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Regulation of Mesenchymal Phenotype by MicroRNAs in Cancer

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Abstract

Epithelial-mesenchymal transition (EMT) is a developmental process that converts epithelial cells into migratory and invasive cells. This process also plays an important role in cancer progression and metastasis by enabling tumor cells to leave primary sites. EMT is regulated by complex transcription networks and post-transcriptional modulators. MicroRNAs are single-stranded non-coding RNAs that represent a novel class of gene regulators. It has been shown that microRNAs are critical regulators of EMT process. The molecular mechanisms of EMT modulation by microRNAs include the suppression of transcription factors that directly regulate EMT and the down-regulation of cellular genes and pathways that are indirectly involved in EMT process. The expressions of microRNAs that control EMT process are dysregulated in cancer. In this review, we summarize the recent progress of microRNAs in EMT regulation.

Keywords

microRNA; cancer; epithelial-mesenchymal transition; transcription; non-coding RNA; migration

INTRODUCTION

EMT is an essential process in tissue generation during embryogenesis [1, 2]. EMT is also involved in wound healing and cancer progression [3, 4]. Specifically, EMT plays an important role in metastasis, a complex process starting from tumor cell invasion into neighboring tissue to outgrowth of macrometastases in the secondary organs, responsible for most cancer deaths in patients [2–4]. Cells undergoing EMT demonstrate three major changes: morphological change from cobble-stone-like epithelial cells to elongated mesenchymal cells; decreased expression of epithelial markers such as E-cadherin and increased expression of mesenchymal markers such as vimentin; and increased motility and invasive capability [1–4]. EMT is considered a reversible reprogramming of epithelial cells [1–4]. Mesenchymal-epithelial transition (MET) is the reverse process, critical for cell differentiation and macrometastatic growth [1–4].

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CONFLICT OF INTEREST

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TRANSCRIPTIONAL REGULATION OF EPITHELIAL-MESENCHYMAL TRANSITION

EMT is known to be regulated by transcriptional network [5, 6]. Several transcription factors have been shown to regulate EMT process. SNAIL family members such as SNAI1 (Snail) and SNAI2 (Slug) maintain the plasticity of stem cells in epithelial compartment [7–10]. They directly regulate epithelial marker CDH1 (E-cadherin) expression at the transcriptional level and induce EMT in cancer progression [7–10]. ZEB family members ZEB1 and ZEB2 bind to the promoter of CDH1 and suppress E-cadherin expression, thus promoting tumor metastasis [11, 12]. Krüppel-like factor family members KLF17 and KLF8 regulate EMT in opposite directions. KLF17 suppresses EMT by repressing another transcription factor Id1 whereas KLF8 induces EMT by repressing E-cadherin expression directly [13, 14]. Other transcription factors involved in EMT process include TWIST, E47, fork-head box protein C2 (FOXC2), Goosecoid, E2-2, homeobox protein SIX1 and paired mesoderm homeobox protein 1 (PRRX1) [15–21]. They regulate EMT through various mechanisms that cause epithelial cells to demonstrate partial or full EMT characteristics [15–21]. In addition, several transcription factors have been found to promote MET process. Grainyhead-like 2 (GRHL2) and ELF5 induce MET by suppressing ZEB1 and SNAI2 respectively when they are over-expressed in mesenchymal cells [22, 23].

In addition to the transcriptional control of EMT, post-transcriptional regulation is also involved in EMT process. RNA binding proteins epithelial splicing regulatory protein 1 (ESRP1) and 2 (ESRP2) were shown to regulate the specific splicing of epithelial isoform CTNND1, which stabilizes E-cadherin at the plasma membrane [24]. Translation of the transcription factors that control EMT such as SNAI1, ZEB2 and TWIST can be enhanced by the expression of Y-box binding protein 1 (YB1) which promotes the translation of these factors through ribosome entry site driven translation initiation [25].

EMT REGULATION BY MicroRNAs

MicroRNAs (miRNAs) are single-stranded non-coding RNAs of 21–23 nucleotides, representing a novel class of gene regulators that function by binding their target messenger RNAs (mRNAs) leading to either suppression of their translation and/or acceleration of their degradation [26, 27]. miRNAs are transcribed by RNA polymerase II as primary transcripts (pri-miRNAs) that require subsequent processing to yield a functional mature miRNA [28]. Pri-miRNAs are processed into shorter stem-loop-structured double-stranded RNAs called precursor miRNA (pre-miRNAs) in the nucleus by a protein complex containing the RNase III enzyme Drosha and DGCR8 (in vertebrates) or Pasha (in invertebrates) [29–31]. Pre-miRNAs are then transported from the nucleus to the cytoplasm and are processed further into mature miRNAs by another RNase III enzyme Dicer [32–36]. Mature miRNAs are incorporated into the effector complex called the RNA-induced silencing complex (RISC) to target single-stranded complementary mRNAs for translational repression or mRNA degradation [37–41]. In miRNA sequences, the 5' seed region (from position 2 to position 8 of mature miRNA) is particularly important for target site recognition, but sequence context and base pairing between regions in the other half of the miRNA and the target site can also contribute to the binding of miRNAs and their target mRNAs [42–44].

It is estimated that some miRNAs control hundreds of gene targets and are involved in the regulation of about 30% of all genes and almost every genetic pathway [43]. They play a critical role in development and physiological processes including EMT [45, 46]. The human miR-200 family, consisting of five family members in two clusters, miR-200a, miR-200b and miR-429 on chromosome 1, and miR-200c with miR-141 on chromosome 12, is prominent in EMT regulation. They share a consensus seed sequence and are expressed as polycistrons [47]. They have been shown to suppress EMT and promote MET by targeting EMT transcription regulator ZEB1 and ZEB2 [47–49]. Interestingly, ZEB1 suppresses miR-200 family expression forming a negative feedback loop by directly binding to the promoter region of miR-200 [50, 51]. In addition to the function of EMT suppression, miR-200 family also promotes macrometastatic growth by promoting MET [52]. Overexpression of miR-200 in mouse mammary tumor 4TO7 cells, which form micrometastases but not macrometastases in lung, promote MET in metastatic cells and thus macrometastases growth [52]. These functions are mediated by directly targeting Sec23a which regulates the secretion of metastasis-suppression protein TINAGL1 and IGFBP4 [52]. These studies demonstrated that the downregulation of miR-200 expression promotes EMT in the early steps of metastasis, but increased expression of miR-200 promoting MET and macrometastatic growth in the later steps of metastasis, thus suggesting that the plasticity of epithelial-mesenchymal state of cancer cells are critical in metastasis process. Similarly to the function of miR-200 family in EMT, miR-205 has been shown to suppress EMT by directly targeting ZEB1 [48]. Downregulation of miR-200 and miR-205 by epigenetic regulation has been shown to be associated with the transformation of epithelial cells [53]. In prostate cancer, miR-205 expression is silenced by promoter hypermethylation [54]. MiR-200 family expression is suppressed in metastatic breast cancer and lung cancer, and its low expression is associated with worse clinical outcomes [48, 55]. In colon cancer, miR-200 expression is decreased at the invasion front of primary tumors, but increased in metastatic tumors [56, 57]. These clinical observations indicate that miR-200 family and miR-205 play critical roles in various stages of cancer progression.

In addition to miR-200 and miR-205, other microRNAs are also involved in EMT regulation (Table 1). MiR-9 promotes EMT and cell invasion by directly suppressing the expression of E-cadherin [58]. MiR-21 promotes EMT and the acquisition of luminal markers in prostate cancer cells by suppressing B cell translocation gene 2 (BTG2) [59]. MiR-29a promotes EMT and metastasis by directly suppressing tristetraprolin (TTP) in cooperation with Ras signaling [60]. Downregulation of miR-101 causes E-cadherin dysregulation by increasing the expression of EZH2 [61]. MiR-103/107 family reduces microRNA biogenesis including miR-200 expression by directly targeting Dicer, thus promoting tumor metastasis in breast cancer [62]. MiR-155 is required for EMT and cell invasion phenotypes induced by TGF- β 3 [63]. MiR-216a induces EMT and drug resistance in liver cancer by directly targeting PTEN and SMAD7 [64]. The miR-221/222 cluster induces EMT in breast cancer cells by directly targeting Dicer, estrogen receptor ESR1 and trichorhinophalangeal syndrome type 1 (TRPS1) [65–67]. MiR-661 promotes EMT and cell invasion in breast cancer cells by directly targeting Nectin1 and StarD-10 [68]. In contrast, miR-15b and miR-194 suppress EMT in human tongue and endometrial cancer cells by directly suppressing BMI1 [69, 70]. MiR-30a represses EMT in non-small cell lung cancer by directly inhibiting the expression

of EMT transcriptional regulator SNAI1 [71]. MiR-204 suppresses EMT in retinal pigment epithelium by directly repressing the expression of TGF3R2 and SNAI2 [72]. MiR-612 suppresses EMT and metastasis in hepatocellular carcinoma by directly targeting AKT2 [73]. Similar to EMT regulation, microRNAs also play critical roles in MET process. MiR-182 and 203 promotes MET in prostate cancer by suppressing the expression of SNAI2 [74].

CONCLUSIONS

EMT has been associated with many aspects of cancer progression including resistance to senescence and cell death, stem cell characteristics, drug resistance, migration, invasion and metastasis. Regulation of EMT process is delicate and involves mechanisms in almost every level of gene expression regulation, transcriptionally and post-transcriptionally. Transcription factors and microRNAs are major classes of regulators that are critical in EMT process. Better understanding of EMT regulation will provide diagnostic and prognostic biomarkers for cancer and provide therapeutic targets for metastatic diseases.

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Table 1

MicroRNA in EMT and MET

miRNA Promoting EMT	Target	Reference
miR-9	E-cadherin	[56]
miR-21	BTG2	[57]
miR-29a	TTP	[58]
miR-101	EZH2	[59]
miR-103/107	Dicer	[60]
miR-155	RhoA	[61]
miR-216a/217	PTEN, SMAD7	[62]
miR-221/222	TRPS1, Dicer, ESR1	[63–65]
miR-661	Nectin1, StarD-10	[66]
miRNA suppressing EMT	Target	Reference
miR-15b	BMI1	[67]
miR-30a	SNAI1	[69]
miR-194	BMI1	[68]
miR-200 family	ZEB1, ZEB2	[45–47]
miR-204	TGF β R2, SNAI2	[70]
miR-205	ZEB1	[46]
miR-612	AKT2	[71]
miRNA promoting MET	Target	Reference
miR-182	SNAI2	[72]
miR-200 family	Sec23a	[50]
miR-203	SNAI2	[72]