Review

MicroRNAs: regulators of cancer metastasis and epithelial-mesenchymal transition (EMT)

Xiang-Ming Ding

Abstract

Tumor metastasis is the main cause of death in patients with solid tumors. The epithelial-mesenchymal transition (EMT) process, in which epithelial cells are converted into mesenchymal cells, is frequently activated during cancer invasion and metastasis. MicroRNAs (miRNAs) are small, non-coding RNAs that provide widespread expressional control by repressing mRNA translation and inducing mRNA degradation. The fundamental roles of miRNAs in tumor growth and metastasis have been increasingly well recognized. A growing number of miRNAs are reported to regulate tumor invasion/metastasis through EMT-related and/or non-EMT–related mechanisms. In this review, we discuss the functional role and molecular mechanism of miRNAs in regulating cancer metastasis and EMT.

Key words MicroRNA (miRNA), cancer metastasis, EMT

Metastasis, the process by which cancer cells spread from a primary site to other parts of the body, causes approximately 90% of cancer-related deaths[1]. The underlying molecular and cellular mechanism of cancer metastasis is still largely unknown.

Epithelial-mesenchymal transition (EMT) is considered an early and key step in the metastatic cascade[2]. EMT is an evolutionarily conserved program in which cells lose their epithelial features and acquire mesenchymal properties through a process involving cytoskeleton remodeling and cell morphologic changes, resulting in increased invasiveness[3]. EMT is regulated by a variety of signaling pathways that originate from the tumor stroma, including transforming growth factor-β (TGF-β), hepatocyte growth factor (HGF), and epidermal growth factor (EGF)[4]. A hallmark of EMT is the loss of E-cadherin (CDH1), a transmembrane glycoprotein that forms the core of adheren junctions between adjacent epithelial cells and plays a critical role in cell-to-cell adhesion[5,6]. A family of E-box–binding transcription factors, including snail family zinc finger 1 (SNAI1), snail family zinc finger 2 (SNAI2), zinc finger E-box–binding homeobox 1 (ZEB1), zinc finger E-box–binding homeobox 2 (ZEB2), and twist basic helix-loop-helix transcription factor 1 (TWIST1), have been reported to induce EMT and tumor metastasis by repressing CDH1[7].

MicroRNAs (miRNAs) are endogenously expressed, small, non-coding RNAs that regulate a variety of biological processes by modulating gene expression at the post-transcriptional level[8]. It is estimated that more than one third of human genes are targeted by miRNAs. Growing evidence shows that miRNAs play an important role in the control of tumor growth and progression[9,10]. Some miRNAs act as oncogenes and some, tumor suppressors, with both classes termed oncomirs[10]. More importantly, miRNAs are also master regulators of EMT and dynamically regulate the balance between EMT and the reverse process, MET. In this review, we focus on the molecular mechanism through which miRNAs regulate EMT and cancer metastasis.

Regulation of Cancer Metastasis by Anti-EMT miRNAs

In 2008, four different groups identified the miR-200 family, which includes miR-200a, miR-200b, miR-200c, miR-141, and miR-429, as a new epithelial marker and regulator of EMT[11-14]. By comparing miRNA expression between epithelial and mesenchymal cells in different cell models, all four groups found that the miR-200 family is highly expressed in epithelial cells. Loss-of-function and gain-of-function analysis showed that miR-200 regulates the EMT and MET processes. Further analysis of the molecular mechanism revealed a double negative feedback loop between the miR-200 family and ZEB1 and ZEB2. Specifically, miR-200 represses ZEB1/ZEB2 expression by directly binding their 3' UTRs, and ZEB1/ZEB2 inhibits miR-200 transcription by binding its promoter[14,15]. Interestingly, two recent studies identified another feedback loop between miR-203 and SNAI1/SNAI2 that also regulates EMT and cancer metastasis[16,17]. Both miR-200 and miR-203 are down-regulated during *in vitro* EMT induced by TGF-β, and this down-regulation is indispensable for EMT.

Author's Affiliation: Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA.

Corresponding Author: Xiang-Ming Ding, Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA. Tel: +1-424-230-6609; Email: dingxm@ucla.edu.

Importantly, miR-200 and miR-203 are significantly down-regulated in the mesenchymal component of endometrial carcinosarcoma, which represents a bona fide example of EMT *in vivo*, and in claudin-low type breast cancer, which contains a majority of mesenchymal-like cells[18,19].

Accumulating evidence shows that EMT-associated transcription factors such as SNAI1/SNAI2 and ZEB1/ZEB2 regulate each other's expression, thus facilitating EMT[7]. Because SNAI2 also represses miR-200 and ZEB1 also represses miR-203[16,20], these or other miRNAs could be the link between reciprocal regulation of SNAI1/SNAI2 and ZEB1/ZEB2. Also, these two feedback loops seem to share similarity in both upstream inducers and operation modes, further creating the contours of a hierarchical framework that defines cellular plasticity.

Similar to CDH1[21], miR-200 and miR-203 are also regulated by epigenetic mechanisms such as DNA methylation and histone methylation[22-24]. There is an inverse correlation between miR-200 and miR-203 promoter methylation status and gene expression in breast cancer cell lines, which is accompanied by permissive and repressive histone modifications at the promoter corresponding to an epithelial and mesenchymal phenotype, respectively[22,25]. Notably, a recent study showed that DNA methylation of the miR-200 family is dynamic and reversible during EMT induced by TGF-β and may play an important role in regulating plasticity between epithelial and mesenchymal states[26].

In addition to miR-200 and miR-203, other miRNAs have been implicated in EMT and cancer metastasis. For example, miR-34 and miR-30a were shown to inhibit EMT by directly targeting SNAI1, a transcriptional repressor of *CDH1*[27-29]. Interestingly, both miR-200 and miR-34 are target genes of p53, linking p53 and the EMT program[27,30,31]. p53 induces the expression of miR-200 and/or miR-34, which further represses the expression of *ZEB1/ZEB2* and *SNAI1/SNAI2* and induces *CDH1* expression, thus leading to MET. In addition, miR-612 inhibits EMT through the suppression of *AKT2* in hepatocellular carcinoma[32]. miRNAs associated with EMT are summarized in **Table 1**.

Several recent studies demonstrated that the induction of EMT can generate cells with properties of stem cells or cancer stem cells, which are capable of both tumor initiation and sustenance of tumor growth[33,34]. Induction of TGF-β or ectopic expression of EMT-inducing transcription factors in human mammary epithelial cells and transformed mammary cells resulted in the generation of stem-like cells[33]. Emerging evidence indicates that miRNAs control the stemness of cancer stem cells. Shimono *et al.*[35] showed the down-regulation of miR-200c links breast cancer stem cells with normal stem cells. Namely, miR-200c blocked the expression of *BMI1*, strongly suppressing mammary duct formation by normal mammary stem cells and breast cancer stem cell–driven tumor formation. ZEB1 links the activation of EMT and maintenance of stemness in one cell by suppressing the expression of stemness-inhibiting miRNAs, including miR-200, miR-203, and miR-183[20]. Linking EMT and cancer stem cells to specific miRNAs will provide a better understanding of how metastatic cancer arises, and targeting these miRNAs may provide new ways to strike cancer at its root.

Table 1. MicroRNAs (miRNAs) associated with epithelial-mesenchymal transition (EMT)

miRNA	Effect on EMT	Upstream regulator(s)	Downstream target(s)	Reference(s)
miR-200s	Suppress	ZEB1/2, SNAI1/2, P53	ZEB1/2, SNAI2	[11–13, 15, 31]
miR-203	Suppress	ZEB1, SNAI1/2	SNAI1/2	[16, 17, 20]
miR-204	Suppress	NA	SNAI2, TGFβR2	[72]
miR-205	Suppress	TGF-β	ZEB1/2	[11]
miR-34	Suppress	SNAI1, P53	SNAI1	[27, 29]
miR-1	Suppress	SNAI2	SNAI2	[73]
miR-153	Suppress	NA	SNAI1, ZEB2	[74]
miR-30a	Suppress	NA	SNAI1	[28]
miR-124	Suppress	NA	SNAI2	[75]
miR-612	Suppress	NA	AKT2	[32]
miR-9	Promote	MYC	CDH1	[36]
miR-103/107	Promote	NA	DICER1	[38]
miR-221/222	Promote	FOSL1	TRPS1	[39]
miR-155	Promote	SMAD4	RHOA	[40]
miR-181a	Promote	TGF-β	Bim	[41]
miR216a/217	Promote	NA	PTEN, SMAD7	[42]
miR-27	Promote	NA	APC	[76]
miR-197	Promote	NA	p120 catenin	[77]
miR-490-3p	Promote	NA	ERGIC3	[78]

NA, not available.

Regulation of Cancer Metastasis by Pro-EMT miRNAs

miR-200 family members and miR-203 are biomarkers of the epithelial and differentiated phenotype and thus are considered inducers of MET. However, there is also evidence for miRNAs promoting the transition to a mesenchymal phenotype. For example, miR-9 directly targets *CDH1*, leading to increased cell invasiveness and a context-dependent EMT-like conversion[36]. Similarly, increased miR-92a expression reduces *CDH1* expression, resulting in the promotion of cancer cell motility and invasiveness[37]. The miR-103/107 family attenuates miRNA biosynthesis by targeting *DICER1*, a key component of the miRNA processing machinery[38]. At the cellular level, miR-103/107 induces EMT by down-regulating miR-200. Functionally, miR-103/107 confers migratory capacities *in vitro* and empowers metastatic dissemination of otherwise nonaggressive cells *in vivo*. miR-221/222, identified as a cluster of basal-like, subtype-specific miRNAs, promote EMT in breast cancer cells by targeting trichorhinophalangeal 1 (*TRPS1*)–mediated inhibition of ZEB2[39]. miR-155 and miR-81a are induced by TGF-β and promote EMT and cancer invasion[40,41], in contrast to miR-200 and miR-203, which are inhibited by TGF-β. miR-155, which is overexpressed in several malignancies, was reported to be a direct transcriptional target of TGF-β/SMAD4 signaling. miR-155 promotes EMT by targeting RhoA GTPase, which regulates cellular polarity and tight junction formation and stability[40]. miR-81a promotes EMT and cancer metastasis by repressing *BIM*[41]. In addition, miR-216a/217 induced EMT and promoted drug resistance and recurrence by targeting *PTEN* and *SMAD7* in liver cancer[42]. Taken together, cancer cells exploit these miRNAs to regulate the EMT/MET–associated cancer metastasis by targeting different genes involved in EMT/MET process.

The Regulation of Cancer Metastasis by Non-EMT–Associated miRNAs

Cancer metastasis is a complex, multistep process involving the escape of neoplastic cells from a primary tumor (local invasion), intravasation into the systemic circulation, survival during transit through the vasculature, extravasation into the parenchyma of distant tissues, establishment of micrometastases, and ultimately, outgrowth of macroscopic secondary tumors (colonization)[1]. miRNAs are well suited to regulate cancer metastasis because of their capacity to coordinately repress numerous target genes, thereby potentially enabling their intervention at multiple steps of the invasion-metastasis cascade[43]. miR-31 is one such multi-functional miRNA that acts by repressing a cohort of pro-metastatic targets including *RHOA*, radixin (*RDX*), and integrin α5 (*ITGA5*)[44]. In addition to miR-31, several other anti-metastatic miRNAs have been identified in a number of cancers, as summarized in **Table 2**. miR-335 and miR-126 were the first two miRNAs found to suppress metastasis in human breast cancer[45]. miR-335 suppresses metastasis and migration by targeting *SOX4* and tenascin (*TNC*), whereas miR-126 targets *SDF1A* to inhibit cell proliferation, adhesion, and migration[45,46]. let-7 is widely viewed as a tumor suppressor[47]. Consistent with this, the expression of let-

7 family members is down-regulated in many cancer types compared with normal tissue, as well as during tumor progression[10]. Upon restoration in breast cancer stem cells, let-7 inhibited mammosphere-forming ability *in vitro* and metastatic ability *in vivo* by targeting *RAS* and high mobility group AT-hook 2 (*HMGA2*)[48-50]. There is also a very clear link between loss of let-7 expression and the development of poorly differentiated, aggressive cancers. miR-191/425 cluster, which is induced by estrogen receptor alpha (ERα) , reduced cell proliferation and impaired tumorigenesis and metastasis by repressing *SATB1, CCND2,* and *FSCN1* in breast cancer[51]. miR-33a suppresses bone metastasis in lung cancer by targeting parathyroid hormone-like hormone (PTHLP), a potent stimulator of osteoclastic bone resorption[52].

In addition to anti-metastatic miRNAs, a number of miRNAs are pro-metastatic. miR-21 was one of the first miRNAs to be described as an oncomir[10,53]. Because most of the targets of miR-21, including programmed cell death 4 (*PDCD4*), *PTEN*, tropomyosin 1 (*TPM1*), and *RHOB*, are tumor suppressors, miR-21 has been associated with a wide variety of cancers[54-57]. For example, miR-21 was found to promote invasion, intravasation, and metastasis in ovarian cancer and colon cancer[55,56]. miR-10b, which is induced by TWIST, positively regulates cell migration and invasion by targeting *HOXD10*, a repressor of pro-metastatic genes such as *RHOC*, plasminogen activator, urokinase receptor (*PLAUR*), and matrix metallopeptidase 14 (*MMP14*)[58,59]. Clinically, the level of miR-10b expression in primary breast carcinomas associates with cancer progression[58]. In addition, miR-10b promotes metastasis of hepatocellular and esophageal carcinomas by targeting cell adhesion molecule 1 (*CADM1*) and Kruppel-like factor 4 (*KLF4*), respectively[60,61]. miR-10a was found to be a key mediator of metastatic behavior in pancreatic cancer, exerting its effects by suppressing homeobox B1 (*HOXB1*) and homeobox B3 (*HOXB3*)[62]. Inhibiting miR-10a expression (with retinoic acid receptor antagonists) or function (with specific inhibitors) is a promising starting point for anti-metastatic therapies. miR-373 and miR-520c stimulate tumor cell migration and invasion, at least in part through direct suppression of *CD44*, mechanistic target of rapamycin (*MTOR*), and sirtuin 1 (*SIRT1*)[63,64]. Also, miR-373 expression is significantly higher in metastatic tumors than in non-metastatic tumors[63]. Interestingly, although miR-200 was reported as an anti-EMT miRNA that inhibits tumor invasion, a recent study by Korpal *et al*.[65] showed that miR-200 promotes metastatic colonization by targeting Sec23 homolog A (*Sec23a*). Altogether, miRNAs regulate cancer metastasis through the inhibition of the genes involved in different steps of the cancer metastasis cascade.

miRNAs as Novel Targets for Cancer Therapy

Because miRNAs play a critical role in tumor formation, maintenance, and progression, intensive efforts have been made to develop miRNA-based therapeutic strategies for cancer treatment. It was only 10 years ago that the first human miRNA was discovered, yet an miRNA-based therapeutic has already entered phase 2 clinical trials[66]. This rapid progression from discovery to development promises to yield an attractive new class of therapeutics. Mimics of let-7 and miR-34 are under preclinical development to target a broad

Table 2. miRNAs associated with tumor metastasis (non-EMT)

miRNA	Effect on metastasis	Upstream regulator	Downstream target(s)	Cancer type(s)	Reference(s)
miR-31	Suppress	NA	RHOA, RDX, ITGA5	Breast	[44]
miR-335	Suppress	NA	SOX4, TNC	Breast, gastric	[45]
miR-126	Suppress	NA	SDF1α	Breast,	[45, 46]
let–7	Suppress	LIN28,MYC	RAS, HMGA2	Breast, colon	[49, 50]
miR-191/425	Suppress	ERα	SATB1, CCND2, FSCN1	Breast	[51]
miR-33a	Suppress	TTF1	PTHrP, HMGA2	Lung	[52, 79]
miR-363	Suppress	NA	PDPN	Head and neck	[80]
miR-218	Suppress	EZH2	UGT8	Pancreatic	[81]
miR-29b	Suppress	GATA3	EGFA, ANGPTL4, PDGF, LOX, MMP9, ITGA6, ITGB1, TGFB	Breast	[82]
miR-195	Suppress	NA	IKKα, TAB3	Liver	[83]
miR-148a	Suppress	HBx	HPIP	Liver	[84]
miR-290	Suppress		Arid4b	Breast	[85]
miR-137	Suppress	HMGA1	FMNL2	Colorectal	[86]
miR-138	Suppress	NA	SOX4, HIF-1α	Ovarian	[87]
miR-140-5p	Suppress	NA	TGFBR1, FGF9	Liver	[88]
miR-143	Suppress	NA	ERK5, AKT	Bladder, esophageal	[89, 90]
miR-218	Suppress	NA	CAV2	Renal	[81]
miR-23b/27b	Suppress	NA	RAC1	Prostate	[91]
miR-7	Suppress	NA	KLF4	Breast	[92]
miR-26a	Suppress	NA	EZH2	Nasopharyngeal	[93]
miR-29c	Suppress	NA	TIAM1	Nasopharyngeal	[94]
miR-30a	Suppress	NA	PIK3CD	Colorectal	[95]
miR-145	Suppress	NA	ADAM17, FBSCN1	Melanoma, liver	[96, 97]
miR-148b	Suppress	NA	AMPKα1	Pancreatic	[98]
miR-194	Suppress	NA	BMP1, p27	Lung	[99]
miR-520h	Suppress	Resveratrol	PP2A/C	Lung	[100]
miR-22	Suppress	NA	TIAM1	Colon	[101]
miR-100	Suppress	NA	mTOR	Bladder	[102]
miR-145	Suppress	NA	COL5A1, Ets1	Meningiomas, gastric	[103, 104]
miR-122	Promote	NA	CAT1	Colorectal	[105]
miR-1908	Promote	NA	ApoE, DNAJA4	Melanoma	[106]
miR-199a-5p	Promote	NA	ApoE, DNAJA4	Melanoma	[106]
miR-199a-3p	Promote	NA	ApoE, DNAJA4	Melanoma	[106]
miR-10b	Promote	Twist	HOXD10, CADM1, RHOB, KLF4, Tiam1	Breast, liver, esophageal, glioma	[58–61]
miR-21	Promote	NA	PTEN, PDCD4, TPM1	Breast, colon	[53–55]
mir-550a	Promote	NA	CPEB4	Liver	[107]
miR-24	Promote	NA	PTPN9, PTPRF	Breast	[108]
miR-373	Promote	NA	CD44, mTOR, SIRT1	Breast, fibrosarcoma	[63, 64]
miR-520c	Promote	NA	CD44, mTOR, SIRT2	Breast, fibrosarcoma	[63, 64]
miR-93	Promote	NA	LATS2	Breast	[109]

NA, not available.

spectrum of solid tumors. Therapeutic delivery of let-7—either in the form of a let-7 mimic or a virus—leads to a robust inhibition of tumor growth in human non–small cell lung cancer xenografts and the KRAS-G12D transgenic mouse model[67,68]. Similarly, systemic delivery of the miR-34 mimic blocked tumor growth in mouse models of lung and prostate cancers[69,70]. Conversely, several studies show that miRNAs can be targeted therapeutically to suppress metastasis. For example, Ma *et al*.[71] demonstrated that systemic treatment of tumor-bearing mice with miR-10b antagomirs, a class of chemically

modified anti-miRNA oligonucleotides, suppressed breast cancer metastasis. These antagomirs did not reduce primary mammary tumor growth but markedly suppressed formation of lung metastases in a sequence-specific manner[71].

Perspective

Bioinformatic prediction and experimental validation have revealed that many miRNAs and their target genes are involved

in cancer metastasis (**Tables 1** and **2**). However, the upstream regulators of these miRNAs still remain elusive. Understanding how these oncomirs are regulated will be valuable for promoting or suppressing their expression and thereby for subsequently inhibiting cancer metastasis. The challenge in identifying regulators of mature miRNAs is a lack of information on the sequence of primary miRNAs, which are difficult to amplify because of their low stability

and expression levels. However, as next-generation sequencing technology continues to advance, RNA-sequencing will provide novel insight on difficult-to-study primary miRNAs. We anticipate that more upstream regulators of miRNAs will be identified in the future.

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