Review

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Long non-coding RNAs as emerging regulators of epithelial to mesenchymal transition in gynecologic cancers

Xiaojing Lin[1,2,3,§], Junjun Qiu[1,2,3,§], Keqin Hua[1,2,3,*]

[1] *Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China;*
[2] *Shanghai Medical College, Fudan University, Shanghai, China;*
[3] *Shanghai Key Laboratory of Female Reproductive Endocrine-Related Diseases, Fudan University, Shanghai, China.*

Summary **Gynecologic cancer is a vital global healthcare issue with high rates of mortality and morbidity. Tumor metastasis attributes to most of the death suffering from solid tumors. The epithelial-mesenchymal transition (EMT) plays a pivotal role in initiating metastasis. Long non-coding RNAs (lncRNAs), a well-known group of non-coding RNAs, and a prominent topic in life science research, are misregulated in many malignancies and some are EMT-associated. In the case of gynecologic cancers, several EMT-associated lncRNAs have been identified and found to be implicated in cancer aggressiveness and progression. Mechanically, these lncRNAs participate in the EMT-related metastatic process in multiple ways including interaction with polycomb repressive complex 2 (PRC2), regulation of EMT signaling networks, mediation of EMT-transcription factors (EMT-TFs) and EMT markers, and cooperation with microRNAs (miRNAs). Further studies on these EMT-associated lncRNAs and identification of more relevant lncRNAs are imperative for the lncRNAs-based clinical management of high rate of metastasis in patients with gynecologic cancers.**

Keywords: Long non-coding RNA, epithelial-mesenchymal transition, metastasis, ovarian cancer, endometrial cancer, cervical cancer

1. Introduction

Gynecologic cancer is a life-threatening disorder for women due to the difficulty of early diagnosis and the high incidence of metastasis. There are five common gynecologic cancers: ovarian, cervical, endometrial (uterine), vaginal, and vulvar, the first three of which are the most frequent (*1*). Cancer metastasis, which is a complex multistep process regulated by multiple factors and genes, accounts for 90% of cancer-associated deaths. The epithelial mesenchymal transition (EMT), during which epithelial cells exhibit mesenchymal-like properties through cytoskeleton remodeling and morphological changes, is a crucial step in the initiation of metastasis (*2*). Emerging evidence has identified long non-coding RNAs (lncRNAs) as potent determinants of gene regulation and cancerous phenotype during tumorigenesis and tumor progression. Lately, an increasing body of lncRNAs have been found to take part in tumor invasion/metastasis regulation through EMT-based mechanisms in gynecologic cancers. This review summarizes the current findings and regulatory roles of several known EMT-related lncRNAs in gynecologic cancers and lays the foundation for potential use of these lncRNAs in cancer management.

2. Key regulators of EMT in cancer

EMT, a complex and tightly regulated developmental program, triggers tumor aggressiveness and progression when this regulation is improperly controlled. The EMT process is defined by (I) an absence of baso-apical polarization; (II) a reduction in cell adhesive forces; (III) the emergence of motility; and (IV) invasive properties. Multiple signals, such as growth factors (fibroblast growth factor (FGF), epidermal growth factor (EGF), human growth factor (HGF), transforming growth factor-β (TGF-β)), differentiation factors (Wnt, Notch, sonic hedgehog(SHH), nuclear

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**Address correspondence to:*
Dr. Keqin Hua, Department of Gynecology, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China.
E-mail: huakeqinjiaoshou@163.com

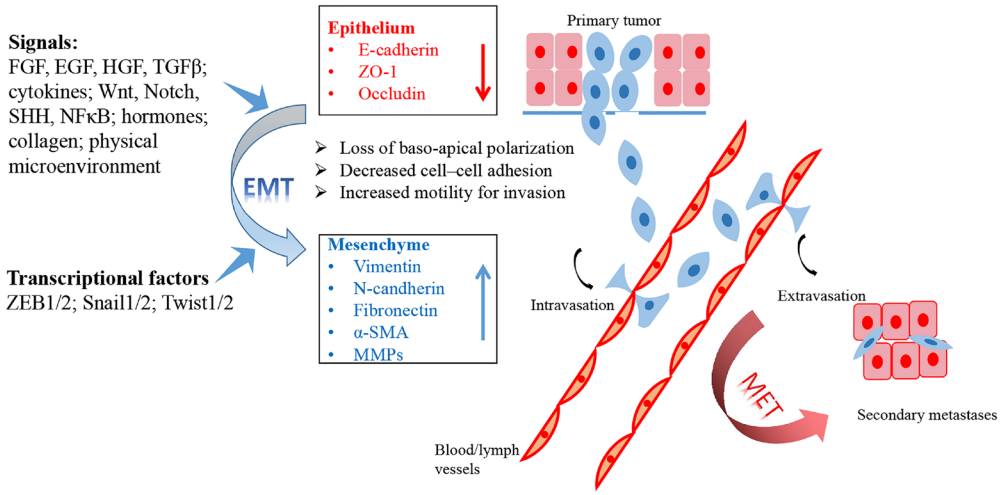

Figure 1. The regulatory network of EMT and its role in tumor metastasis. Multiple signals and factors induce EMT accompanied by alteration on EMT molecular markers, cell morphology and biological behaviors, and then trigger the primary tumor to locally infiltrate and to subsequently intravasate into nearby blood and lymphatic vessels, by which the cells are transported though the systems to extravasate into distant tissue where MET facilitates the formation of secondary metastases with epithelial characteristics.

factor kappa light-chain-enhancer of activated B cells (NF-κB)), cytokines, and hormones (estrogen), as well as extracellular matrix components (collagen), and the physical microenvironment (hypoxia, oxidative and metabolic stress, UV light) (*3*) can induce various EMT-transcription factors (EMT-TFs) including the zinc finger E-box binding homeobox (ZEB1/2), the zinc finger Snail (Snail1/2) and basic helix-loop-helix families (Twist1/2). A prominent feature of the EMT is gene expression alterations in epithelial and mesenchymal markers, with decreases in the former and increases in the latter. E-cadherin (CDH1), zona occludens 1 (ZO-1), and occludin (OCLN) serve as epithelial markers while N-cadherin, vimentin, fibronectin 1 (FN1), α-smooth muscle actin (α-SMA), and some matrix metalloproteinases (MMPs) represent mesenchymal markers (*4*). In general, the induction of the EMT by several signals enables primary tumors to locally infiltrate, intravasate into and transport through the circulatory system, and finally extravasate into distant tissue, where mesenchymal to epithelial transition MET (MET) facilitates the formation of secondary metastases with epithelial characteristics (Figure 1).

3. Roles of lncRNAs in cancer

The growing use of high-throughput sequencing resources has revealed a great many lncRNAs, which are more than 200 nucleotides (nt) in length and constitute 76% of RNA transcripts (*5*). According to their location in the genome: lncRNAs are divided into five categories (I) sense, (II) antisense, (III) bidirectional, (IV) intronic and (V) intergenic. Growing evidence reveals that lncRNAs participate in cellular biological processes through diverse molecular mechanisms, including genomic stability, epigenetic modification, transcription, post-transcription, translation and post-translational modification (*6*).

3.1. *Genomic stability*

Chromosomal instability is thought to be closely correlated with cancer initiation. lncRNAs are involved in the maintenance of chromosomal stability. For instance, noncoding RNA activated by DNA damage (NORAD) preserves fidelity of the chromosome by sequestering PUMILIO, which targets and represses messenger RNA (mRNAs) critical for accurate chromosome segregation (*7*). This regulatory relationship also contributes to an emerging concept that a main class of lncRNAs function as molecular decoys.

3.2. *Epigenetic regulation*

lncRNAs epigenetically modulate target genes *via* recruiting chromatin remodeling protein complexes, especially polycomb repressive complex 1 (PRC1) and polycomb repressive complex 2 (PRC2), and this has been demonstrated as a major regulatory mechanism (*8*). The details will be discussed in section 4.1.

3.3. *Transcriptional regulation*

Most lncRNAs described so far act by modulating transcription through recruiting proteins and/or complexes (transcription initiation factor complex) to specific target DNA sequences (*9,10*). In particular, promoter enhancer lncRNAs could exert enhancer-like functions and positively regulate gene expression by forming chromatin loops (*11*). Colorectal cancer

associated transcript 1 (CCAT1-L) is an example of an enhancer lncRNA that works to maintain myelocytomatosis oncogene (MYC) enhancer-promoter interacting structures, resulting in MYC gene transcription (*12*).

3.4. *Post-transcriptional regulation*

Post-transcription regulation includes interactions with microRNAs (miRNAs), coordination with mRNA and alternative splicing.

3.4.1. *Interaction with miRNAs*

lncRNA-miRNA-mRNA interactions are a significant regulatory mechanism through which lncRNAs sequester miRNA and hinder degradation of downstream RNA. The details will be discussed in section 4.4.

3.4.2. *Coordination with mRNA*

Several other classes of lncRNAs contribute to post-transcriptional regulation *via* coordinating specific mRNA and repressing either translation or degradation of targeted mRNA. One example is the transcription factor spi-1 proto-oncogene (PU.1) and its antisense lncRNA spi-1 proto-oncogene antisense (PU.1 AS), which form an mRNA/AS lncRNA complex and consequently represses PU.1 mRNA translation (*13*). In addition to translational regulation, lncRNAs may also modulate the stability of mRNA by complementarily binding with 3'-untranslated regions (3'UTRs) of mRNAs. Upon exposure to cellular stressors, the upregulation of the antisense transcript of β-secretase-1 (BACE1-AS) stabilizes BACE1 mRNA *via* a positive post-transcriptional feed-forward mechanism (*14*).

3.4.3. *Alternative splicing*

lncRNAs are also involved in the alternative splicing process. The ZEB2 natural antisense transcript (ZEB2 NAT), for instance, regulates alternative splicing by interaction with ZEB2 mRNA. It inhibits ZEB2 mRNA splicing by overlapping and binding to its alternative splice site (*15*).

3.5. *Post-translational regulation*

In some cases, there is evidence that lncRNAs are able to post-translationally modulate proteins. Signaling pathway-related lncRNAs, in particular, could alter the modification of key proteins and regulate the activation and deactivation of specific signaling pathways. For example, NF-κB-interacting lncRNA (NKILA) hinders NF-κB activation by affecting the phosphorylation state of the inhibitor of κB (IκB) (*16*).

3.6. *Encoding small peptides*

Although a majority of lncRNAs have no potential for encoding protein, some possess short open reading frames (ORFs of fewer than 100 amino acids) (*17*). Studies focusing on the micropeptide-coding potential of lncRNAs start from muscle-specific lncRNAs. Anderson DM *et al*. reported that one lncRNA expressed in skeletal muscle could be translated to generate a physiology-associated factor, myoregulin (MLN) (*18*). Other research found that the lncRNA LINC00961 encoded a new polypeptide, small regulatory polypeptide of amino acid response (SPAR), the expression level of which is altered under acute injury conditions (*19*). Similarly, the RNA and peptide levels of HOXB cluster antisense RNA 3 (HOXB-AS3) are decreased in highly metastatic colon (SW620 and HTC-116 high), breast (MDA-MB-231 high), nasopharyngeal (S18), and ovarian (SK-OV-3 high and OVCAR-3 high) cancer cell sublines and in primary tumor tissues in comparison with expression levels in their parental cell lines and non-tumor tissues, respectively. Moreover, as a small peptide rather than an lncRNA, HOXB-AS3 represses colorectal cancer cell biological behavior by blocking hnRNP A1-dependent PKM (pyruvate kinase M) splicing, miR-18a processing, and aerobic glycolysis (*20*).

Together, these findings highlight that lncRNA-encoded polypeptides are more than just translational noise but broaden the breadth and diversity of the effect of lncRNAs on gene regulation. However, few lncRNA-generating small peptides have been functionally verified. More small peptides, which have been largely overlooked in gene annotation primarily due to the difficulty of identifying functional short ORFs in lncRNAs, will be characterized in future work.

4. lncRNAs control of EMT

Numerous evidence has suggested the regulation of the EMT by lncRNAs contributes to the progression of epithelial-derived tumors *via* diverse mechanisms.

4.1. *Interaction with PRC2*

Myriad studies have revealed that lncRNAs can epigenetically silence gene expression through recruiting PRC2 to the promotors of target genes associated with the EMT process. PRC2 functions to trimethylate H3 lysine 27(H3K27me3) of E-cadherin, resulting in transcriptional silencing and cancer progression (*21*). One well known epigenetic-related target of lncRNAs is the HOX transcript antisense intergenic RNA (HOTAIR), whose interaction with PRC2 is active in diverse cancers (*22*). Another example is lncRNA ubiquitin carrier protein 1 (UBC1), which alters the PRC2-mediated H3K27 trimethylation level and facilitates bladder cancer

cell invasion and metastasis (*23*).

4.2. *Regulation of EMT signaling networks*

In addition to epigenetic modification, lncRNAs are also implicated in a complex signaling pathway network.

4.2.1. *TGF-β signaling pathway*

TGF-β, one of the main inducers of EMT, phosphorylates cytoplasmic Smad2 and Smad3 *via* its receptors (TGF-βRI, TGF-βRII, and TGF-βRIII), thereby regulating expression of the EMT-TFs, such as Snail, ZEB, and Twist, accompanied by altered expression of the EMT markers (*24*). Several lncRNAs can respond to a TGF-β signal and participate in malignant transformation. For instance, lnc-ATB, a TGF-β-induced lncRNA, mediates EMT and promotes EMT-mediated metastasis in diverse kinds of cancers (*25-27*).

4.2.2. *Wnt signaling pathway*

The Wnt signaling pathway is another critical regulator of EMT. When the cell receives the Wnt signal, the membrane protein Frizzled and its low-density lipoprotein receptor form a complex, thus activating and stabilizing β-catenin, whose transfer into the nucleus triggers EMT-TF gene expression (*28*). Recent studies have verified that a subset of lncRNAs participate in EMT regulation *via* Wnt/β-catenin signaling. For instance, the imprinted maternally expressed transcript H19 activates the Wnt pathway signal and blocks expression of E-cadherin *via* enhancer of zeste homolog 2 (EZH2) recruitment (*29*). Similarly, lncTCF7 (transcription factor 7) initiates transcription of TCF7 and thus activates the Wnt signaling pathway by recruiting the chromatin remodeling complex to the promoter site (*30*).

4.2.3. *Hypoxia/hypoxia-inducible factor-1α (HIF-1α) pathway*

Multiple pieces of evidence illustrate that many lncRNAs are implicated in the hypoxia/HIF-1α-induced EMT process. For instance, H19 is triggered by both TGF-β and hypoxia, and it stimulates tumor metastasis by the induction of the EMT markers (*31*). In addition, tumor protein p53 pathway corepressor 1 (TP53COR1) forms a positive feedback loop with HIF-1α under hypoxic conditions (*32*). In the case of gynecologic cancer, elevated levels of lncRNA plasmacytoma variant translocation 1 (PVT1) are found in response to hypoxia and are closely related to unfavorable prognosis in patients with cervical cancer (*33*). Mechanistically, lncRNA PVT1 silences miR-195 at the transcriptional level and modulates the EMT phenotype (*34*).

4.2.4. *Other EMT-related pathways*

Additional signaling pathways related to EMT are the mitogen-activated protein kinase (MAPK)/extracellular signal regulated protein kinase (ERK) (*35*), signal transducer and activator of transcription 3 (STAT3) (*36*), phosphatidylinositol 3 kinase (PI3K)/protein kinase (AKT) pathways (*37*). Collectively, the interaction of lncRNAs with various signaling pathways, some of which can crosstalk with other signaling pathways, can affect the process of EMT.

4.3. *Regulation of EMT-TFs and EMT markers*

Certain lncRNAs function by directly regulating the transcription of the EMT-TFs and EMT markers. For example, amine oxidase, copper containing 4 (AOC4P) binds to vimentin, facilitates its degradation, and thus suppresses the EMT process (*38*). Several other lncRNAs (commonly antisense lncRNAs) are reported to form duplexes with their counterparts, to either promote or prevent their translation. For example, ZEB2NAT suppresses E-cadherin expression by interacting with its mRNA counterparts called ZEB2 (*39*). A similar regulatory relationship exists between ZEB1 antisense 1 (ZEB1-AS1) and ZEB1 (*40*). Other examples of antisense transcripts include HNF1A antisense RNA 1 (HNF1A-AS1) (*41*) and 91H (*42*). Although increasing evidence supports the hypothesis that lncRNAs positively or negatively regulate EMT-related factors, thorough study is needed to determine if these effects are direct.

4.4. *Interaction with miRNAs*

Over the last decade, evidence has clearly shown that miRNAs are widely misregulated and play significant regulatory roles in cancer. Emerging evidence indicates that cooperation between lncRNAs and miRNAs contributes to tumor progression *via* diverse pathways.

4.4.1. *miRNAs targeting lncRNAs for degradation*

Numerous studies have demonstrated that miRNAs can bind to lncRNAs and trigger their decay. For example, upregulated miR-9 expression degrades metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) in osteosarcoma cells and thus blocks cell migration and invasion under high doses of 17β-estradiol (*43*). In addition, miR-217 post-transcriptional silencing of MALAT-1 RNA is mediated by argonaute 2 (Ago2), resulting in the mesenchymal transition of bronchial epithelial cells (*44*).

4.4.2. *lncRNAs competitively binding to microRNA*

Evidence is accumulating that lncRNAs function for a competing endogenous RNA (ceRNA) regulatory

relationship where lncRNAs are capable of sponging miRNAs and upregulating downstream mRNA expression. For example, urothelial cancer associated 1 (UCA1) could sponge miR-485-5p in epithelial ovarian cancer. The lack of UCA1 downregulates MMP14, which is targeted by miR-485-5p (*45*). Other examples include MALAT1 (*46*), colon cancer-associated transcript-1 (CCAT1) (*47*) and long intergenic non-protein-coding RNA, regulator of reprogramming (linc-ROR) (*48*).

4.4.3. *lncRNAs acting as precursor RNAs*

Notably, lncRNAs themselves can be precursor RNAs for miRNAs. A well-known lncRNA called H19 has been proven to be able to generate miR-675, which is an EMT-associated gene in prostate cancer (*49*). Another study that one lncRNA exclusively expressed in the kidney regulates EMT *via* directly encoding the miR-200 cluster, which is also evidence supporting lncRNAs as pre-miRNAs (*50*).

4.4.4. *lncRNAs transcriptionally regulating miRNAs*

Beyond the above interactions between lncRNAs and miRNAs, lncRNAs can directly transcriptionally regulate miRNAs. For example, HOTAIR can recruit PRC2 to miR34a, subsequently upregulate Snail and induce EMT-mediated metastasis of gastric cancer cells (*51*).

5. EMT-related lncRNAs in gynecologic cancer

Table 1 and Figure 2 illustrate the roles of the EMT-related lncRNAs in gynecologic cancer, the details of which will be discussed below.

5.1. *MALAT1*

MALAT1, also called NEAT2 (non-coding nuclear-enriched abundant transcript 2), is located on chromosome 11q13.1 and contains 8,000 nucleotides. MALAT1, an EMT-related lncRNA, allows epithelial cells to be malignantly transformed. In ovarian cancer, MALAT1 activates PI3K/Akt signaling and EMT induction. MALAT-1 knockdown leads to downregulation of N-cadherin, vimentin and Snail (*52*). In endometrial cancer (EC), miR-200c binds to MALAT1 to form the MALAT1/miR-200c sponge. When the interaction is interrupted, the cell invasive capacity is decreased and the expression of EMT markers is altered (*46*). In addition, MALAT1 promotes the invasive and metastatic potency of cervical cancer by altered expression of EMT markers (E-cadherin, ZO-1, β-catenin and vimentin) and EMT-TFs (Snail) (*53*).

5.2. *H19*

H19, a famous imprinted gene, is located in an imprinted region of chromosome 11 with 2,300 nucleotides. H19 exerts oncogenic and pro-metastatic properties primarily through the H19/let-7 axis (*54*). In both ovarian and EC, H19 acts to antagonize let-7 and mediate the elevated level of several metastasis-related genes (c-Myc, high-mobility group AT-hook 2(HMGA2), and insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3) (*55*). Furthermore, the knockdown of H19 is accompanied by Snail downregulation and E-cadherin upregulation in EC (*56*).

5.3. *HOTAIR*

HOTAIR is a lncRNA of 2158-nt length located on 12q13.13. HOTAIR has been revealed to be an EMT-related lncRNA and serves as a strong metastatic predictor in cancers (*57*). In cervical cancer, the expression of HOTAIR is positively correlated to a poor prognostic predictor, human papillomavirus oncogenic E7 (HPV-E7). The pro-metastatic potency of HOTAIR is partially ascribed to vascular endothelial growth factor precursor (VEGF), MMP-9, and EMT-associated genes induction (*58,59*). Additionally, HOTAIR regulates the malignant behavior of ovarian cancer SK-OV-3 cells partly by interacting with mitogen-activated protein kinase 1 (MAPK1), but whether EMT is regulated *via* this pathway remains to be resolved (*35*). Qiu JJ *et al*. demonstrated that HOTAIR facilitates epithelial ovarian cancer (EOC) cell invasion and migration by modulating MMPs and EMT-related gene expression (*60*).

5.4. *PVT1*

PVT1 is an oncogenic, intergenic lncRNA derived from 8q24.21 with multiple splicing isoforms (*61*). It is upregulated in various cancer types such as ovarian cancer, cervical cancer, and pancreatic cancer, among others (*62*). In cervical cancer cells, PVT1 can regulate EMT *via* interactions with EZH2 and the complex anchors to the miR-195 promoter region and *via* direct competitive binding with miR-195 (*34*). Recent studies suggest that miR-195 is an important suppressor of EMT in some cancers (*63*). However, the exact mechanism underlying PVT1/ miR-195 axis in cervical cancer and other gynecologic cancers is minimally understood and poorly elucidated.

5.5. *ANRIL*

Antisense non-coding RNA in the INK4 locus (ANRIL) is a 3800-nt long non-coding RNA located in chromosome 9p21. Numerous studies have shown that ANRIL acts as a powerful cancer progressive factor in various cancers (*64*). For example, in ovarian cancer, ANRIL increases migration and invasion by MET and MMP3 modulation and its expression pattern is closely

Table 1. lncRNAs related to EMT in gynecologic cancers

lncRNA	Cancer type	Expression	Potential mechanism (*Ref)*	Author, date
PVT1	Cervical cancer	Upregulated	Binding to EZH2; interacting with miR-195 (*34*).	Shen CJ *et al*, 2017
HOTAIR	Ovarian cancer	Upregulated	Interacting with MAPK1 (*35*); Regulating MMPs and EMT-related genes (*60*).	Tang YW *et al*, 2015; Qiu JJ *et al*, 2014
	Cervical cancer	Upregulated	Regulating VEGF and MMP-9 expression (*58*); Binding to PRC2-complex members (*59*).	Kim HJ *et al*, 2015; Sharma S *et al*, 2015
UCA1	Ovarian cancer	Upregulated	Binding to miR-485-5p and increasing target gene MMP14 (*45*).	Yang Y *et al*, 2016
MALAT1	Endometrial cancer	Upregulated	MALAT1/miR-200c sponge (*46*).	Li Q *et al*, 2016
	Ovarian cancer	Upregulated	Regulating N-cadherin, vimentin and Snail by the PI3K/Akt signaling pathway (*52*).	Jin Y *et al*, 2017
	Cervical cancer	Upregulated	Modulating E-cadherin, ZO-1, β-catenin, vimentin and Snail expression (*53*).	Sun R *et al*, 2016
CCAT1	Ovarian cancer	Upregulated	CCAT1-miR-152/miR-130b-ADAM17/WNT1/STAT3/ZEB1 axis (*47*).	Cao Y *et al*, 2017
Linc-ROR	Endometrial cancer	Upregulated	Linc-ROR/miR-145 sponge (*48*).	Zhou X *et al*, 2014
	Ovarian cancer	Upregulated	Wnt/β-catenin signaling pathway (*84*).	Lou Y *et al*, 2017
H19	Ovarian cancer	Upregulated	H19/let7 axis (*55*).	Yan L *et al*, 2015
	Endometrial cancer	Upregulated	H19/let7 axis (*55*); Increasing Snail and decreasing E-cadherin expression (*56*).	Yan L *et al*, 2015; Zhao L *et al*, 2017
ANRIL	Ovarian cancer	Upregulated	Modulating MET and MMP3 (*65*).	Qiu JJ *et al* ,2015
AB073614	Ovarian cancer	Upregulated	Upregulating MMP-2, MMP-9, β-catenin, Twist, Snail, FN1 and E-cadherin; activating AKT and ERK (*70*).	Cheng Z *et al*, 2015
EBIC	Cervical cancer	Upregulated	Recruiting EZH2 and repressing E-cadherin expression (*73*).	Sun NX *et al*, 2014
NEAT1	Ovarian cancer	Upregulated	Affecting the expression of MMP-2, MMP-9, Snail1 and TGF-β-1 (*76*).	Li P *et al*, 2016
SPRY4-IT1	Ovarian cancer	Downregulated	Altering the expression level of N-cadherin and vimentin (*78*).	Yu J *et al*, 2017
TUG1	Cervical cancer	Upregulated	Upregulating fibronectin, vimentin and cytokeratin (*79*).	Hu Y *et al*, 2017
BANCR	Endometrial cancer	Upregulated	Increasing MMP2/MMP1 expression by activating ERK/MAPK signaling pathway (*82*).	Wang D *et al*, 2016
DNM3OS	Ovarian cancer	Upregulated	Regulating EMT-TFs (Snail and Slug), E-cadherin and N-cadherin; EMT-linked pathways (*86*).	Mitra R, 2017
SOX2OT	Ovarian cancer	Upregulated	Altering the expression of N-cadherin and E-cadherin (*88*).	Han L *et al*, 2018
HOXA11-AS	Ovarian cancer	Upregulated	Affecting the expression of B-catenin, Snail, Twist, vimentin, E-cadherin, invascular endothelial growth factor and MMP-9 (*90*).	Yim GW *et al*, 2017

lncRNA, long noncoding RNA; BANCR, BRAF-activated non-coding RNA; HOTAIR, HOX transcript antisense intergenic RNA; UCA1, urothelial cancer associated 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; CCAT1, colon cancer–associated transcript-1; Linc-ROR, long intergenic non-protein coding RNA, regulator of reprogramming; ANRIL, antisense non-coding RNA in the INK4 locus; EBIC, EZH2-binding lncRNA in cervical cancer; NEAT1, nuclear paraspeckle assembly transcript 1; SPRY4-IT1, SPRY4 intronic transcript 1; TUG1, taurine upregulated gene 1; DNM3OS, DNM3 opposite strand RNA; SOX2OT, SOX2 overlapping transcript; HOXA11-AS, HOXA11 antisense RNA.

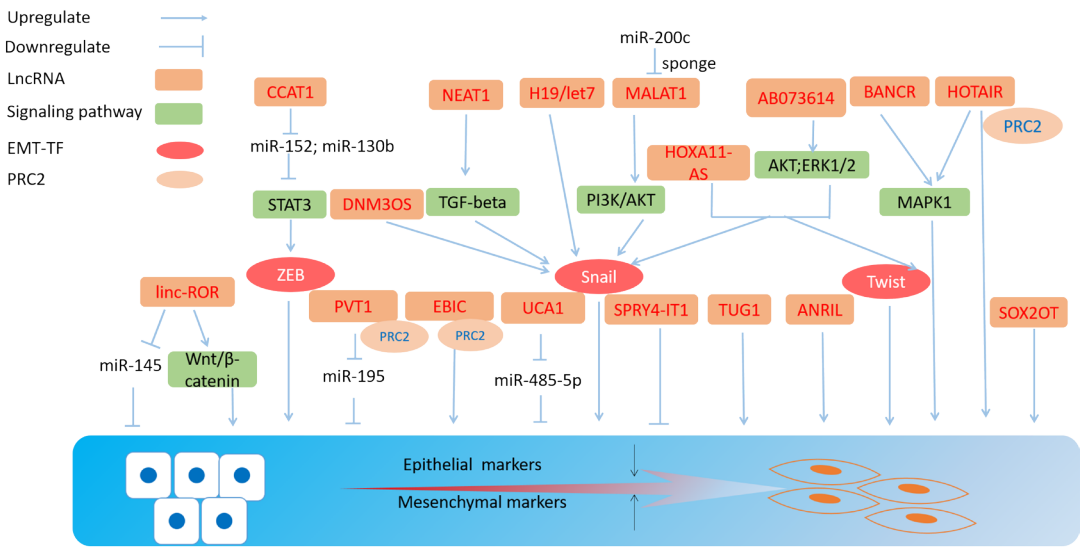

Figure 2. EMT-related lncRNAs and their regulatory network in gynecologic cancers. Schematic diagram shows several lncRNAs participate in EMT-related metastatic process in multiple ways including interaction with PRC2, regulation of EMT signaling networks, mediation on EMT-TFs and EMT markers, and cooperation with miRNAs.

linked to clinical stage, pathological grade, lymph node metastasis, and poor prognosis (*65*). In addition, ANRIL has been found to promote the metastatic and invasive ability of cervical cancer cells (*66,67*), but whether the EMT process is involved remains unclear.

5.6. *UCA1*

Cancer upregulated drug resistant (CUDR), also called UCA1, is located in chromosome 19p13.1 and is 2200-nt in length. It is dysregulated in cancer tissues from various malignancies (*68*). L Lu *et al*. reported that UCA1 is closely associated with tumor aggressiveness of EC and may serve as a prognostic predictor for EC patients (*69*). In EOC, UCA1 serves as a miR-485-5p "sponge" and alters downstream MMP14 expression. Moreover, the high expression level of UCA1 could be indicative of an unfavorable prognosis (*45*).

5.7. *AB073614*

AB073614 is a 1900-nt lncRNA located in the 3q24 chromosomal region. AB073614 was upregulated in ovarian cancer (*70*), glioma tissue(*71*) and colorectal cancer (*72*). Overexpression of AB073614 could be suggestive of tumor progression and poor prognosis. In ovarian cancer cells, downregulated p-AKT and p-ERK suggests that key signaling pathways may be implicated in AB073614-mediated tumor aggressiveness (*70*).

5.8. *EBIC*

EZH2-binding lncRNA in cervical cancer (EBIC) is a 1500-nt lncRNA located in chromosome 12q22. In cervical cancer, lncRNA-EBIC represses E-cadherin and enhances cell invasion *via* interacting with EZH2, but the mechanism underlying this process remains to be formally demonstrated (*73*). In addition, it should also be determined whether EBIC is a cervical cancer-specific lncRNA or a universally expressed lncRNA in cancers.

5.9. *CCAT1*

CCAT1 is a 2628-nt lncRNA mapping to chromosome 8q24.21 near c-MYC, a well-known transcription factor. Upregulation of CCAT1 might be a universal rule in a variety of cancer types, suggesting that CCAT1 has oncogenic potential in development and progression of tumors (*74*). Cao Y *et al*. reported that in EOC, the pro-metastatic effect of CCAT1 is through interaction with miR-130b and miR-152, protecting target genes, such as ADAM17, Wnt1, STAT3 and ZEB1, from degradation (*47*).

5.10. *NEAT1*

Nuclear paraspeckle assembly transcript 1 (NEAT1) encodes two transcriptional variants, namely, NEAT1-1 and NEAT1- 2, which are 3.7 kb and 23 kb in length respectively, and situated on chromosome 11. The expression level of NEAT1 is elevated in multiple types of cancers, including lung, esophageal and gastric cancers, while it is downregulated in acute promyelocytic leukemia (*75*). In ovarian cancer, silencing NEAT1 significantly affects the expression of cell invasion-related proteins (MMP-2, MMP-9, Snail1 and TGF-β-1) (*76*). Despite these findings, however, the precise role of NEAT1 remains to be characterized.

5.11. *SPRY-IT1*

SPRY4 intronic transcript 1 (SPRY4-IT1) is a 687-nt

unspliced polyadenylated transcript located on human chromosome 5q31.3. Multiple studies have characterized SPRY4-IT1 as a tumor suppressor in different cancer types, such as non-small cell lung cancer, breast cancer, and endometrial cancer (*77*). In ovarian cancer, knockdown of SPRY4-IT1 leads cancer cells to a more aggressive phenotype, partially through regulation of N-cadherin and vimentin (*78*). The mechanism contributing to this disregulation, however, is still unclear.

5.12. *TUG1*

Taurine upregulated gene 1 (TUG1) is a 7.1 kb lncRNA located in the 22q12 chromosomal region. Abundant studies have revealed that TUG1 promotes cancer cell invasion and radio-resistance *via* EMT (*79,80*). In cervical cancer, TUG1 knockdown suppresses expression of EMT related proteins (fibronectin, vimentin and cytokeratin) (*79*). Nonetheless, further research is required to elucidate the precise mechanism underlying TUG1 and its effects on target genes.

5.13. *BANCR*

BRAF-activated non-coding RNA (BANCR) derives from chromosome 9 with a length of 693-bp (*81*). Previous studies have reported that BANCR plays a pivotal part in malignant transformation. In EC, elevated BANCR activates the ERK/MAPK signaling pathway, upregulates MMP2/MMP1 expression and thus accelerates the progression of cancer cells (*82*).

5.14. *linc-RoR*

linc-ROR is a 2.6 kb lncRNA encoded at chromosome 18q21.31. linc-ROR is involved in cancerous cell growth and metastasis in various malignancies (*83*). In ovarian cancer, linc-ROR promotes EMT-mediated cancer cell metastasis *via* Wnt/β-catenin signaling pathway activation (*84*). In EC, linc-RoR functions as an miR-145 "sponge" during carcinogenesis (*48*).

5.15. *DNM3OS*

DNM3 opposite strand RNA (DNM3OS) is a noncoding 7.9kb fragment transcribed from 1q24.3. It was identified as an important regulator during development (*85*). Recent studies have pointed out that DNM3OS is highly expressed in the mesenchymal subtype compared with its epithelial counterpart. In ovarian cancer, DNM3OS promotes metastasis through EMT-linked genes (Snail, Slug, E-cadherin and N-cadherin) and pathways based on The Cancer Genome Atlas (TCGA) database and experimental evidence. Of note, DNM3OS may be a poor prognostic predictor of ovarian cancer (*86*).

5.16. *SOX2OT*

SOX2 overlapping transcript (SOX2OT) is mapped to chromosome 3q26.3. Several studies have revealed a tumorigenic role of SOX2OT in cancers, including breast cancer, lung cancer and hepatocellular carcinoma (*87*). In ovarian cancer, SOX2OT silencing suppresses cell aggressiveness accompanied by decrease in N-cadherin and increase in E-cadherin (*88*).

5.17. *HOXA11-AS*

HOXA11 antisense RNA (HOXA11-AS) is located in chromosome 12q22 near the gene HOXA11 (Homeobox genes A11). In several cancers, HOXA11-AS is differentially expressed compared to normal tissues, such as glioma, uterine cervix carcinoma, and lung adenocarcinoma (*89*). In Serous Ovarian Cancer, the elevated level of HOXA11as promotes cell invasion and migration through EMT-associated gene alteration, including EMT-TFs (Snail and Twist), vimentin E-cadherin, invascular endothelial growth factor and MMP-9 (*90*).

Other EMT-associated lncRNA in gynecologic cancer detected from TCGA database include myocardial infarction associated transcript (MIAT) and maternally expressed 3 (MEG3), but more study is needed to experimentally verify its correlation with EMT (*86*).

6. lncRNA-based diagnostics and therapies

Numerous lncRNAs are misexpressed in human cancers and some appear to be highly cancer specific. In addition, many lncRNAs contained in body fluids can be detected by current laboratory technology. These factors contribute to lncRNAs as an attractive approach for noninvasive biomarkers and therapeutic targets. For example, in prostate cancer, prostate cancer associated 3 (PCA3) has an advantage over the current method of using serum prostate-specific antigen (PSA) as a biomarker, due to its higher specificity and sensitivity (*91*). In addition, the overexpression of the hepatocellular carcinoma (HCC) lncRNA HULC is detected in blood of HCC patients (*92*). Current studies have highlighted the role of exosome-contained lncRNAs in fields of diagnosis and prognosis. To date, exosomal transfer of lncRNAs has been increasingly verified and implicated in EMT processes. For instance, ZNFX1 antisense RNA1 (ZFAS1) is found to be elevated in both tumor tissues and body fluid-derived exosomes of gastric cancer. Exosome-mediated transfer of ZFAS1 could increase the expression of ZFAS1, decrease epithelial markers and upregulate the mesenchymal markers of recipient cells, leading to enhanced proliferation and migration potential (*93*). Another example is HOTAIR, one of the earliest detectable and enriched lncRNAs in body fluids of patients with different types of cancer (*94*).

Additionally, several other EMT-related lncRNAs, including UCA1, lincRNA-p21, growth arrest specific 5 (GAS5), MALAT-1 and H19, are also secreted within exosomes (*95-97*). However, the concrete roles of these exosome-derived lncRNAs are rarely defined. Current advanced technologies allow therapies based on lncRNAs to be more achievable either to silence or to overexpress. For example, lung cancer metastasis could be prevented by antisense-mediated silencing of MALAT1 *in vivo* (*98*). Moreover, breast cancer progression can be hindered through systemic knockdown of MALAT1 using antisense oligonucleotides (*99*). Overall, lncRNA-targeted cancer therapies are promising; however, they are still in their infancy and require further development of experimental strategies, siRNA/antisense delivery strategies, and clinical trials.

7. Conclusions and future perspectives

Metastasis is one of the most significant factors leading to the poor outcomes of patients with gynecologic malignancies. Over the past few years, mounting evidence has linked numerous lncRNAs to the cellular EMT process in ways relevant to tumor metastasis. Despite existing advances, the accurate regulatory role of lncRNAs in the EMT process is rarely understood in the case of gynecologic cancers. For one thing, more efforts are required to know the exact underlying mechanisms. Additionally, lncRNA-based diagnostics and therapies face many challenges pertaining to application. The former includes development of effective and convenient detectation technology, avoidance of degradation by body fluid components and exploration of the tissue origin of circulating lncRNAs. The later involves the need for safe and effective delivery, and minimization of off-target effects. Therefore, future studies should focus more on investigating the existing form and function of circulating lncRNA to make an efficient diagnosis, discover disease-specific lncRNAs and develop novel therapeutic agents to directly target lncRNAs. Taken together, understanding the specific role and precise mechanisms of lncRNAs in the EMT process will open up promising perspectives in disease management.

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