligonucleotides, or miRNA "sponges," which have several tandem repeats of the miRNA target sites. Each of these strategies has been modified to achieve more efficient delivery and fewer off-target effects. The addition of a 2′-*O*-methyl group to antisense oligonucleotides or using the agents in conjunction with locked nucleic acid–oligonucleotides inhibitors enhances their specificity and reduces their off-target binding, and conjugating antisense oligonucleotides with cholesterol increases the serum stability and cellular uptake of these agents (Elmen et al., 2008; Kredo-Russo and Hornstein, 2011). To promote the systemic delivery of antisense oligonucleotides, researchers can adjust the lengths and pharmacological modifications of the agents to increase their circulation time and cellular uptake. Double-stranded RNA oligonucleotides are more effective than single-stranded RNA oligonucleotides. However, double-stranded RNA oligonucleotides initiate a greater innate immune response because they activate the double-stranded RNA-dependent protein kinase R (De Paula et al., 2007). The administration of naked RNA oligonucleotides is limited because of the nuclease degradation of these agents in body fluids. Thus, these agents can be applied locally, but not all parts of the tumor tissue can be exposed to the drug.

The systemic administration of miRNA-based therapeutics has some disadvantages, including complement activation, cell toxicity, and immunogenicity. Therefore, efficient delivery and adequate safety are two main goals in miRNA-based therapy. Moreover, the heterogeneous tumor stroma not only blocks the distribution of therapeutic agents but also causes unequal responses to the therapies, thereby hindering the desired outcome.

Other challenges that hamper the effect of miRNA-based targeted therapies include drug resistance, unfavorable side effects, low in vivo instability, drug-induced toxicity in normal tissues, and improper distribution in the tissue of interest. Understanding the role of miRNAs in the tumor microenvironment may also help researchers to apply system biology-based approaches to model complicated interactions. Some miRNA-based approaches in preclinical studies or clinical trials are summarized in Table 3.

TABLE 3. MiRNA-Based Therapeutics in Preclinical Studies or Clinical Trials

miRNA	Pathologic condition	Approach	Drug	Mechanism/clinical outcome	Experimental stage	Company	Reference
miR-122	HCV infection	LNA-modified oligonucleotide complementary to miR-122	RG-101	Long-lasting suppression of HCV viremia	Phase II clinical trial	Regulus Therapeutics (San Diego, CA)	regulusrx.com
miR-122	Chronic HCV infection	LNA-modified oligonucleotide complementary to miR-122	Miravirsen (SPC3649)	Removes the "helper molecule" instead of directly targeting the virus and decreases cholesterol levels	Approved by the US FDA	Santaris Pharma A/S (Copenhagen, Denmark)	santaris.com
miR-34	HCC; solid cancers with liver metastasis; and hematologic malignancies	Replacement therapy; miRNA mimic delivered using a liposomal delivery formulation	MRX34	Induces cell cycle arrest, senescence, and apoptosis by controlling the TP53 pathway	Phase I clinical trial	Mirna Therapeutics (Austin, TX)	Bader (2012); Bouchie (2013); mirnarx.com
miR-21	Fibrosis	Anti-miR-21 inhibitor	–	Reduces expression of extracellular matrix proteins and improves organ function in models of heart and kidney fibrosis	Preclinical studies	Regulus Therapeutics (San Diego, CA)	regulusrx.com
miR-21 and miR-221	HCC and Alport syndrome	Anti-miR inhibitor	RG-012	Delays tumor progression, resulting in a survival rate of 80% at the study endpoint	Preclinical studies	Regulus Therapeutics (San Diego, CA)	regulusrx.com
miR-10b	GBM	Anti-miR inhibitor	–		Preclinical studies	Regulus Therapeutics (San Diego, CA)	regulusrx.com
miR-33 (a/b)	Atherosclerosis and cardiovascular disease	2′-Fluoro-methoxyethyl-phosphorothioate-modified antisense miR-33 oligonucleotides (anti-miR-33)	–	Decreases VLDL triglycerides and increases HDL	Preclinical studies	Regulus Therapeutics (San Diego, CA)	regulusrx.com
miR-208	Chronic heart failure	LNA-based anti-miR	MGN-9103	Blocks cardiac hypertrophy, myosin switching, and fibrosis in response to stress	Preclinical studies	miRagen Therapeutics (Boulder, CO)	miragentherapeutics.com

HCV, hepatitis C virus; LNA, locked nucleic acid; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; GBM, glioblastoma; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein.

Delivery Vehicles for miRNA-Based Therapy

The three main vehicles for delivering RNA interference or miRNA-based therapies are viruses, cationic liposomes, and cationic polymers. Although viral vectors effectively deliver their information to cells, their use is limited owing to their toxicity and immunogenicity. In contrast, lipid-based vehicles for miRNA-based therapies have less immunogenicity and can deliver payloads of various sizes. The efficiency of these diverse delivery systems has been described elsewhere (Zhang et al., 2013).

Exosomes: Natural Delivery Vehicles in the Tumor Microenvironment

Besides cell-to-cell contact and cells' release of soluble signals, exosomes (30–100 nm) of endocytic origin are another form of microcommunication tools in the tumor stroma that facilitate the systemic transport of signals. Cells use exosomes for juxtacrine (cell–cell), paracrine (cell–ECM), and endocrine (cell–distal tissue) signaling through their protein, messenger RNA, and noncoding RNA cargoes, which pleiotropically affect the regulatory mechanisms in the recipient cells. Because they also act as vehicles for transporting protein, DNA, mitochondrial DNA, or RNA, exosomes may be used as potential powerful tools for cell-specific anticancer therapies (Bobrie et al., 2011; Wang and Lotze, 2014). Most importantly, tissue- and cell-specific miRNA profile detection assays have revealed that exosomes secreted by cancer cells contain certain miRNAs. Exosomes stabilize and protect miRNAs from nucleases present in the ECM as well as in the circulation and body fluids. In breast cancer, high levels of secretory miR-223-enriched exosomes have been found to be associated with cancer invasiveness (Yang et al., 2011). Once the exosomes deliver their miRNA cargoes to the recipient cells, miRNAs fulfill their regulatory roles (Tian et al., 2014).

Unique miRNA expression patterns in exosomes may serve as diagnostic and/or prognostic cancer biomarkers (Schwarzenbach et al., 2011; Zuo et al., 2011). Specific tumor cells secrete specific miRNA-bearing exosomes, and these secretions are distinct from those of other cells in the same niche (Grange et al., 2011). Several investigators have demonstrated that miRNAs can be selectively packaged into exosomes and that signal molecules can be used to direct their release to the cell stroma. These miRNAs potentiate the tumor microenvironment toward metastasis (Yang et al., 2011; Montecalvo et al., 2012; Stoorvogel, 2012). Mittelbrunn et al. (2011) described the unidirectional transfer of miRNA-bearing exosomes from T cells to antigen-presenting cells during the formation of functional immune synapses (Mittelbrunn et al., 2011). This highlights targeted packaging of miRNAs in the form of exosomes, leading us to the conclusion that similar mechanisms might also happen once tumor cells are communicating with their neighbors.

Exosome-secreted miRNAs affect the expression of target genes in recipient cells via conventional regulatory mechanisms or novel mechanisms. For example, miR-21 and miR-29a have been shown to bind to Toll-like receptors in the neighboring immune cells and to promote an inflammatory response in the tumor microenvironment (Fabbri et al., 2012). This mechanism has also been indicated in pathologic conditions other than cancer. The extracellular let-7 miRNA family has been shown to identify Toll-like receptor 7 on the surface of macrophages and macroglia and to induce neurodegeneration, thereby causing damage to the central nervous system (Lehmann et al., 2012). These findings suggest that extracellular miRNAs have regulatory roles as signaling molecules or "hormones" (Fabbri, 2012) that configure the ECM in favor of disease progression.

Understanding the mechanisms underlying exosomal transportation and the related signaling pathways in the tumor microenvironment will help researchers to identify the means to overcome common problems in cancer therapy, including drug resistance, off-target effects, inefficient drug delivery, and immunogenicity.

Exosome Delivery: Opportunities and Challenges

A common deficiency of most of these delivery systems is their nonspecificity to malignant tissues. In contrast, exosomes, owing to their natural presence in the tumor microenvironment and their ability to transfer intercellular information, have advantages over a myriad of other strategies for delivering miRNA-based targeted therapies to cancer cells. With a distinctive composition of proteins and lipids on their surface, exosomes can selectively target even distant cancer cells through molecules involved in cellular recognition. Exosome membrane is rich in sphingomyelin, ceramide, and cholesterol. This characteristic distinguishes exosomes from the cell membrane and facilitates their uptake by recipient cells (Kosaka et al., 2010; Roma-Rodrigues et al., 2014).

Unlike some other delivery systems, exosomes are immunologically compatible and able to cross the blood–brain barrier. Engineering exosome-producing cells to express cancer-specific markers on their surfaces leads to the specific uptake of exosomes by cancer cells. This strategy can be used to increase the efficacy of tissue-specific delivery (Marcus and Leonard, 2013). Exosomes can also be delivered to a specific subcellular location. However, isolating and enriching exosomes remains a challenge. Another challenge in using exosomes to deliver miRNA therapies is loading the desired cargo onto the exosomes. Ohno et al. (2013) efficiently encapsulated miRNAs into exosomes by manipulating exosome-producing cells to overexpress the cargo miRNA. Using a cell-specific protein present in the membrane of the exosomes, they were able to deliver these encapsulated miRNAs to EGFR-expressing breast cancer cells. However, the researchers were unable to encapsulate miRNA into HEK-293-derived exosomes using electroporation (Ohno et al., 2013). Harnessing exosomes' natural capability as cell-to-cell messengers, Pegtel et al. (2010) used exosomes to deliver miRNAs into the cytoplasm of recipient cells. As cell-based delivery vehicles, exosomes sufficiently deliver their functional message to recipient cells without negative side effects; thus, exosomes are attracting attention in molecular medicine as potential modulators of disease-mediated processes. Exosomal transfers of miR-155 inhibitors and mimics to macrophages (Momen-Heravi et al., 2014), synthetic miR-143 to osteosarcoma cells (Shimbo et al., 2014), and miR-192 to the endothelial cells of an in vivo bone metastasis model (Valencia et al., 2014) have all resulted in little cellular toxicity and had substantial effects on miRNA regulation in the recipient cells. Munoz et al. (2013) used anti-miR-9-loaded exosomes to successfully sensitize glioblastoma cells to temozolomide, which increased cell death and caspase activity. Other approaches that use miRNA-based drug delivery in combination with chemotherapy and/or radiotherapy have also been successful owing to the cancer's elevated sensitivity to the drug and the drug's increased penetration of and distribution within the target tissue (Huang et al., 2012; Cortez et al., 2014).

Other promising vehicles for delivering miRNA-based therapies are high-density lipoprotein transporters (Vickers et al., 2011). For example, treatment with miR-223-bearing high-density lipoprotein complexes has been found to confer anti-inflammatory properties in endothelial cells by downregulating intercellular adhesion molecule 1, a miR-223 target (Tabet et al., 2014).

CONCLUSION

In this review, we elucidated the miRNA-based mechanisms underlying the complex epithelial–stromal interactions that promote carcinogenesis and tumor progression. In the recent years, miRNAs have emerged as strong targets for anti-cancer therapies. In view of the fundamental role of miRNAs in the microcommunications of tumor stroma, unraveling the mechanisms underlying the actions of these small molecules within the tumor niche is of critical importance for efficient molecular-based therapies. However, the lack of sufficient knowledge about the miRNA pathways implicated in oncogenesis remains a serious challenge in the formulation of targeted miRNA-based therapies for cancer.

Considering the cellular composition of tumor tissues will change the face of different steps of experimental procedures from sample collection to miRNA expression profiling. The development of three-dimensional systems which simulate the tumor microenvironment conditions and advanced computational approaches for miRNA pathway analysis and their contribution to the tumor stroma also seems promising for the future of miRNA-based therapeutics.

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