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Review

Missing Links in Epithelial-Mesenchymal Transition: Long Non-Coding RNAs Enter the Arena

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Abstract
Cancer metastasis occurs through a series of sequential steps, which involves dissemination of tumor cells from a primary site and colonization in distant tissues. To promote the invasion-metastasis cascade, carcinoma cells usually initiate a cell-biological program called epithelial-mesenchymal transition (EMT), which is orchestrated by a set of master regulators, including TGF-β, Snail, ZEB and Twist families. The biological activities of these molecules are tightly regulated by a variety of cell-intrinsic pathways as well as extracellular cues. Recently, accumulating evidence indicates that long non-coding RNAs (lncRNAs) represent some of the most differentially expressed transcripts between primary and metastatic cancers. LncRNAs including MALAT1, HOTAIR, H19, LncRNA-ATB, and LincRNA-ROR have been reported to be involved in the process of EMT, mainly through cross-talking with master regulators of EMT. Thus, understanding the different and precise molecular mechanisms by which functional lncRNAs switch EMT on and off is important for opening up new avenues in lncRNA-directed diagnosis, prognosis, and therapeutic intervention against cancer.

Introduction

The epithelial-mesenchymal transition (EMT), initially recognized as essential during embryonic development, has more recently been implicated in promoting carcinoma invasion and metastasis. The full accomplishment of the EMT process requires a complex genetic program that, together with the loss of the epithelial character, implies the acquisition of mesenchymal and motility properties. EMT can be exploited by normal or

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tumor epithelial cells to enable them to dissociate from their neighbours and migrate [1]. Several transcription factors have been identified as master regulators of EMT, including Snail, ZEB and Twist families, and their expression is tightly regulated at different steps of transcription, translation and protein stability control by a variety of cell-intrinsic pathways as well as extracellular cues [2]. A full understanding of the gene regulation network during this transition is essential but still far beyond completion.

Long non-coding RNAs (lncRNAs) are a large class of transcripts longer than 200 nucleotides with limited protein coding potential [3]. Presently, only a small number of lncRNAs have been characterized functionally, and most of them are shown to exert their effects by regulating various aspects of gene expression, such as transcription, splicing, translation, protein stability control, etc [4-10] (Fig. 1). Many lncRNAs are shown to regulate important cancer hallmarks, including proliferation [11], senescence [12], apoptosis [13], metablism [14], drug-resistance [15], and metastasis [16, 17]. Metastases are the major cause of death from cancer [18] and probably derived from primary tumor cells that have undergone EMT [19]. Recently, an increasing number of studies report that lncRNAs represent some of the most differentially expressed transcripts between primary and metastatic cancers [20, 21]. Therefore, the crosstalk between lncRNAs and EMT regulators is an important topic in the field of cancer metastasis, and lncRNAs may be the missing links in the well-known EMT networks.

Here, we provide updated and new perspectives on recent advances made in understanding lncRNA mechanisms underlying EMT and tumor metastasis. We highlight, when possible, the mechanisms by which the lncRNAs function and how they are themselves regulated. We explore several known lncRNAs, which may potentially be involved in EMT as well as those which have only recently been discovered and provide interesting targets for further characterization.

LncRNAs involved in EMT and tumor metastasis

MALAT1

Metastasis-associated lung adenocarcinoma transcript 1(MALAT1), also known as NEAT2, is one the most well-known lncRNAs which have an important role in metastasis. Early report showed that patients with non-small cell lung cell cancer (NSCLC) exhibiting high expression of the MALAT1 transcript were five times more likely to develop metastasis compared to those with low expression [22]. Since this discovery, investigations have been initiated to characterize the MALAT1 transcript and the mechanisms by which it functions. MALAT1 is highly conserved amongst mammals and highly expressed in the nucleus [23]. It regulates the expression of metastasis-associated genes [24] and enhances cell motility by influencing the expression of motility-related genes [25]. Interestingly, recent data revealed that MALAT1 could facilitate tumor metastasis by promoting EMT properties. For example, Ying and colleagues found that MALAT1 expression was remarkably increased in metastatic bladder cancer compared with primary tumors. Using an *in vitro* model, they demonstrated that MALAT1 promoted EMT by activating Wnt signaling. Downregulation of MALAT1 resulted in a decrease of the EMT-associated ZEB1, ZEB2 and Slug levels, and an increase of E-cadherin levels [26]. Mechanistic study revealed that MALAT1 is associated with suppressor of zeste 12(SUZ12) and this association results in decrease of E-cadherin expression and increase of N-cadherin and fibronectin expression [27]. Moreover, MALAT1 was reported to upregulate Snail expression to promote EMT process in colon cancer [28]. Recent studies also showed that MALAT1 could function as a competitive endogenous RNA (ceRNA) for multiple EMT-suppressive miRNAs, such as miR-200c in endometrioid endometrial carcinoma [29], miR-124 in nasopharyngeal carcinoma [30], and miR-218 in colorectal cancer [31]. In another study conducted in patients with NSCLC, Shen and colleagues discovered that MALAT1 promoted lung cancer brain metastasis via the induction of EMT [32]. However, a recent study demonstrated that, by forming a ribonucleic complex with the RNA-binding protein

HuR, MALAT1 binds the CD133 promoter region to repress its expression and suppresses EMT in breast cancer (Fig. 2b, ii) [33]. Thus, further studies are necessary to understand the precise role of MALAT1 in EMT and metastasis and the molecular determinants of its function.

HOTAIR

HOX transcript antisense intergenic RNA (HOTAIR), one of the first lncRNAs described to have a fundamental role in cancer metastasis, is located in the HOXD locus and exhibits cell-type and tissue-specific expression patterns [34]. HOTAIR expression is upregulated in malignant tissues and is associated with an increase in invasion and metastasis in breast, lung, colorectal, and hepatocellular carcinoma [35-38]. Mechanistic study revealed that enforced expression of HOTAIR in epithelial cancer cells induced genome-wide re-targeting of Polycomb repressive complex 2 (PRC2) to an occupancy pattern more resembling embryonic fibroblasts, leading to altered histone H3 lysine 27 methylation and gene expression [35]. Similar to MALAT1, recent data demonstrated that HOTAIR overexpression is also closely related to enhanced EMT characteristics. A study conducted by Padua et al. revealed that HOTAIR is required for EMT and stemness maintenance of cancer cell lines [39]. They found that treating cells with transforming growth factor-beta (TGF-β) resulted in increased HOTAIR expression and triggered the EMT program, while ablation of HOTAIR expression by siRNA prevented the EMT program stimulated by TGF-β1. In another study conducted in colon cancer cell lines, Wu et al. found that depletion of HOTAIR led to increased expression of E-cadherin and downregulation of Vimentin and MMP9, suggesting that HOTAIR may be a pleiotropic modulator participating in EMT [40]. Further study revealed that HOTAIR-PRC2 complex epigenetically silences a tumor-suppressive microRNA miR-34a, which controls the downstream targets c-Met (HGF/c-Met/Snail pathway) and Snail, thus contributing to the process of EMT and tumor metastasis in gastric cancer (Fig. 2b, i) [41]. Moreover, Wu et al. demonstrated that HOTAIR contributes to the direct suppression of E-cadherin by recruiting enhancer of zeste homolog 2 (EZH2) to the E-cadherin promoter [42]. Supporting evidence were found that HOTAIR expression levels were negatively correlated with those of E-cadherin in gastric cancer and oral squamous cell carcinoma tissues [41, 42]. Besides, Hong et al. demonstrated that HOTAIR also functions as a ceRNA for miR-217, thus regulating HIF-1α/AXL signaling and promoting EMT process in renal cell carcinoma [43]. Despite much progress in recent years, our knowledge of the relationship between HOTAIR and EMT is still unsatisfactory and further studies are necessary to understand the precise role of HOTAIR in the process of EMT.

H19

The H19 gene belongs to a highly conserved imprinted gene cluster that plays important roles in embryonal development and growth control. H19 expression is strongly induced during embryogenesis and downregulated after birth, except in adult skeletal muscle and heart. Over the last decade, a role for H19 acting either as a tumor suppressor [44] or an oncogene [45] has been reported. Since then, accumulating evidence suggests that H19 is also significantly associated with EMT process and tumor metastasis. In a study conducted in hepatocellular carcinoma (HCC), Zhang et al. revealed that H19 associates with the protein complex hnRNP U/PCAF/RNApol II and activates miR-200 family (pivotal repressors of EMT [46]) by increasing histone acetylation, thus contributing to mesenchymal-to-epithelial transition (MET) and suppression of tumor metastasis [47]. In another study conducted in prostate cancer, Zhu et al. found that H19 and H19-derived miR-675 were significantly downregulated in the metastatic prostate cancer cell line compared with the non-metastatic prostate epithelial cell line. Ectopic expression of H19 resulted in increased level of miR-675, which directly binds to the 3'UTR of TGFBI (an extracellular matrix protein involved in EMT and cancer metastasis) mRNA to repress its translation [48]. However, several other works demonstrated that H19 may promote the EMT process rather than impeding it [49, 50]. Luo et al. found that H19 levels are remarkably upregulated in bladder cancer tissues, and ectopic

expression of H19 promotes bladder cancer cell migration *in vitro* and *in vivo*. Mechanistic study demonstrated that H19 is associated with EZH2, which results in Wnt/β-catenin activation and subsequent repression of E-cadherin [49]. Moreover, Matouk et al. found that H19 expression level was tightly correlated with tumor metastatic potential and numerous established inducers of EMT (such as TGF-β and hypoxia) could upregulate H19 and miR-675 concomitantly with the induction of EMT markers. Through a mechanism involving miR-675, H19 upregulated Slug expression and decreased E-cadherin protein level. Interestingly, Slug also activated the promoter of H19 gene and upregulated its expression, thus forming a positive feedback loop between Slug and H19/miR-675, which regulates E-cadherin expression [50]. In a recent study, Zhou et al. revealed that H19 could mediate breast cancer cell plasticity during the EMT and MET processes by differentially sponging miR-200b/c and let-7b [51]. Taken together, the above data suggest that the functional role that H19 exerts in EMT and tumor metastasis is context-dependent and should be investigated carefully.

LncRNA-ATB

LncRNA activated by TGF-β (LncRNA-ATB) was recently described to promote the invasion-metastasis cascade in HCC [52]. As its name suggests, LncRNA-ATB is induced by TGF-β in multiple cancer types, including breast, colorectal, gastric, and hepatocellular carcinoma [52-55]. LncRNA-ATB plays an essential role in both the early-stage invasion process and the late-stage colonization phase of metastasis *in vivo* [52]. Mechanistic study demonstrated that the functional role that LncRNA-ATB plays in early-stage invasion is closely related to the EMT process. By competitively binding the miR-200 family, LncRNA-ATB upregulated ZEB1 and ZEB2 expression and then induced EMT (Fig. 2b, iii). Depletion of LncRNA-ATB abrogated TGF-β-induced EMT *in vitro* and decreased the number of circulating tumor cells (CTCs) in whole blood from orthotopic tumor models *in vivo*, in a miR-200-dependent manner. However, miR-200 overexpression only partially rescued LncRNA-ATB-induced metastasis *in vivo*, indicating the involvement of additional downstream players. Indeed, LncRNA-ATB stabilized interleukin-11 (IL-11) mRNA and elevated IL-11 secretion, thus activating STAT3 signaling which promotes organ colonization of disseminated tumor cells [52]. In another study conducted in HER2-positive breast cancer, Shi et al. found that LncRNA-ATB was remarkably upregulated in trastuzumab-resistant breast cancer cell lines and tissues. They demonstrated that LncRNA-ATB could promote trastuzumab resistance and invasion-metastasis cascade in HER2-positive breast cancer by competitively binding miR-200c, thus upregulating ZEB1 and ZNF-217, and then inducing EMT [53]. Despite much progress in recent years, our knowledge of the relationship between LncRNA-ATB and EMT is still limited and further studies are necessary to understand the versatile roles exerted by LncRNA-ATB.

LincRNA-ROR

First identified as a lincRNA whose expression is linked to pluripotency [56], lincRNA-regulator of reprogramming (LincRNA-ROR) is now considered to play a crucial role in the process of EMT and tumor metastasis. High expression of LincRNA-ROR is observed in multiple cancer types, including breast, bladder, and nasopharyngeal carcinoma [57-59]. Ectopic expression of LincRNA-ROR in cancer cells was associated with enhanced migration, invasion and EMT *in vitro* and metastasis *in vivo*. Mechanistically, The EMT-promoting effects of LincRNA-ROR are mostly attributed to its function as a miRNA sponge for several key miRNAs. One such miRNA is miR-205, a tumor-suppressive miRNA which targets ZEB1 and ZEB2. Silencing of LincRNA-ROR promoted the degradation of miR-205 target genes, resulting in impaired EMT and metastatic potential [57]. miR-145, a well-known miRNA commonly downregulated in various cancers [60], is another miRNA that can be competitively absorbed by LincRNA-ROR. In a study conducted in triple-negative breast cancer, Eades et al. found that LincRNA-ROR could competitively bind miR-145, which targets small GTPase ADP-ribosylation factor 6 (ARF6), leading to enhanced endocytosis of E-cadherin and reduced cell-cell adhesion [61]. It is worth noting that LincRNA-ROR transcripts were quite abundant

Table 1. LncRNAs involved in EMT and tumor metastasis

LncRNA	Description	Changes in cancer	Expression correlation with tumor metastasis	Known molecular mechanisms	References
BANCR	BRAF-activated non-coding RNA	Up/Down	Positive/ Negative	Activates the ERK pathway/ Upregulates E-cadherin, downregulates N-cadherin and Vimentin	Melanoma [63], CRC [64], NSCLC [65]
CCAT1	Colon cancer associated transcript-1	Up	Positive	Upregulates CCND1/ Acts as a ceRNA for miR-181b	CRC [66], Pancreatic [67], Glioma [68]
CCAT2	Colon cancer associated transcript-2	Up	Positive	Upregulates ZEB2, N-cadherin and Vimentin, downregulates E-cadherin	Prostate [69], Glioma [70], Gastric [71]
GHET1	Gastric carcinoma highly expressed transcript 1	Up	Positive	Physically associates with IGF2BP,increases the stability of c-Myc	Gastric [72], Bladder [73]
H19	H19, imprinted maternally expressed transcript	Up/Down	Positive/ Negative	Activates miR-200 family/ Upregulates miR-675 to repress TGFBI expression/ Activates the Wnt/β-catenin pathway/ Upregulates Slug, downregulates E-cadherin/ Acts as a ceRNA for let-7b, miR-200b/c, and miR-141	HCC [47], Prostate [48], Bladder [49], Breast [50,51] Gastric [74]
HNF1A-AS1	HNF1A antisense RNA 1	Up	Positive	Upregulates H19, modulates chromatin and nucleosome assembly/ Upregulates CCND1, N-cadherin and β-catenin, downregulates E-cadherin	EAC [75], LAC [76]
HOTAIR	HOX transcript antisense RNA	Up	Positive	Activated by TGF-β/ Silences miR-34a by binding to PRC2/ Upregulates Vimentin and MMP9, downregulates E-cadherin/ Acts as a ceRNA for miR-217 to upregulate HIF-1α	Breast [35,39], Colon [36,40], Gastric [41], OSCC [42], RCC [43], NSCLC [77]
HOTTIP	HOXA distal transcript antisense RNA	Up	Positive	Upregulates HOXA9 by forming Twist1-WDR5-HOTTIP complex/ Upregulates HOXA13	Prostate [78], Pancreatic [79]
HULC	Highly up-regulated in liver cancer	Up	Positive	Acts as a ceRNA for miR-200a to upregulate ZEB1	Gastric [80], HCC [81]
LincRNA-ROR	LincRNA-Regulator of reprogramming	Up	Positive	Acts as a ceRNA for miR-205 to upregulate ZEB2/ Acts as a ceRNA for miR-145 to upregulate ARF6	Breast [57,82], Pancreatic [83]
LncRNA-ATB	LncRNA-activated by TGF-β	Up	Positive	Acts as a ceRNA for miR-200 family to upregulate ZEB1, ZEB2 and ZNF217	HCC [52], Breast [53], CRC [84]
LncRNA-EBIC	EZH2-binding lncRNA in cervical cancer	Up	Positive	Binds to EZH2 and represses E-cadherin	Cervical [85]
LncRNA-Hh	Hedgehog signaling associated lncRNA	Up	Unknown	Induced by Twist, directly targets GAS1 to activate hedgehog signaling	Breast [86]
LncRNA-HIT	HOXA-associated transcript induced by TGF-β	Up	Positive	Activated by TGF-β, downregulates E-cadherin	Breast [87]
lncTCF7	WNT Signaling Pathway Activating Non-Coding RNA	Up	Positive	Activated by IL/STAT3 signaling, upregulates Vimentin, downregulates E-cadherin	HCC [88]
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1	Up	Positive	Activated by TGF-β/ Associates with SUZ12 to repress E-cadherin and upregulate N-cadherin and fibronectin/ Forms HuR-MALAT1 complex to repress CD133 Expression	NSCLC [22,32], Bladder [26,27], OSCC [89]
MEG3	Maternally expressed gene 3	Down	Negative	Silences E-cadherin and miR-200 family by binding to JARID2 and EZH2/ Inhibits Rac1 at posttranscriptional level / Acts as a ceRNA for miR-421 to upregulate E-cadherin	Lung [90], Breast [91], Thyroid [92]
NEAT1	Nuclear enriched abundant transcript 1	Up	Positive	Upregulates β-catenin and N-cadherin, downregulates E-cadherin/ Upregulates ZEB1 by repressing miR-204	ccRCC [93], NPC [94], Breast [95]
PlncRNA-1	NA	Up	Positive	Upregulates Vimentin and N-cadherin, downregulates E-cadherin	HCC [96]
PVT1	Plasmacytoma variant translocation 1 gene	Up	Positive	Upregulates ZEB1, Snail and N-cadherin, downregulates p21 and E-cadherin	Pancreatic [97], Esophageal [98]
SNHG6	Small Nucleolar RNA Host Gene 6	Up	Positive	Acts as a ceRNA for miR-101 to upregulate ZEB1	Gastric [99]
SPRY4-IT1	SPRY4 intronic transcript 1	Up/Down	Positive/ Negative	Epigenetically silenced by EZH2/ Downregulates E-cadherin, upregulates Vimentin	NSCLC [100], Gastric [101], Glioma [102]
TUG1	Taurine up-regulated gene 1	Up	Positive	Activated by TGF-β/ Acts as a ceRNA for miR-145 to upregulate ZEB2/ Acts as a ceRNA for miR-300	CRC [103], Bladder [104], Gallbladder [105]
treRNA	Translational regulatory lncRNA	Up	Positive	Suppresses the translation of E-cadherin mRNA/ Silenced by miR-190a at posttranscriptional level	Breast [106], HCC [107]
UCA1	Urothelial cancer associated 1	Up	Positive	Activated by TGF-β/ Acts as a ceRNA for miR-145 to upregulate ZEB1 and ZEB2/ Upregulates N-cadherin, Vimentin and Snail, downregulates E-cadherin	Bladder [108], Breast [109], Gastric [110]
ZEB1-AS1	ZEB1 antisense RNA 1	Up	Positive	Upregulates ZEB1 via enhancer-like mechanisms/ Upregulates MMP2, MMP9, N-cadherin, and Integrin-β1, downregulates E-cadherin	HCC [111], Glioma [112]
ZFAS1	ZNFX1 antisense RNA 1	Up	Positive	Acts as a ceRNA for miR-150 to upregulate ZEB1, MMP14 and MMP16/ Downregulates E-cadherin and ZO-1,Upregulates Vimentin and N-cadherin	HCC [113], Gastric [114], Colon [115]

in the cytoplasm of self-renewing embryonic stem cells (ESCs) [62], which supports the hypothesis that LincRNA-ROR interacted with miRNAs in the cytoplasm. However, other potential mechanisms underlying the EMT-promoting effects of LincRNA-ROR are likely to be involved and deserve further investigation in the near future (Table 1).

Crosstalk between EMT regulators and lncRNAs

TGF-β and LncRNAs

The multifunctional cytokine TGF-β orchestrates an intricate signaling network to modulate tumorigenesis and progression. TGF-β exerts its tumor-suppressive role by inducing cell-cycle arrest and apoptosis. Nevertheless, TGF-β also promotes tumor progression through enhancing proliferation, migration, and invasion, in part by its ability to induce EMT [116]. Recent evidence, addressing the crosstalk between the TGF-β signaling pathway and lncRNAs in cancer, found that several members of the TGF-β pathway are

targeted by lncRNAs, and the production of hundreds of lncRNAs is induced by TGF-β treatment (Fig. 2a). For example, Li et al. showed that knockdown of MALAT1 could inhibit TGF-β production by modulating recruitment of transcription factor Sp1 to the LTBP3 gene promoter in mesenchymal stem cells from patients with multiple myeloma [117]. In addition, Fan et al. reported that TGF-β could also induce MALAT1 expression and EMT in bladder cancer cells and targeted inhibition of MALAT1 suppressed the migratory and invasive properties induced by TGF-β [27]. Maternally expressed gene 3 (MEG3), located in the imprinted DLK1-MEG3 locus on human chromosome 14q32.3, is another key lncRNA which could regulate TGF-β pathway through epigenetic mechanisms. In a study conducted in breast cancer, Mondal et al. found that MEG3 and EZH2 share common target genes, including the TGF-β pathway genes. Genome-wide mapping of MEG3 binding sites revealed that MEG3 modulates the activity of TGF-β genes by binding to distal regulatory elements. MEG3 binding sites have GA-rich sequences, which guide MEG3 to the chromatin through RNA-DNA triplex formation [118]. Moreover, several other lncRNAs were reported to regulate the TGF-β signaling pathway in a variety of different ways, including plasmacytoma variant translocation 1 (PVT1), p53 induced non-coding transcript (PINT), and Linc00974. Takahashi et al. demonstrated that PVT1 knockdown could upregulate Smad4 and apoptosis-associated genes related to the TGF-β pathway [119]. Marin-Bejar et al. revealed that PINT could promote cell proliferation and survival by regulating the expression of genes of the TGF-β, MAPK and p53 pathways in mouse cells [120]. Linc00974 was reported to be involved in a Linc00974-miR-642-KRT19-TGF-β signaling pathway [121]. In this study, Tang et al. revealed that Linc00974 hyperexpression could induce the upregulation of KRT19 via ceRNA network, resulting in the activation of the TGF-β and Notch pathways as detected by cDNA microarray. Although our current knowledge on the complex role of lncRNAs in TGF-β signaling pathways is poor, the lncRNAs remain of great therapeutic potential for antagonizing the deregulation of TGF-β pathway in cancer. Further studies of the lncRNA-TGF-β signaling network will definitely help expand our understanding of the pathogenesis of human malignancies.

Snail/Slug and LncRNAs

Of the three vertebrate Snail proteins, Snai1 (also known as Snail) and Snai2 (also known as Slug) activate the EMT programme during development, fibrosis and cancer [122]. Snail factors bind to E-box consensus sequences in the E-cadherin promoter with the help of local modifications of chromatin structure after the recruitment of SIN3A, histone deacetylases HDAC1 and HDAC2, and components of PRC2 complex. In addition to being tightly regulated at the transcriptional level, Snail factors undergo posttranslational modifications that control their nuclear localization or degradation [123]. In recent years, accumulating evidence suggests that Snail factors and lncRNAs could regulate each other reciprocally, thus adding another layer of complexity to the regulation of Snail activity (Fig. 2a). Orom et al. found that a set of lncRNAs exhibit enhancer-like function in human cell lines, and depletion of some of these lncRNAs led to decreased expression of their neighboring protein-coding genes, such as Snail and Slug [124]. It was reported previously that Snail protein could recruit chromatin modifier EZH2 to a broad repertoire of epithelial genes but the underlying mechanism remains largely unknown [125]. Recently, Battistelli et al. revealed that HOTAIR mediates a physical interaction between Snail and EZH2 and the Snail-repressive activity depends on the formation of a tripartite Snail/HOTAIR/EZH2 complex [126]. In a TGF-β-induced EMT model, Matouk et al. demonstrated that H19 could upregulate Slug expression concomitant with the suppression of E-cadherin protein through a mechanism involving miR-675. In turn, Slug also bound and activated the promoter of H19 to upregulate its expression, thus forming a positive feedback loop between Slug and H19/miR-675 [50]. Besides H19, several other lncRNAs are now reported to play a pivotal role in regulating the expression and activity of Snail factors, such as LINC01013 [127], lnc-GNAT1-1 [128], and Lnc-CC3 [129]. However, our current knowledge of the crosstalk between lncRNAs and Snail factors is still limited and further studies are necessary to understand the precise relationship between them.

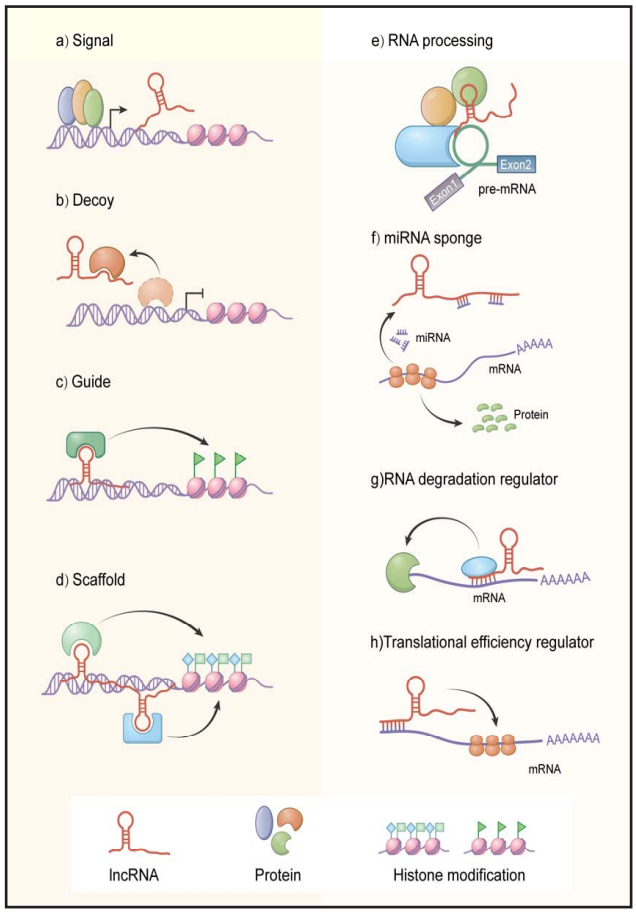

Fig. 1. Models of lncRNA mechanisms of action. (a) lncRNA expression can faithfully reflect the combinatorial actions of transcription factors or signaling pathways to indicate gene regulation in space and time. (b) lncRNAs can act as decoys that titrate away DNA-binding proteins, such as transcription factors. (c) lncRNAs can act as guides to recruit proteins, such as chromatin-modifying enzymes, to target genes. (d) lncRNAs may act as scaffolds to bring two or more proteins into a complex or spatial proximity. (e) lncRNAs may be integral components of the nuclear paraspeckle and contribute to post-transcriptional processing of mRNAs. (f) lncRNAs may harbor the recognition sites for functional miRNAs, thus titrate miRNAs away from their mRNA targets. (g) lncRNA/mRNA duplexes can direct exosome-mediated RNA degradation. (h) lncRNAs bound with the mRNA would positively or negatively modulate the translation efficiency, depending on the mRNA and lncRNA structures.

ZEB and LncRNAs

Like Snail proteins, ZEBs bind E-boxes and function as transcriptional repressors and activators, thereby repressing some epithelial junction and polarity genes and activating mesenchymal genes that define the EMT phenotype. ZEB expression often follows activation of Snail expression, consistent with Snail directly targeting the ZEB1 gene. Besides, numerous studies have reported that ZEB factors can also be regulated by other mechanisms such as miRNA-mediated gene silencing and Polycomb-mediated sumoylation [122]. Interestingly, recent work showed that lncRNAs are involved in regulation of ZEB in a variety of different ways (Fig. 2a). First, lncRNAs could upregulate ZEB expression via ceRNA regulatory networks. As mentioned above, Yuan et al. demonstrated that LncRNA-ATB upregulates ZEB1 and ZEB2 expression by competitively binding the miR-200 family, thus contributing to the EMT process (Fig. 2b, iii)[52]. ZFAS1, a lncRNA that is frequently amplified in HCC, functions as an oncogene in HCC progression by binding miR-150, thus derepressing its inhibitory effect on ZEB1 [113]. Moreover, Hou et al. found that LincRNA-ROR is associated with miRNPs and functions as a ceRNA for miR-205. Specifically, LincRNA-ROR prevents the degradation of miR-205 target genes, including the EMT inducer ZEB2 [57]. Secondly, lncRNAs could upregulate ZEB expression via enhancer-like mechanisms. In a study conducted in HCC, Li et al. revealed that an lncRNA named ZEB1-AS1 is frequently upregulated in HCC samples, especially in metastatic tumor tissues. The ZEB1-AS1 gene is located in physical contiguity with ZEB1 and positively regulates the ZEB1 expression. ZEB1 depletion partially abrogates ZEB1-AS1-induced EMT and tumor metastasis, suggesting ZEB1-AS1 and ZEB1 play a critical role in HCC progression [111]. Thirdly, lncRNAs also contribute to pathogenic splicing of ZEB genes. Beltran et al. found that maintenance of 5'-

UTR ZEB2 intron is dependent on the expression of a natural antisense transcript (NAT) that overlaps the 5' splice site in the intron. Ectopic overexpression of NAT in epithelial cells prevents splicing of the ZEB2 5'-UTR, increases the levels of ZEB2 protein, and consequently downregulates E-cadherin mRNA and protein [130].

Twist and LncRNAs

As with Snail, Twist expression downregulates epithelial gene expression and activates mesenchymal gene expression. In cancer cells, Twist1 represses E-cadherin and induces N-cadherin expression independently of Snail and probably through the association with other proteins. Recent study showed that more than 99 lncRNAs and 3164 genes are differentially expressed in the Twist-induced EMT process, suggesting that Twist contributes to invasion and metastasis by inducing wide-ranging transcriptional and functional changes of lncRNAs and signaling pathways [131]. Zou et al. found that lncRNA-Hh, transcriptionally regulated by Twist, directly targets GAS1 to stimulate the activation of hedgehog signaling, thus endowing Twist-induced EMT cells to gain the cancer stem cell-like stemness properties [86]. Moreover, several reports showed that lncRNAs could in turn regulate Twist expression in multiple cancer types. In a study conducted in gastric cancer, Cai et al. demonstrated that FRLnc1 overexpression could promote cancer cell migration and metastasis and identified TGF-β1 and Twist as the downstream effectors of FRLnc1 [132]. In CRC, Niu et al. revealed that AK027294 downregulation significantly inhibited CRC cell migration and promoted cell apoptosis by regulating Twist, caspase-3, caspase-8, Bcl-2, MMP12, MMP9 expression [133]. In gallbladder cancer, LincRNA-ROR and AFAP1-AS1 are also reported to regulate Twist expression to promote EMT process [134, 135]. Previous work demonstrated that lncRNAs could directly interact with proteins to function as scaffolds for chromatin-remodeling complexes or other regulatory complexes [136]. One recent study showed that, an lncRNA named HOTTIP, could form a complex with Twist and WDR5, leading to the upregulation of HOXA9 and aggressive cellular phenotypes such as invasion and migration [78]. Together, these data suggest that the crosstalk between Twist and lncRNAs is rather complex and further studies are needed to investigate the more detailed underlying mechanisms.

Conclusion

EMT is a complex, multifunctional, and tightly regulated process that plays anessential role in tumor metastasis. EMT-activating signaling pathways and EMT-inducing transcription factors (EMT-TFs) are responsible for driving EMT and conferring aggressive mesenchymal properties to epithelial cells. Over the past few years, lncRNAs, which belong to a novel heterogeneous class of ncRNAs, are emerging as promising biomarkers and therapeutic targets for EMT and metastasis. Accumulating evidence has indicated that lncRNAs are widely dysregulated in a variety of malignancies to impact epithelial plasticity by targeting different signaling pathways, EMT-TFs, and EMT-related genes. The distribution and levels of lncRNAs in various locations such as distal metastases, have been exploited as potential diagnostic and prognostic biomarkers for cancer. Technologies have been advanced to achieve more sensitive and reliable detection and effective targeting of lncRNAs for cancer treatment. Despite these advances, there remain many challenges, such as limited knowledge of lncRNA functional mechanisms, targets, and binding partners, the challenges of effective delivery, stability, immunogenicity, and bioavailability of lncRNA-targeted therapeutics, all of which will be formidable tasks to undertake for the future studies. Overall, lncRNAs have shed new light on our understanding of cancer pathways and brought our understanding of tumorigenesis to a new horizon. Understanding the different and precise molecular mechanisms by which functional lncRNAs switch EMT on and off is important for opening up new avenues in lncRNA-directed diagnosis, prognosis, and therapeutic intervention against cancer.

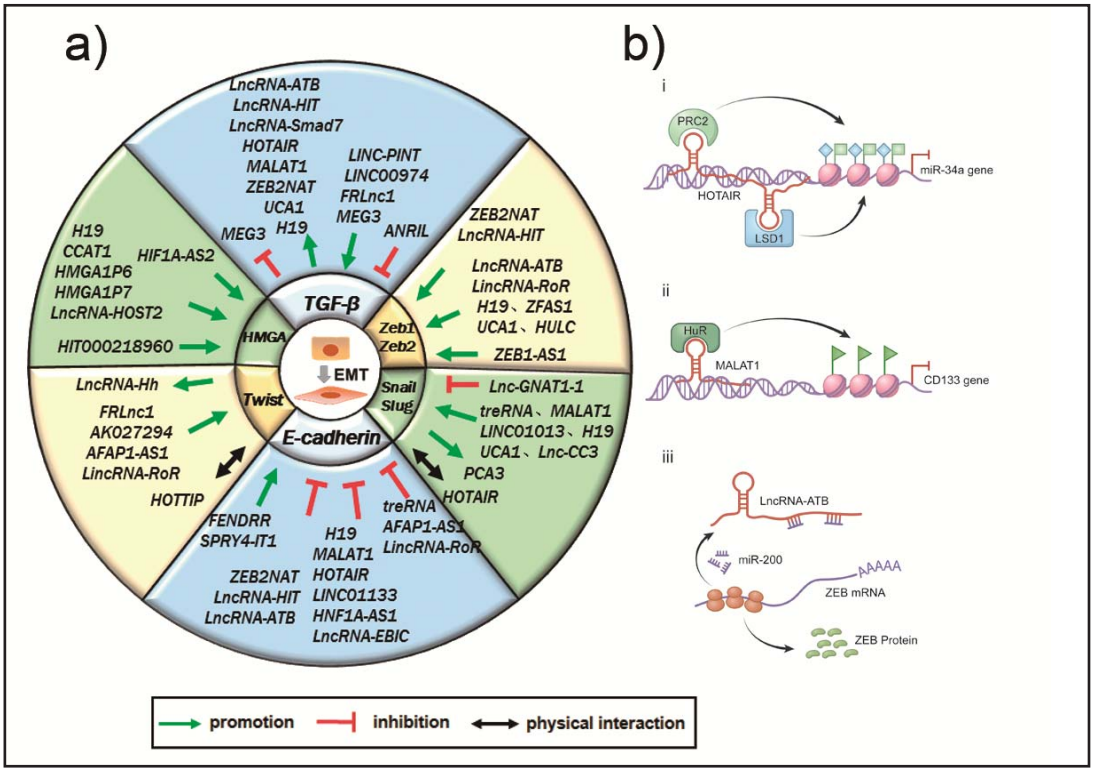

Fig. 2. Crosstalk between EMT core regulators and lncRNAs. (a). EMT can be regulated by many signaling pathways, transcription factors, and transcriptional/post-transcriptional regulators, such as TGF-β, ZEB, Snail, Twist, HMGA, etc. These EMT core regulators are reciprocally regulated by different lncRNAs, and some of EMT-inducing transcription factors (EMT-TFs) exert their effects by directly interacting with lncRNAs. (b) Selected examples of lncRNAs and their molecular partners or genomic targets are shown for mesenchymal and motility properties.

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Disclosure Statement

The author declares that they have no competing interests

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