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Post-transcriptional regulatory network of epithelial-to-mesenchymal and mesenchymal-to-epithelial transitions

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Abstract

Epithelial-to-mesenchymal transition (EMT) and its reverse process, mesenchymal-to-epithelial transition (MET), play important roles in embryogenesis, stem cell biology, and cancer progression. EMT can be regulated by many signaling pathways and regulatory transcriptional networks. Furthermore, post-transcriptional regulatory networks regulate EMT; these networks include the long non-coding RNA (lncRNA) and microRNA (miRNA) families. Specifically, the miR-200 family, miR-101, miR-506, and several lncRNAs have been found to regulate EMT. Recent studies have illustrated that several lncRNAs are overexpressed in various cancers and that they can promote tumor metastasis by inducing EMT. MiRNA controls EMT by regulating EMT transcription factors or other EMT regulators, suggesting that lncRNAs and miRNA are novel therapeutic targets for the treatment of cancer. Further efforts have shown that non-coding-mediated EMT regulation is closely associated with epigenetic regulation through promoter methylation (e.g., miR-200 or miR-506) and protein regulation (e.g., SET8 via miR-502). The formation of gene fusions has also been found to promote EMT in prostate cancer. In this review, we discuss the post-transcriptional regulatory network that is involved in EMT and MET and how targeting EMT and MET may provide effective therapeutics for human disease.

Keywords: Long non-coding RNA (lncRNA), microRNA (miRNA), Epithelial-to-mesenchymal transition (EMT), Mesenchymal-to-epithelial transition (MET)

Introduction

EMT is a process whereby epithelial cells lose both polarity and cell-to-cell contacts. Cells undergoing EMT acquire a mesenchymal phenotype, which is characterized by an epithelial-to-mesenchymal switch in marker expression, such as the loss of epithelial markers (e.g., E-cadherin, claudin, and occludin) and gain of mesenchymal markers (e.g., vimentin and N-cadherin). The reverse process, known as mesenchymal-to-epithelial transition (MET), has also been reported [1]. EMT and MET are important in organ development, stem cell biology, wound healing, and cancer progression. Many signals, transcriptional factors, and post-transcriptional regulatory networks can induce EMT. Post-transcriptional regulatory networks include the miRNA and lncRNA families. Therefore, in this review, we focus on miRNA and lncRNA, which may be effective diagnostic and therapeutic targets in cancer. Specifically, we describe several lncRNAs that regulate EMT in cancer, as well as miRNAs that regulate multiple signaling pathways involved in EMT and transcription factors of E-cadherin.

EMT and MET regulate important processes, including disease

EMT and MET have central roles in embryogenesis and cancer metastasis [2]. EMT is an integral part of tissue remodeling that occurs during embryogenesis [1]. MET also contributes to embryonic development [3]. In adults, EMT can be activated to promote wound healing after tissue injury [4]. EMT induction allows cancer cells to disseminate from the primary tumor, invade surrounding tissues, and eventually generate metastases by colonizing

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remote sites via blood or lymphatic routes. Metastatic cells can then revert back via MET to re-acquire epithelial characteristics similar to those of cells in the primary tumor [4].

EMT and MET are essential to the regulation of stem cell pluripotency [4]. Tumors contain cancer stem cells (CSCs), which are a small subpopulation of cells that are capable of self-renewal, differentiation, and tumorigenicity. Evidence suggests that EMT induction enhances self-renewal and the acquisition of CSC characteristics [5]. Thus, therapeutics that target EMT may be useful for reducing CSC populations in cancer.

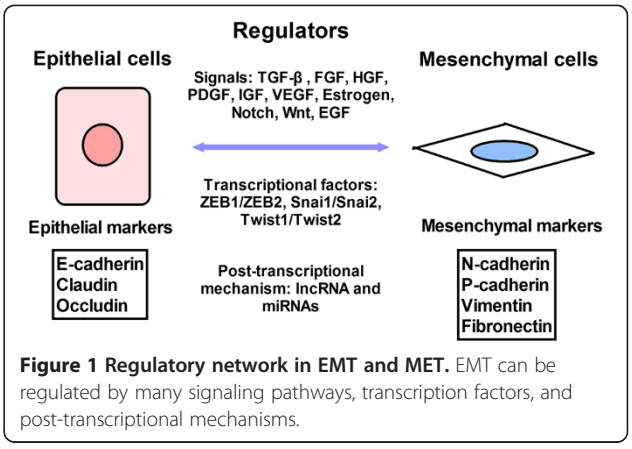

Figure 1 Regulatory network in EMT and MET. EMT can be regulated by many signaling pathways, transcription factors, and post-transcriptional mechanisms.

Key regulators involved in EMT and MET

During EMT, epithelial cells lose cell-to-cell interactions, undergo morphological challenges, and increase their cellular motility. The most important mediator of cell-to-cell adhesion is the cadherin family of proteins, which promotes the formation of adherens junctions that act as glue to hold the cells within tissues together. The most characterized cadherins include E-, N-, and P-cadherin. E-cadherin plays an important role in epithelial cell-to-cell interactions because it is responsible for holding neighboring epithelial cells together in a classic cobblestone structure. During EMT, E-cadherin is replaced by abnormal expression of N- or P-cadherin. The downregulation of E-cadherin leads to the release of β-catenin, and the latter translocates to the nucleus and functions as an activator for transcription factors, promoting cellular adhesion, tissue morphogenesis, and cancer development.

Other proteins that mediate EMT include vimentin and fibronectin. Vimentin is an intermediate filament protein that is upregulated in cells undergoing EMT. During EMT, vimentin expression causes epithelial cells to acquire a mesenchymal shape and increased motility [6]. Fibronectin mediates cellular interactions with the extracellular matrix and is important for migration, differentiation, growth, and cell adhesion. Like vimentin, fibronectin is also upregulated during EMT and can therefore be used as a biomarker for EMT (Figure 1).

EMT is regulated by many signaling pathways, transcriptional factors, and post-transcriptional factors. Many signals, including transforming growth factor-β (TGF-β), fibroblast growth factor (FGF), human growth factor (HGF), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF) (and its receptor [IGFR]), vascular endothelial growth factor (VEGF), estrogen receptor (ERα), Notch, Wnt, and epidermal growth factor (EGF) may be involved in EMT. These pathways ultimately activate the transcription of EMT-related transcription factor families, including ZEB (ZEB1 and ZEB2), the zinc finger Snail (SNAI1 and SNAI2), and the basic helix-loop-helix (e.g., Twist1 and Twist2) [7]. By regulating the expression of E-cadherin, these transcription factors dynamically modulate EMT, cell adhesion, and motility. In addition to transcription factors, EMT is regulated by post-transcriptional mechanisms, including lncRNA and miRNA (Figure 1).

Regulation of EMT by lncRNAs

LncRNA, which is larger than 200 nt, consists of a heterogeneous group of RNA molecules that are involved in a broad spectrum of cellular processes and in cancer progression [8]. Studies have demonstrated that lncRNAs are aberrantly expressed in a variety of human cancers, such as gastric cancer [9,10], bladder cancer [11,12], and breast cancer [13]. Interestingly, a recent report revealed that several lncRNAs may be involved in EMT regulation [14].

Several important lncRNAs are reported to induce EMT, including highly upregulated in liver cancer (HULC), metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1), H19, and HOX transcript antisense intergenic RNA (HOTAIR).

HULC overexpression in gastric cancer was found to be correlated with lymph node metastasis, distant metastasis, and advanced tumor node metastasis stage [9]. Silencing of HULC effectively reversed the EMT phenotype [9]. MALAT-1 expression was remarkably increased in primary tumors that subsequently metastasized compared with those that did not metastasize. MALAT-1 promoted EMT by activating Wnt signaling *in vitro* [11]. H19 enhanced bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression [12].

The expression level of HOTAIR was significantly correlated with lymph node metastasis and TNM stage in gastric cancer. The results of *in vitro* studies suggested that HOTAIR promoted EMT by regulating Snail [10]. HOTAIR remodels the gene expression pattern of breast epithelial cells into a pattern that more closely resembles that of embryonic fibroblasts, leading to increased cancer invasiveness and metastasis [13]. HOTAIR resides in the mammalian HOXC locus and recruits the polycomb repressive complex 2 to specific target genes genome

wide, leading to histone H3 lysine 27 trimethylation and epigenetic silencing of metastasis-suppressor genes.

The findings described above indicate that lncRNA has a role in tumor diagnosis and therapy. Recently, the therapeutic potential of targeting MALAT-1 was demonstrated, as free uptake of antisense oligonucleotides that target MALAT-1 in tumors prevented lung metastasis in nude mice [15]. Together, these results suggest that therapy is needed that hinders cancer progression by targeting specific lncRNAs that are implicated in EMT and therefore metastasis.

Regulation of EMT by miRNA

A second post-transcriptional mechanism that contributes to EMT involves miRNAs, which are 22-nucleotide non-coding RNAs that suppress gene expression through mRNA destabilization or translational inhibition. They are deregulated in a wide variety of human cancers [16] and have been shown to contribute to the control of cell growth, differentiation, and apoptosis, which are important to cancer development and progression [17]. MiRNAs can regulate multiple signaling pathways involved in EMT. Specifically, they can directly target transcription factors of E-cadherin and other EMT regulators.

MiRNAs regulate signaling pathways involved in EMT

Many miRNAs influence the EMT process by targeting the expression of specific ligands, receptors, and signaling pathways (Figure 2). Increasing evidence indicates that miRNAs regulate EMT by targeting key EMT regulators, including FGF (and its receptor [FGFR]), HGF, IGF (and IGFR), ERα, Notch, and Wnt. MiR-15 and miR-16 were downregulated in cancer-associated fibroblasts (CAFs) surrounding prostate tumors. This downregulation promoted tumor growth and progression through reduced post-transcriptional repression of FGF-2 and its receptor FGFR1, which act on both stromal and tumor cells to enhance cancer cell survival, proliferation, and migration [18]. Emerging evidence indicates that miR-198 is downregulated in hepatocellular carcinoma compared with in normal liver parenchyma, and forced expression of miR-198 inhibited HGF's promotion of hepatocellular carcinoma cell migration and invasion in a c-MET-dependent manner [19]. A recent report showed that miR-7 suppresses Snail, increases E-cadherin expression, and partially reverses EMT by targeting IGF1R, generating a novel miR-7/IGF1R/Snail axis in gastric cancer [20]. As we know, ERα signaling opposes EMT by inhibiting TGF-β and cytokine signaling through Smad and nuclear factor-κB. Another report demonstrated that miR-206,

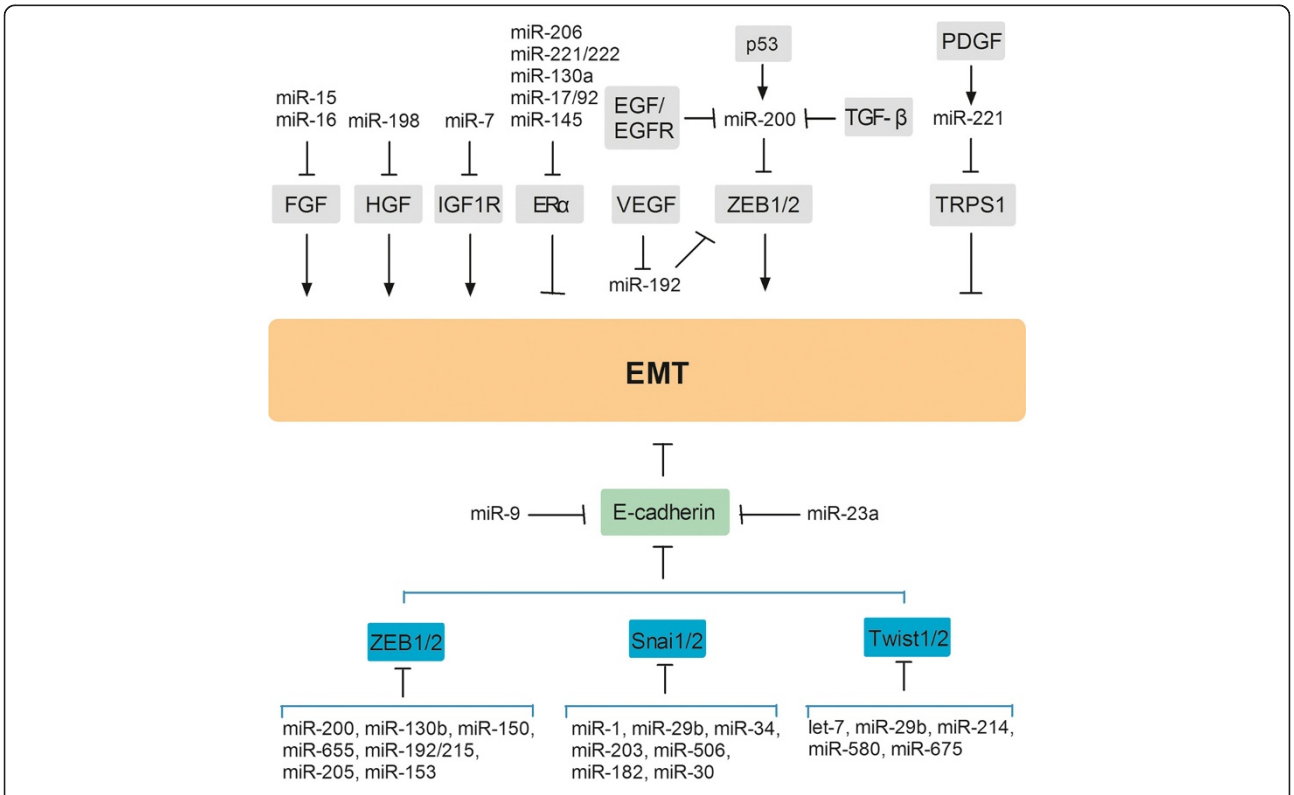

Figure 2 MiRNA-regulating signaling pathways and transcription factors are involved in EMT. MiRNA influences EMT by targeting ligands, receptors, signaling pathways and transcription factors.

miR-221, miR-222, miR-130a, miR-17, miR-92, and miR-145 could suppress ERα and promote EMT [21]. MiR-34a can regulate EMT by directly targeting Notch1 and Jagged1 [22]. Furthermore, a recent study illustrated that miR-200 members can target Jagged1, thereby mediating the downregulation of ZEB1 [23]. The Wnt/β-catenin signal pathway promotes EMT in cancer, and miR-200a was found to inhibit Wnt/β-catenin by targeting ZEB1 and ZEB2. MiR-200 can directly target β-catenin mRNA, inhibiting its translation and blocking Wnt/β-catenin signaling in meningioma [24].

MiRNA can also regulate EMT by targeting signaling pathways, including the TGF-β, PDGF, VEGF, and EGF pathways. TGF-β is a well-known EMT initiator. Exposing epithelial cells to TGF-β promotes the loss of epithelial morphological features, the increased expression of EMT marker genes such as ZEB1 and ZEB2, and the decreased expression of miR-200 [25]. Furthermore, downregulating paracrine TGF-β can inhibit and reverse EMT by downregulating ZEB1 and ZEB2 and upregulating miR-200b and miR-200c [26]. Inhibition of the Smad signaling pathway completely blocked the TGF-β1-mediated decrease in miR-200, suggesting that TGF-β1-induced suppression of the miR-200 family is regulated via Smad [27]. In addition, miR-99a and miR-99b may function as modulators within a complex network of factors that regulate TGF-β-induced EMT [28].

Anping Su et al. demonstrated that downregulation of TRPS1 by miR-221 is critical for the PDGF-mediated EMT phenotype [29]. VEGF was reported to suppress EMT by inhibiting the expression of miR-192 [30], which increases E-cadherin levels via repressed translation of ZEB2 mRNA [31]. Similarly, it was reported that EGF and EGFR can promote EMT by downregulating the miR-200 family in anaplastic thyroid cancer cells [32]. Furthermore, miR-155 overexpression suppressed EGF-induced EMT, decreased migration and invasion, inhibited cell proliferation, and increased chemosensitivity to DDP in human Caski cervical cancer cells [33]. Together, these data underscore the importance of miRNAs in EMT and malignant tumor progression.

MiRNAs that regulate E-cadherin transcription factors ZEB1 and ZEB2

The expression of E-cadherin is mainly controlled by three families of transcription factors: SNAI1 and SNAI2, ZEB1 and ZEB2, and Twist1 and Twist2. Several miRNAs directly target these families to modulate EMT in cancer (Figure 2). Members of the miR-200 family (miR-200a, miR-200b, miR-200c, miR-141, and miR-429) have emerged as important regulators of EMT, in part by targeting ZEB1 and ZEB2. Moreover, some signaling pathways, including p53, regulate EMT by regulating the miR-200-ZEB1 and ZEB2 regulatory loop.

The miR-200 family is usually downregulated in human cancer cells and tumors as a result of aberrant epigenetic gene silencing. The results of recent studies suggest that members of the miR-200 family play a critical role in suppressing EMT and cancer invasion and metastasis [34] by targeting transcriptional repressors of ZEB1 and ZEB2 [35]. Meanwhile, ZEB1 can directly suppress miRNA-200 family members in cancer cells, including miR-141 and miR-200c [36,37]. It was also reported that ZEB1 and ZEB2 repressed the expression of miR-200a, miR-200b, and miR-429 by binding to a conserved pair of ZEB-type E-box elements located proximal to the transcription start site in the promoter region [38]. Therefore, ZEB1 and ZEB2 and miR-200 family members repress expression of each other in a reciprocal feedback loop, which may lead to amplification of EMT. Targeting this loop may be a new therapeutic strategy for cancer.

Pathways that suppress EMT by upregulating miR-200 and repressing ZEB1 and ZEB2

Several molecules have been found to upregulate the miR-200 family and consequently suppress EMT. For example, both P300 and PCAF act as cofactors for ZEB1, forming a P300/PCAF/ZEB1 complex on the miR200c/141 promoter. This results in lysine acetylation of ZEB1 and releases ZEB1's suppression of miR-200c/141 transcription [39]. Smad3 was also reported to upregulate miR-200 family members at the transcriptional level in a TGF-β-independent manner [40]. p53 has been reported to transactivate miR-200 family members by directly binding to the promoters that repress ZEB1 and ZEB2 expression, leading to inhibition of EMT [41,42]. Similarly, NPV-LDE-225 suppressed EMT by upregulating E-cadherin and inhibited N-cadherin, Snail, Slug, and ZEB1 by increasing miR-200a, miR-200b, and miR-200c [43].

Pathways that promote EMT by suppressing miR-200 and upregulating ZEB1 and ZEB2

In addition to their role in regulating EMT, miR-200 family members are negatively regulated by multiple signaling pathways. For example, in one study, overexpression of Stat3 [44], PDGF-D [45], Notch-1 [46], and DCLK1 [47] in cancer cells led to significant downregulation of miR-200 family members; this resulted in upregulation of ZEB1, ZEB2, and SNAI2 expression and acquisition of the EMT phenotype. IDH1 and IDH2 mutants also caused an EMT-like phenotype; this phenotype was dependent on upregulation of the transcription factor ZEB1 and downregulation of miR-200 family members [48]. Other miRNAs can induce EMT by downregulating miR-200 through DICER, such as miR-103 or miR-107 [49]. Similarly, miR-130b silencing can restore DICER1 to a threshold level that allows miR-200 family members to repress EMT in endometrial cancer [50]. All of these

findings indicate that these molecules promote EMT by suppressing miR-200.

Fusion genes are formed when chromosomal instability causes two genes that normally exist in isolation to fuse together [51]. Interestingly, a well-known gene fusion in prostate cancer that is produced by deletion of a 3-mega base region between *ERG* and *TMPRSS2* [52] (also reviewed in [Parker 2014 Journal of Pathology]) has also been found to upregulate ZEB1 and ZEB2 expression [53]. Specifically, expression of the *TMPRSS2-ERG* fusion gene caused epithelial immortalized prostate epithelial cells to undergo morphological changes consistent with those of mesenchymal cells while downregulating expression of the epithelial marker *CDH1* [53]. This finding highlights the complex ways in which EMT can be facilitated at the genetic level, simply by the fusion of two genes.

Epigenetic regulation of miR-200

MiR-200 family members can also be epigenetically regulated. It was reported that miR-200c expression was epigenetically regulated in CRC [54]. Rui Neves et al. also showed that the miR-200c/141 cluster is repressed by DNA methylation of a CpG island located in the promoter region of these miRNAs in invasive breast cancer cells [55].

The miR-200 family consists of five members in two clusters: miR-200b ~ 200a ~ 429 and miR-200c ~ 141. Studies have illustrated DNA methylation in two regions (#1 and #2) of a 2.5-kb large CpG island that is 2 kb upstream in miR-200b ~ 429 and in smaller CpG-enriched regions associated with miR-200c ~ 141. These regions can be demethylated by 5-Aza-20-deoxycytidine and the histone deacetylase inhibitor trichostatin A [56]. Aberrant DNA methylation of the CpG island or the CpG-enriched regions is closely linked to miR-200 inappropriate silencing in cancer cells [57]. Other factors may also be involved in miR-200 repression, such as ZEB1 and Twist1. A recent study showed that induction of ZEB1 and ZEB2 increased the methylation of miR-200 promoters [58]. Twist1 was also reported to directly associate with miR-200 promoters as a transcriptional repressor of miR-200 [56] (Figure 3A).

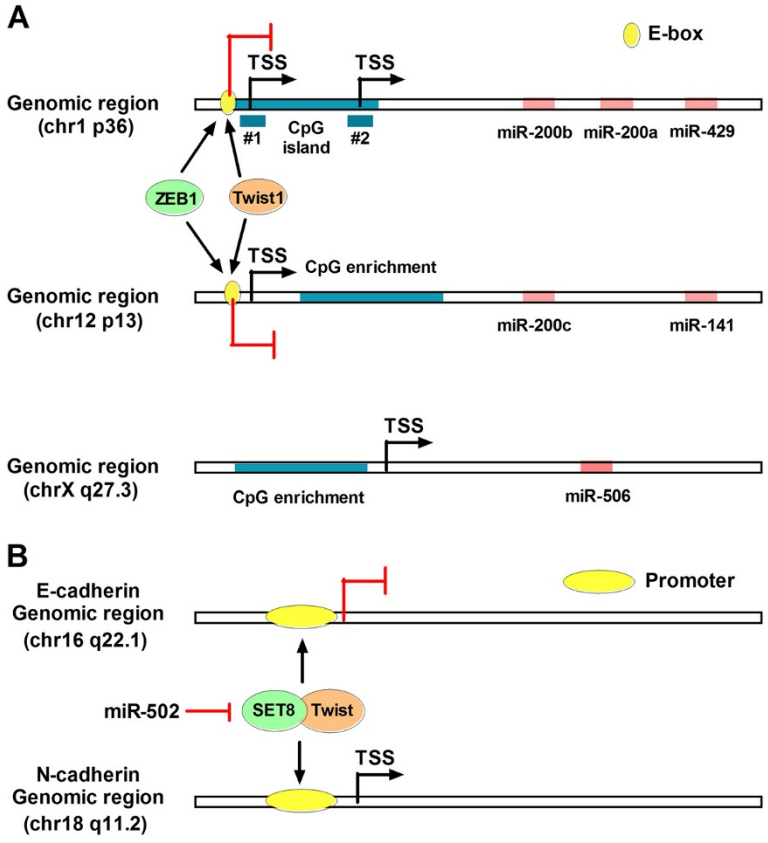

Figure 3 MiR-200 and miR-506 DNA methylation genomic loci and promoters of E- and N-cadherin. A. Graphical depiction of the miR-200b ~ 429 and miR-200c ~ 141 genomic loci, with putative transcription start sites (TSS) indicated by arrows. ZEB1 and Twist1 bound the E-box consensus in the promoters proximal to the putative miR-200 TSS and repressed miR-200 expression. The genomic position of miR-506 and five candidate methylation-regulated positions are also shown. **B**. SET8 interacted with Twist to regulate E-cadherin or N-cadherin promoter. MiR-502 suppressed SET8 directly and promoted E-cadherin expression.

MiRNAs other than miR-200 inhibit EMT by targeting ZEB1 and ZEB2

In addition to miR-200 family members, other miRNAs have been identified that regulate EMT by directly targeting ZEB1 and ZEB2. For example, miR-130b [59], miR-150 [60], and miR-655 [61] inhibit EMT by directly targeting ZEB1. Ectopic expression of miR-192 and miR-215 increased E-cadherin levels by targeting ZEB2 [31]. MiR-205, which is induced by p63, was reported to inhibit EMT by targeting ZEB1 and ZEB2 [35] in breast cancer [62] and prostate cancer [63]. MiR-153 is a novel regulator of EMT that targets ZEB2 and SNAI1 [64].

MiRNAs that regulate SNAI1 and SNAI2

MiR-34 inhibits EMT by directly targeting SNAI1 [65]. Moreover, SNAI1 can repress transcription of miR-34 genes, resulting in a SNAI1/miR-34 feedback loop that is analogous to the reciprocal ZEB/miR-200 feedback loop [66]. MiR-34 targets a set of highly conserved sites in the 3′ untranslated region (UTR) of Wnt and EMT genes, specifically *WNT1*, *WNT3*, *LRP6*, *AXIN2*, *β-catenin*, and *LEF1*, resulting in suppression of TCF/LEF transcriptional activity and the EMT process [67].

MiR-203 was found to be repressed by SNAI1 during SNAI1-induced EMT in MCF7 breast cancer cells. Meanwhile, miR-203 repressed endogenous SNAI1, forming a double-negative miR203/SNAI1 feedback loop [68]. miR-203 targeted SNAI2 [69], and SNAI2 directly bound to the miR-203 promoter to inhibit its transcription. Therefore, miR-203 also formed a double-negative feedback loop with SNAI2 in which each inhibited the other's expression, thereby controlling EMT [70]. In another double-feedback loop, miR-200 and SNAI2 regulate EMT. While SNAI2 is targeted by miR-200, SNAI2 directly binds E-boxes in the miR-200a/b promoter regions and represses miR-200a/b transcription. Therefore, SNAI2 and miR-200 act in a self-reinforcing regulatory loop that leads to amplification of EMT [71].

The results of a recent report suggest that miR-506 is a novel microRNA that inhibits EMT [72]. Integrated genomic analyses revealed a miRNA-regulatory network that is involved in EMT in serous ovarian cancer (Figure 4). MiR-506 augmented E-cadherin expression, inhibited cell migration and invasion, and prevented TGFβ-induced EMT by targeting SNAI2. MiR-506 expression is downregulated in an integrated mesenchymal subtype of serous ovarian cancer through methylation of CpG sites on the miR-506 promoter (Figure 3A). The nanoparticle delivery of miR-506 in orthotopic ovarian cancer mouse models led to E-cadherin induction and reduced tumor growth [72].

Several other miRNAs also target SNAI1 and SNAI2, such as miR-182 [69], miR-30 [73], miR-1 [71], and miR-29b [74] (Figure 2).

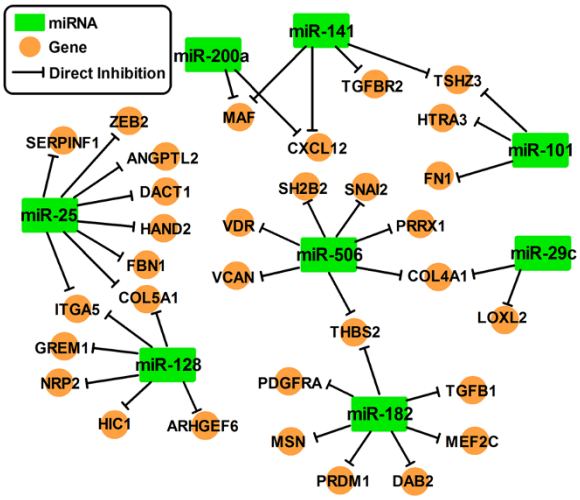

Figure 4 MiRNA-gene network involved in EMT. The miRNA-gene network shows the eight key miRNA and EMT signature genes that are predicted to be regulated. This figure is modified from one in a Cancer Cell journal paper [72].

MiRNAs that regulate Twist1 and Twist2

The transcription factor Twist is a highly conserved basic helix-loop-helix transcription factor that promotes EMT and tumor metastasis. Apart from let-7d [75], miR-29b [74], and miR-214 [76], miR-580 was also reported to act as a negative regulator of Twist1 that induces EMT in breast cancer [77]. MiR-675 similarly directly downregulates Twist1 expression, leading to EMT [78] (Figure 2).

The results of a recent study showed that SET8 promotes EMT and enhances the invasive potential of breast cancer cells in vitro and in vivo by interacting with Twist. SET8 interacts with Twist to regulate the E-cadherin or N-cadherin promoter [79]. Fengju Song *et al.* identified a single-nucleotide polymorphism within the miR-502 seed-binding region in the 3′-UTR of the *SET8* genethat modulates SET8 expression [80]. Thus, miR-502 may suppress EMT by inhibiting SET8 (Figure 3B).

MiRNAs directly regulate E-cadherin

Both miR-9 [81] and miR-23a [82] directly target E-cadherin, leading to increased cell motility and invasiveness (Figure 2). As miR-9 can be regulated by c-Myc and Prospero homeobox 1, overexpression of both [83,84] led to EMT; it also resulted in a significant decrease in E-cadherin and increase in vimentin through the upregulation of miR-9. In addition, miR-9 promoted EMT and metastasis by directly regulating KLF17 expression [85].

MiRNAs regulate vimentin and fibronectin

MiR-506 was reported to inhibit TGFβ-induced EMT by directly targeting vimentin in a human breast cancer cell line [86]. MiR-30 was reported to suppress the migratory

ability and invasiveness of breast cancer cell lines by directly targeting vimentin [87]. Furthermore, MiR-17-3p [88], as well as miR-124 and miR-203 [89], repressed vimentin expression by targeting its 3′UTR. miR-138 suppressed cell migration and invasion by directly targeting vimentin in renal cell carcinoma [90] and squamous cell carcinoma cells [91].

The results of another report suggested that miRNA-200b suppresses TGF-β1-induced EMT by directly targeting the 3′UTR of fibronectin [92]. Similarly, miR-17 resulted in decreased cell adhesion and migration by directly targeting fibronectin [93].

Since miRNAs play important roles in EMT and cancer metastasis, there is growing interest in using them in therapeutic applications [94]. Downregulation of the miRNAs that promote cancer progression may provide effective therapeutics for patients by using specific oligomers, called antagomirs that compete with the target mRNA to bind to miRNA. Krutzfeldt *et al.* found that antagomirs are powerful tools to silence specific miRNA *in vivo* and may represent a therapeutic strategy for silencing miRNAs in disease [95]. Meanwhile, the restoration of tumor-suppressive miRNA in tumors by external delivery may serve as a promising therapeutic option [96]. A report suggested that miR-200b and miR-200c were significantly associated with survival in gastric cancer patients; miR-200b suppressed ZEB1, augmented E-cadherin, inhibited cell migration, and suppressed tumor growth in a mouse model [97]. Furthermore, delivery of miR-200 members into the tumor endothelium resulted in marked reductions in metastasis and angiogenesis [98].

Conclusions and future directions

A plethora of miRNAs, including miR-200 family members and miR-506, have been found to directly regulate the expression of the target genes that are known to play critical roles in EMT regulation (Figure 4). As shown in Table 1, aside from regulating the signaling pathways and transcriptional factors described above, miRNAs regulate other genes to modulate EMT in various cancer types.

Targeting EMT and MET may provide effective therapeutics for cancer. However, therapeutic intervention may be complex because EMT occurs at an early stage of metastasis and MET occurs at later stages. MiRNAs that inhibit EMT, such as miR-141, were found in the circulation of patients with metastatic colon cancer, and high levels of plasma miR-141 were predictive of poor survival [122]. As miR-141 may promote MET, it is conceivable that miR-141 promotes tumor growth at distant sites at a late stage of metastasis, a theory that warrants further investigation. A recent report by Oscar *et al.* provided supporting evidence that MET is essential for the colonization and metastasis of differentiated carcinomas because of EMT-associated growth arrest [123]. Jeff *et al.* also demonstrated that activation of EMT promotes local tumor invasion, intravasation, and extravasation of the systemic circulation; MET is essential for establishing macrometastases [124]. As EMT is associated with decreased cell proliferation and MET promotes metastatic growth, it is still unknown whether EMT inhibition is a logical approach to preventing metastasis.

Table 1 MiRNAs that regulate EMT and their targets in different cancer types

Cancer type	miRNA	Target	Reference
Breast	miR-24	Net1A	[99]
	miR-29a	TTP	[100]
	miR-106b-25	SMAD7	[101]
	miR-221/222	TRPS1	[102]
	miR-374a	WIF1, PTEN, WNT5A	[103]
	miR-375	MTDH	[104]
	miR-448	SATB1	[105]
	miR-506	Vimentin, SNAI2, CD151	[86]
	miR-661	Nectin-1, StarD10	[106]
GC	miR-7	IGF1R	[20]
	miR-27	APC	[107]
	miR-106b-25	SMAD7	[101]
	miR-197	p120 catenin	[108]
HCC	miR-21	PTEN, hSulf-1	[109]
	miR-194	BMI-1	[110]
	miR-490-3p	ERGIC3	[111]
	miR-491	MMP-9	[112]
	miR-612	AKT2	[113]
HNSCC	miR-138	Vimentin, ZEB2, EZH2	[91]
LAD	Let-7c	Bcl-xl	[114]
Liver	miR-216a/217	PTEN, SMAD7	[115]
Lung	miR-365	HMGA2	[116]
Melanoma	miR-137	CtBP1	[117]
NSCLC	miR-134	FOXM1	[118]
	miR-149	FOXM1	[119]
Ovarian	miR-187	Dab2	[120]
Pancreatic	miR-126	ADAM9	[121]

Abbreviations: Net1A Neuroepithelial cell transforming 1, *TTP* Tristetraprolin, *TRPS1* Trichorh inophalangeal 1, *WIF1* Wnt inhibitory factor-1, *MTDH* Metadherin, *SATB1* Special AT-rich sequence-binding protein-1, *GC* Gastric cancer, *IGF1R* Insulin-like growth factor-1 receptor, *APC* Adenomatous polyposis coli, *HCC* Hepatocellular carcinoma, *hSulf-1* Human sulfatase-1, *BMI-1*, B lymphoma mouse Moloney leukemia virus insertion region 1, *ERGIC3* Endoplasmic reticulum-Golgi intermediate compartment protein 3, *HNSCC* Head and neck squamous cell carcinoma, *LAD* Lung adenocarcinoma, *CtBP1* Carboxyl-terminal binding protein 1, *NSCLC* Non-small cell lung cancer, *FOXM1* Forkhead box M1, *Dab2* Disabled homolog-2, *ADAM9* Disintegrin and metalloproteinase domain-containing protein 9.

Most studies have shown that, as post-transcriptional regulators, lncRNA and miRNA play important roles in EMT and are important markers and tools in cancer diagnosis, prognosis, and therapeutics. However, lncRNA and miRNA have multiple targets that are involved in multiple different physiological processes; therefore, the role of therapeutics that target lncRNA or miRNA should be validated *in vivo* to determine their overall physiological effect.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
All authors contributed to discussing and writing this manuscript. All authors have read and approved the final manuscript.

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