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MicroRNA control of epithelial–mesenchymal transition and metastasis

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Abstract

The great majority of cancer deaths are due to metastasis, which remains a poorly understood pathological process. The formation of a metastasis reflects a succession of complex steps leading to the macroscopic outgrowth of disseminated tumor cells at the secondary site. In the past 5 years, certain microRNAs (miRNAs) have been shown to regulate either a single step or multiple steps of metastasis, doing so by downregulating the expression of their target genes. In this review, we discuss recent studies on the functions and molecular mechanisms of miRNAs in regulating epithelial–mesenchymal transition (EMT) and cancer metastasis.

Keywords

MicroRNA (miRNA); Cancer; Metastasis; Epithelial; mesenchymal transition (EMT); Mesenchymal–epithelial transition (MET)

1 Introduction

Around 90% of cancer-related mortality is caused by metastasis, a multi-step process in which tumor cells disseminate from the primary site, enter lymphatic or blood circulation, arrest at distant anatomic sites, exit the vasculature, and colonize distant organs through metastatic outgrowth [1]. The current understanding of the molecular and cellular determinants of metastasis is largely limited.

miRNAs are endogenously expressed ~22 nt non-coding RNAs that negatively regulate the expression of their targeted genes [2]. Over the past decade, a growing list of miRNAs has been identified in various tissues and in different species. Recently, the miRNA database (www.mirbase.org) released the latest miRbase version (v18), which contains 18,226 entries representing hairpin precursor miRNAs, expressing 21,643 mature miRNA products, in 168 species. It is estimated that over one third of the human genome is targeted by miRNAs [3].

miRNAs bind to perfect or imperfect complementary sequences of target mRNAs at the miRNA recognition elements (MREs) of their 3′UTR through a “seed” region [3], leading to cleavage of target mRNAs and/or inhibition of their translation [4]. Interestingly, RNAs that compete with each other through common MREs, termed competing endogenous RNAs (ceRNAs), are proposed to regulate key oncogenes and tumor suppressor genes [5]. ceRNAs can be either mRNAs or RNAs produced from pseudogenes and other non-coding genes.

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For instance, RNAs that share miRNA binding sites with *PTEN*, such as its pseudogene *PTENP1*, positively regulate expression levels of PTEN by acting as endogenous miRNA decoys or sponges [6–8].

Numerous profiling and functional experiments have identified oncogenic and tumor-suppressing miRNAs, collectively termed “oncomirs” [9, 10]. Moreover, specific metastasis-regulating miRNAs, collectively termed “metastamirs” [11], have been found to be either positively or negatively associated with metastasis. In the following sections, we will review the roles of various metastamirs, as well as the functional targets and downstream pathways controlled by these non-coding RNAs.

2 miRNAs that regulate EMT/MET

Recently, it has been suggested that epithelial cancer cells may convert to motile mesenchymal ones by undergoing an epithelial–mesenchymal transition (EMT) [12, 13]. EMT is characterized by loss of cell adhesion, repression of E-cadherin expression, acquisition of mesenchymal markers (including N-cadherin, Vimentin, and Fibronectin), and increased cell motility and invasiveness [12]. Both EMT and mesenchymal–epithelial transition (MET), the reversion of EMT, are essential for developmental processes, including mesoderm formation, neural crest development, heart valve development, and secondary palate formation [14]. On the basis of recent studies, it is proposed that EMT can be resurrected by primary tumor cells in order to acquire motility and invasiveness, and that MET is important for the final stage of metastasis in which extravasated cancer cells revert to an epithelial state and proliferate into a macroscopic secondary tumor [14].

Interestingly, a seminal study by the Weinberg Lab demonstrated that induction of the EMT program can generate cells with properties of stem cells or cancer stem cells (CSCs) [15]—defined operationally as tumor-initiating cells [16]. Hence, the invasion step of the metastasis cascade may involve a cell-type conversion process which endows epithelial cancer cells with both motility and self-renewal ability, whereas the metastatic colonization step may reflect differentiation of CSCs into non-CSCs at the metastatic site. These steps have been shown to be orchestrated by pleiotropically acting molecules—transcription factors and miRNAs.

Several transcription factors, including Snail [17], Slug [18], Twist [19], ZEB1 [20], and ZEB2 [21], have been identified as inducers of EMT and tumor metastasis. More recently, miR-205 and the miR-200 family (miR-200a, miR-200b, miR-200c, miR-141, and miR-429, which share a consensus seed sequence) have emerged as new epithelial markers and repressors of EMT [22, 23] and stem cell properties [24]. The miR-200 family members function to promote MET and inhibit induction of EMT, doing so by directly targeting the mRNAs encoding ZEB1 and ZEB2 [22, 23]. Conversely, ZEB1 represses the transcription of miR-200 genes by directly binding to their promoter region, thereby forming a double-negative feedback loop [22, 25, 26]. Expression of the miR-200 family is lost in regions of metaplastic breast cancers lacking E-cadherin, whereas ZEB1 and ZEB2 are highly abundant in invasive mesenchymal cells [22].

On the other hand, the fact that the miR-200 family promotes the conversion of mesenchymal cells to epithelial-like cells suggests that these miRNAs may favor metastatic outgrowth. Expression of the miR-200 family members in the highly metastatic 4T1 mouse mammary tumor cell line is higher than that in its isogenic cell line, 4TO7, which is capable of forming micrometastases but not macrometastases [27, 28]. When ectopically expressed in 4TO7 cells, miR-200 promoted MET and enabled formation of macroscopic metastases in the lung and liver after these cells were injected intravenously into recipient mice [27, 28]. This effect was mediated, at least in part, by direct targeting of Sec23a, a COPII vesicle

component that modulates the secretion of metastasis-suppressing proteins, such as Igfbp4 and Tinagl1 [28]. Collectively, these findings suggest a model in which the miR-200 miRNA family suppresses EMT and cancer cell dissemination, but promotes metastatic colonization after tumor cells have already disseminated to distant organs (Fig. 1).

Besides the miR-200 family, additional miRNAs have also been reported to regulate EMT (Table 1). miR-9, a MYC/MYCN-induced miRNA, directly targets the E-cadherin-encoding mRNA *CDH1*, leading to increased cell motility/invasiveness and a context-dependent EMT-like conversion [29]. Overexpression of miR-9 in otherwise non-metastatic epithelial breast tumor cells induced micro-metastasis formation in the lungs of recipient mice, whereas silencing of miR-9 in highly malignant cells inhibited metastasis [29]. The miR-103/107 family attenuates miRNA biosynthesis by targeting Dicer [30]. miR-103/107 can induce EMT by downregulating miR-200 levels, and empower metastatic dissemination of otherwise non-aggressive breast cancer cells *in vivo* [30]. The miR-221/222 miRNA cluster has been found to target ESR1 (estrogen receptor) [31], Dicer [32], and TRPS1 (trichorhinophalangeal syndrome type 1) [33], leading to EMT induction in breast cancer cells [33]. Treatment of the NMuMG mammary epithelial cells with TGF-β markedly induced miR-155, whose knockdown suppressed TGF-β-induced EMT, migration, and invasion, and this regulation has been attributed to the ability of this miRNA to target RHOA [34]. In non-small cell lung cancer cells, miR-30a inhibits EMT by directly targeting Snail, a transcription repressor of *CDH1* [35]. In retinal pigment epithelium, miR-204 plays a critical role in maintaining epithelial barrier function and cell physiology by directly targeting TGFβR2 and SNAIL2 [36]. Taken together, cancer cells may exploit these miRNAs to acquire cellular plasticity and accomplish different steps of the metastatic process.

3 Other miRNAs involved in metastasis

The link between miRNAs and metastasis was first provided by a study which reported that overexpression of miR-10b in otherwise non-metastatic breast tumors triggered tumor invasion and distant metastasis in xenotransplanation models [37]. Since then, a growing body of evidence has demonstrated the existence of pro-metastatic and anti-metastatic miRNAs (Table 2) (Fig. 2).

Twist, a potent inducer of EMT, can bind to the promoter region of *mir-10b* and activate its transcription [37]. The miR-10b miRNA directly targets the mRNA encoding HOXD10, a transcriptional repressor of several genes involved in cell migration and extracellular matrix (ECM) remodeling, including RHOC, α3 integrin, uPAR, and MT1-MMP (MMP-14) [37, 38]. In breast cancer cells, *HOXD10* is also targeted by a metastasis-promoting, long non-coding RNA, HOTAIR [39]. Moreover, HOXD10, RHOC, uPAR, and MMP-14 are functional effectors of miR-10b in glioblastoma cells and mediate the effect of this miRNA on promoting invasiveness of such tumor cells [40, 41]. In human esophageal cancer cells, miR-10b promotes migration and invasion by targeting KLF4 [42]. Other targets of miR-10b include BCL2L11/Bim, TFAP2C/AP-2, CDKN1A/p21, and CDKN2A/p16 in glioblastoma [43].

Just like certain oncoproteins (e.g., HER2/ERBB2) which not only initiate tumor formation but also confer invasiveness and metastatic ability on cancer cells, several miRNAs, initially identified as oncomirs, have been found to promote migration, invasion, and metastasis. miR-21 is one of the best established oncomir that is overexpressed in most types of cancer analyzed [44]. In the Tet-Off miR-21 transgenic mice, 16-fold overexpression of miR-21 led to development of pre-B-cell lymphoma, which was reversed within a few days of doxycycline treatment, demonstrating that miR-21 is a *bona fide* oncogenic miRNA and that

miR-21-driven tumors are addicted to this oncomir [45]. miR-21 targets a number of tumor suppressors, including PDCD4, PTEN, TPM1, and RHOB [46–55], some of which have established inhibitory effects on cancer cell detachment, migration, and invasion steps of the metastatic cascade (Fig. 2). Consistent with this, miR-21 was found to promote invasion, intravasation, and metastasis in breast cancer and colon cancer [47, 49]. Another example is miR-373, which was initially identified in a forward genetic screen as an oncogenic miRNA acting to target the tumor suppressor LATS2 in testicular germ-cell tumors [56]. Later, miR-373 stood out again in a functional genomics screen as a miRNA that promoted cell migration. This miRNA also induced metastasis of otherwise non-metastatic MCF-7 breast cancer cells *in vivo*, which was mediated by targeting of CD44. In breast cancer patients, lymph node metastases exhibited upregulation of miR-373 compared with paired primary tumors [57].

Additional pro-metastatic miRNAs identified in a number of cancer types are listed in Table 2. Although each tumor type has its distinct miRNA signature, some of these miRNAs are deregulated in multiple types of cancer. For instance, miR-21 is aberrantly overexpressed in breast, colorectal, prostate, ovarian, and oral cancer, and it appears to target a group of tumor suppressor and metastasis suppressor genes involved in multiple tumor types [44]. miR-10b, which was initially shown to be highly expressed in breast tumors from metastasis-positive patients [37], has also been found to be upregulated in highly aggressive glioma [40, 41, 43] and pancreatic adenocarcinoma [58, 59]. These results suggest that some miRNAs may have a widespread role in tumor invasion and/or metastasis across different tumor types.

Besides the pro-metastatic roles played by miRNAs, a number of miRNAs act as anti-metastatic regulators. miR-335, miR-206, miR-126, and miR-31 are among the first metastasis-suppressing miRNAs discovered through expression profiling analysis of metastatic and non-metastatic cell lines [60, 61]. Mechanistically, miR-335 targets SOX4, TNC, and PTPRN2 to remodel the ECM of cancer cells and to inhibit cell migration [61], while miR-206 activates cancer cell apoptosis and inhibits cell migration through modulating expression of NOTCH3 and SRC1/3 [62]. In cancer cells, miR-126 targets the pro-angiogenic factor VEGF [63] and CRK [64], an adaptor protein involved in cell proliferation, adhesion, and migration. Interestingly, the action of miR-126 goes beyond cell-autonomous effects on tumor cells, as this miRNA also inhibits endothelial recruitment, angiogenesis, and colonization at the meta-static site by targeting IGFBP2, PITPNC1, and MERTK [65]. miR-31 is a multi-functional miRNA that regulates several steps of metastasis, including local invasion, anoikis, extravasation, and metastatic colonization; these effects can be explained by concomitant suppression of three pro-metastatic gene products, RHOA, radixin, and integrin α5 (Fig. 2) [60, 66–68].

Expression of the let-7 miRNA family members is down-regulated in a variety of cancers and in stem cells [69, 70]. These miRNAs were initially found to inhibit tumor formation by downregulating oncogenic proteins, RAS and HMGA2 (Fig. 2) [71, 72]. Subsequently, it was reported that restoring let-7 expression in breast CSCs suppressed proliferative potential and mammosphere-forming ability *in vitro*, as well as tumorigenicity and metastatic ability *in vivo* [73]. These results are in consonance with recent findings that CSCs are responsible for the development of metastatic lesions [74, 75], and suggest that therapeutic strategies centered on restoration of let-7 miRNAs may not only shrink the primary tumor but also block dissemination of metastatic CSCs.

4 Implications of miRNAs in cancer diagnosis, prognosis, and therapeutics

Studies on miRNAs not only illuminate the molecular basis of metastasis but also have implications for diagnosis, prognosis, and treatment of cancer. Expression of 217 mammalian miRNAs and 16,000 mRNAs were profiled simultaneously in 334 normal tissues and cancer specimens. A number of miRNAs showed upregulation or downregulation in tumors, and the expression pattern of these miRNAs classified cancer types better than that of mRNAs [76]. Recently, it has been reported that cancer-associated miRNAs can be detected in serum or plasma of patients, and may effectively discriminate tumor-bearing individuals from healthy controls, which suggests the potential of using specific circulating miRNAs as non-invasive or minimally invasive cancer biomarkers [77, 78]. For instance, serum levels of miR-141 can distinguish between healthy individuals and patients with prostate cancer [77]. In colorectal cancer patients, the levels of miR-92a and miR-29a are significantly elevated in their plasma [79, 80]. These studies open new avenues for cancer detection and follow-up examination.

miRNAs that correlate with clinical outcomes provide promise for improved prognosis. In breast cancer patients, tumors with low expression of miR-335 and miR-126 have a higher probability of developing metastasis at distant sites compared with tumors expressing high levels of these two miRNAs [61]. miR-210, a hypoxia-induced miRNA, is an independent prognostic marker in breast cancer, and its expression levels show an inverse correlation with disease-free and overall survival outcomes [81, 82]. miR-21, the most studied oncomir, has been identified as an indicator of poor prognosis in multiple cancer types, including breast cancer [48], squamous cell carcinoma [83], astrocytoma [84], and gastric cancer [85].

miRNAs that are critical for tumor formation, maintenance, and progression might serve as targets for therapeutic intervention. Intensive efforts have been made to develop miRNA-based therapeutic strategies. For example, in an orthotopic model of pancreatic cancer, systemically delivered miR-34 or miR-143/145 mimics inhibited tumor growth without detectable toxicity [86], although the effect on metastasis remains unclear. On the other hand, miRNAs that promote tumor formation and/or metastasis can be targeted *in vivo*. For instance, therapeutic silencing of miR-10b using “antagomirs”—chemically modified, cholesterol-conjugated antisense miRNA inhibitors, resulted in sequence-specific inhibition of metastasis in a mouse mammary tumor model [87]. An attractive property of miRNAs is their ability to downregulate target genes in one or more pathways or networks at multiple levels [88]. Thus, targeting a single miRNA is expected to influence multiple miRNA target genes and their associated signaling pathways.

miRNA-based agents have been shown to modulate sensitivity to traditional cancer drugs. Treatment with miR-21 inhibitors can sensitize breast cancer cells to Topotecan and Taxol [89]. Expression of miR-205 in SKBR3 breast cancer cells directly targets HER3, leading to increased responsiveness to tyrosine kinase inhibitors Gefitinib and Lapatinib [90]. Although these results are based on *in vitro* experiments and need to be validated *in vivo*, they suggest that manipulating miRNA expression may improve cancer management, and that combination treatment with miRNA-based agents and other therapeutic drugs could be beneficial.

5 Concluding remarks

Combining expression profiling, functional characterization, mechanistic experiments, and clinical validation, studies in the past five years have identified a number of miRNAs that play diverse roles at multiple steps of tumor progression and metastasis. Although it is not fully understood how these miRNAs are deregulated in cancer, several mechanisms have been investigated. In particular, epigenetic silencing of cancer-implicated miRNAs by CpG

island hypermethylation has been found in human tumor cells [91]. The miRNA–mRNA interactions are complex: each miRNA can potentially target hundreds of mRNAs, and each mRNA can be targeted by several distinct miRNAs. Thus, besides individual miRNA analysis, a comprehensive and systematic strategy will be necessary for future studies to elucidate the network of miRNAs and underlying pathways. Furthermore, genetically engineered animal models will shed new light on metastasis regulation by miRNAs. A survey of published miRNA knockout mouse models has revealed that many miRNAs are dispensable for normal development (likely due to functional redundancy under physiological conditions), but play essential roles under pathological conditions, such as cancer and cardiac disorder. Hence, generation and analysis of compound mouse mutants are expected to advance our understanding of the roles and mechanisms of miRNAs in metastatic progression, and to provide insight into clinical applications of miRNAs.

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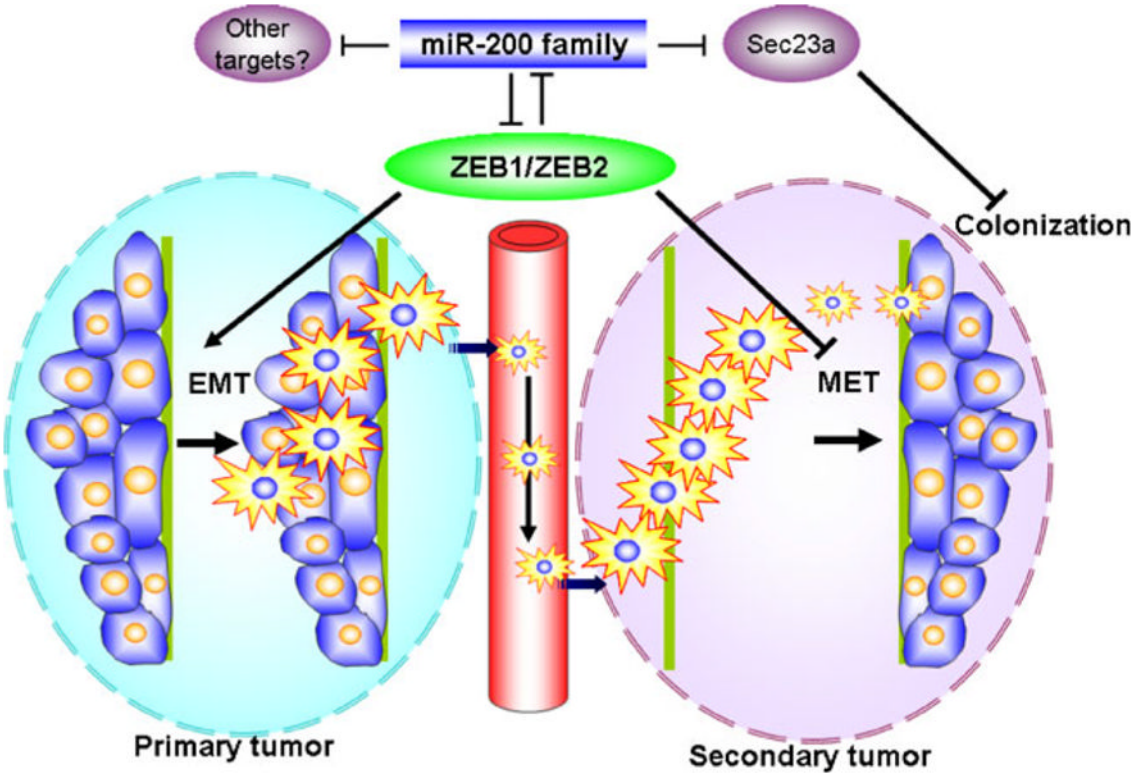

Fig. 1.
Schematic diagram of miR-200's regulation of EMT/MET and metastasis. The miR-200 family members target ZEB1/ZEB2 and Sec23a, and play opposing roles at early and late steps of metastasis

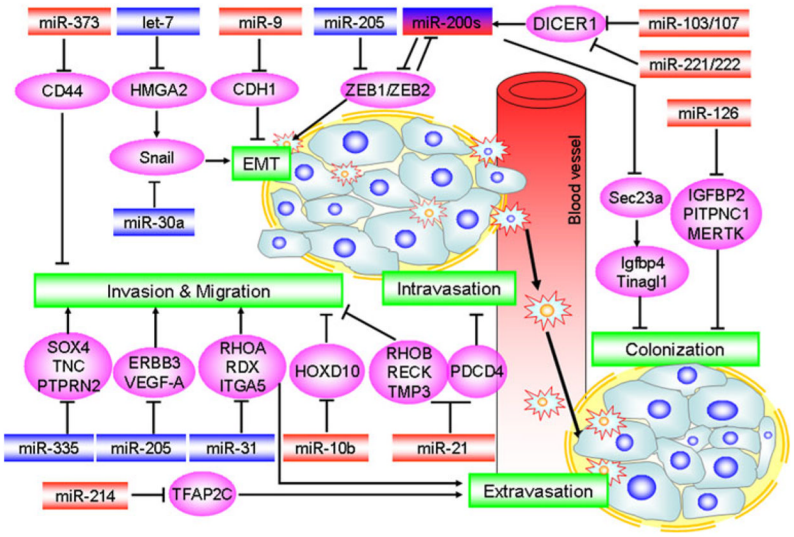

Fig. 2.

miRNAs that regulate metastasis. Metastasis consists of multiple steps: epithelial–mesenchymal transition (EMT), local invasion, intravasation, extravasation, and colonization (as indicated by *green boxes*). miRNAs and their target genes are indicated in *red*/*blue boxes* and *pink circles*, respectively. *Red box*: metastasis-promoting miRNAs; *blue box*: metastasis-suppressing miRNAs

Table 1

miRNAs involved in EMT/MET

miRNA	Effect on EMT	Target	Reference
miR-9	Promote	CDH1	[29]
miR-15b	Suppress	BMI1	[92]
miR-27	Promote	APC	[93]
miR-29a	Promote	TTP	[94]
miR-30a	Suppress	Snail	[35]
miR-103/107	Promote	DICER1	[30]
miR-155	Promote	RHOA	[34]
miR-194	Suppress	BMI1	[95]
miR-200 family	Suppress	ZEB1/ZEB2, Sec23a	[23, 25, 28, 96, 97]
miR-205	Suppress	ZEB1/ZEB2	[22]
miR-204	Suppress	TGFβR2, SNAIL2	[36]
miR-221/222	Promote	TRPS1, ESR1, DICER1	[31–33]
miR-661	Promote	StarD10, Nectin-1	[98]

Table 2

Additional miRNAs (besides those regulating EMT/MET) with functional roles in tumor invasion and metastasis

miRNA	Role in invasion/metastasis	Cancer type	Target	Reference
let-7 family	Suppress	Hepatocellular, colorectal, gastric, breast	MYC, BCL2L1, RAS, HMGA2, MMP11, PBX3, COL1A2, MYH9, RAB40C	[73, 99–104]
miR-7	Suppress	Glioblastoma, breast	Pak1, EGFR	[105, 106]
miR-10a	Promote	Pancreatic	HOXB1, HOXB3	[107]
miR-10b	Promote	Breast, nasopharyngeal, esophageal, glioblastoma	HOXD10, KLF4, LMP1, BCL2L11/Bim, TFAP2C/AP-2, CDKN1A/p21, CDKN2A/p16	[37, 40–43, 87, 108]
miR-16	Suppress	Prostate	CDK1, CDK2	[109]
miR-17–92	Promote	Breast, colorectal	CTGF, Tsp1	[110, 111]
miR-21	Promote	Breast, colorectal, gastric, lung, pancreatic, prostate, bladder, ovarian, hepatocellular	PDCD4, PTEN, CDC25A, RHOB, TIAM1, TPM1, MARCKS, NF1B, SPRY2	[46–55]
miR-22	Suppress	Breast	CDK6, SIRT1, SP1	[112]
miR-31	Suppress	Breast	RHOA, RDX, ITGA5	[60, 66–68]
miR-122	Suppress	Hepatocellular	ADAM17, RHOA, RAC1	[113, 114]
miR-126	Suppress	Breast, lung	CRK, VEGF	[61, 63, 64]
miR-146a/b	Suppress	Breast, pancreatic, glioma, prostate, gastric	EGFR, ROCK1 IRAK1, NFKB1	[115–120]
miR-194	Suppress	Liver	CDH2, DNMT3A, HBEGF	[121]
miR-206	Suppress	Breast, rhabdomyosarcoma	ESR1, MET	[122, 123]
miR-214	Promote	Melanoma	TFAP2C	[124]
miR-335	Suppress	Gastric, breast	BCL2L2, SP1, SOX4, TNC	[61, 125, 126]
miR-373	Promote	Breast, testicular germ cell	CD44, LATS2	[56, 57]
miR-378	Promote	Breast, glioblastoma	Sufu, Fus-1	[127]
miR-520c	Promote	Breast	CD44	[57]