REVIEW

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The Role of lncRNAs in the Epithelial-Mesenchymal Transition in Cervical Cancer: A Narrative Review

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Abstract

Objective: In this context, the aim of this study was to compile the main works that address the relationship between lncRNAs and Epithelial-Mesenchymal Transition (EMT) in cervical cancer. **Methods:** Data extraction was conducted using the PubMed database, where a search for selected studies on lncRNAs involved in EMT in cervical cancer was performed. The search was based on the following keywords: "Epithelial-Mesenchymal Transition" AND "Uterine Cervical Neoplasms" and "lncRNA and EMT and cervical cancer." **Result:** Included in this study were 16 lncRNAs, which encompass expression level, microRNAs, targets, clinical significance, and references. Among the 16 lncRNAs observed, it was found that 5 of them can regulate EMT by modulating microRNAs. It was also noted that these biomolecules are capable of regulating the expression of important EMT genes, such as *SNAIL, SLUG, and TWIST*, thus influencing cancer invasion and metastasis. In addition to these, 11 lncRNAs were found, which can regulate biological pathways such as Wnt/β-catenin and AKT/mTOR, playing fundamental roles in EMT. In conclusion, the future prospects of lncRNAs in therapy and inhibition of EMT are promising. **Conclusion:** Considering the relevance of EMT to cancer progression and the involvement of lncRNAs in this biological process, it becomes important to better understand their role and the possibility of targeting them therapeutically, which can represent significant advancements in the treatment not only of cancer but also of other diseases.

Keywords: Cervical cancer- Epithelial-mesenchymal transition- lncRNAs- Biomarkers- Prognosis

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Introduction

Cervical cancer (CC) is one of the primary gynecological health concerns, being considered the third most common type of tumor among women [1]. The prevalence of this fatal disease has been gradually increasing worldwide, with an estimated 17,010 new cases projected for each year of the 2023-2025 triennium, representing a crude incidence rate of 15.38 cases per 100,000 women [2]. Constituting, thus, an important public health issue, especially in developing countries, where it accounts for 85% of new cases and deaths from this malignant neoplasm [3].

Among the factors associated with CC are early onset of sexual activity and infection with the Human Papillomavirus (HPV), with emphasis on HPV types 16 and 18, as well as multiple sexual partners, smoking, immunodeficiency, and family history [4]. Although HPV infection is considered the main risk factor, it is worth noting that additional genetic and epigenetic changes are necessary for disease progression [5].

Within the epigenetic changes, non-coding RNAs (ncRNAs) stand out. ncRNAs are abundant and functional in the genome, thus garnering attention in molecular research due to their potential as biomarkers in various human diseases, including cancer [6]. ncRNAs can be divided into two categories based on nucleotide length: small RNAs (<200 nucleotides) and long ncRNAs (lncRNAs) (>200 nucleotides). Small RNAs include microRNA (miRNA), transfer RNA (tRNA), transfer RNA-derived small RNAs (tsRNA), small nuclear RNAs (snRNA), and small nucleolar RNAs (snoRNAs)[7].

Long non-coding RNAs (lncRNAs) are involved in gene regulation at the transcriptional and post-

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transcriptional levels [8, 9]. These biomolecules have gained prominence due to their therapeutic potential in different types of cancers, including CC [10]. Furthermore, they have been extensively investigated because of their role in regulating biological processes such as proliferation, apoptosis, and epithelial-mesenchymal transition (EMT) [11].

EMT is a complex biological process that plays a significant role in the progression of CC. During EMT, epithelial cells lose their morphological and functional characteristics, acquiring mesenchymal cell features, and increasing their capacity for invasion and migration into adjacent tissues [12]. This biological process is related to metastasis and poor prognosis [13]. lncRNAs are capable of regulating the expression of important genes in EMT, such as *SNAIL, SLUG, and TWIST* [14].

In this context, considering the relevance of EMT to cancer progression and the involvement of lncRNAs in this biological process, this study aims to gather works that address the relationship between lncRNAs and EMT, as it can provide new insights into CC and help develop new therapeutic strategies for treating this disease.

LncRNAs and Epithelial-Mesenchymal Transition

LncRNAs are important regulators of EMT through the control of microRNAs (miRNAs), acting as endogenous RNA competitors (ceRNAs). MiRNAs, in turn, can regulate the expression of genes involved in EMT [15]. Table 1 demonstrates the main lncRNA-miRNA-RNA axes involved in EMT in CC.

SPRY4-IT1/miR-101-3p/ZEB1

The lncRNA SPRY4-IT1 (SPRY4 Intronic Transcript 1) plays an important role in the regulation of cell growth, proliferation, and apoptosis [21]. According to the study by [16], the inhibition of SPRY4-IT1 or the activation of *miR-101-3p* can prevent EMT and reduce the migration and invasion of CC cells. These results suggest that SPRY4-IT1 and its signaling pathway *miR-101-3p*/*ZEB1* may be potential targets for the treatment of this neoplasm [16]. The *ZEB1* gene is a key regulator of EMT and tumor invasion. Its activity can promote the expression of MMPs (metalloproteinases), which are involved in the degradation of the extracellular matrix, an essential process for cancer progression and metastasis formation [22].

Regarding other types of cancers, SPRY4-IT1 promotes proliferation, migration, and metastasis in breast cancer [23], colorectal cancer [24], and gastric cancer [25]. In nasopharyngeal carcinoma cells, this lncRNA acts by inhibiting proliferation, migration, and metastasis, also capable of inducing significant G2/M phase arrest and apoptosis [26].

OIP5-AS1/miR-147a/IGF1R

The lncRNA OIP5-AS1 is involved in various biological and pathological processes, including oncogenesis, as well as different miRNAs in various types of cancers [27], such as lung cancer [28], endometrial cancer [29], and colon cancer [30].

This lncRNA has been observed with high expression in CC tumor tissues, positively regulating the level of *E-cadherin*, which is a key protein in EMT. Additionally, it promotes migration, invasion, and EMT of cancer cells through the miR-147a/IGF1R pathway [27]. The *IGF1R* signaling is involved in the EMT process induced by interferon-induced transmembrane protein 2 (*IFITM2*), thus contributing to cancer growth and metastasis [31].

CRNDE/miR-4262/ ZEB1

The long non-coding RNA Colorectal Neoplasia Differential Expressed (CRNDE) was initially discovered in colorectal cancer and is involved in various processes related to cancer hallmarks [32]. According to the study conducted by [19], this lncRNA is highly expressed in CC samples compared to normal cervical tissues. CRNDE overexpression has been associated with increased progression and worse prognosis for patients, also regulating the miR-4262/*ZEB1* axis through activation of the Wnt/β-catenin pathway in CC.

Other studies have also demonstrated the association of CRNDE with CC, suggesting that this lncRNA is involved in cell growth and metastasis. However, its biological function and underlying mechanism in CC tumorigenesis still require further investigation [33, 34].

SNHG16/ miR-216-5p/ZEB1

The small nucleolar RNA host gene 16 (SNHG16) is an lncRNA involved in carcinogenesis progression [35]. Overexpression of SNHG16 in CC is associated with worse overall survival of patients, and through bioinformatics tools, it was observed that this lncRNA interacts with miR-216, which in turn regulates *ZEB1* [20]. Based on this information, it is plausible to suggest that SNHG16 may be involved in EMT regulation, potentially facilitating tumor progression.

Additional studies demonstrate that SNHG16 is involved in cancer hallmarks such as proliferation and

Table 1. lncRNAs Related to EMT in CCU and Regulating microRNAs.

LncRNAs	microRNA - Target	Clinical finding or biological processes	Reference
SPRY4-IT1 ↑*	miR-101-3p/*ZEB1*	Contributes to migration and invasion	Fan et al. [16]
LncRNA-CTS ↑	miR-505/ *ZEB2*	Associated with FIGO III-IV and lymph node metastasis	Feng et al. [17]
OIP5-AS1 ↑	miR-147a/ *IGF1R*	Promotes cell migration, invasion, and EMT.	Zhang et al. [18]
CRNDE ↑	microRNA-4262/ *ZEB1*	Associated with FIGO I–IIa and IIb-III and lymph node metastasis	Ren et al. [19]
SNHG16 ↑	miR-216-5p/*ZEB1*	Associated with tumor progression.	Zhu et al. [20]

SPRY4-IT1, SPRY4 Intronic Transcript 1; LncRNA-CTS, (Not found); OIP5-AS1, OIP5 Antisense RNA 1; CRNDE, Colorectal neoplasia differentially expressed; SNHG16, Small Nucleolar RNA Host Gene 16; ZEB1, Zinc finger E-box binding homeobox 1; ZEB2, Zinc finger E-box Binding homeobox 2; IGF1R, Insulinlike growth factor1 receptor. *, High expression.

Table 2. lncRNAs and Pathways Related to EMT in CC

LncRNAs	Target	Clinical finding or biological processes	Reference
HOXC13-AS ↑*	Wnt/β-catenin	Associated with proliferation, invasion, and EMT.	Wang et al. [37]
HIF1A-AS2 ↑	Vimentin N-cadherin	Associated with proliferation, invasion, and cell migration.	Deng et al. [38]
ROR1-AS1 ↑	E-cadherin β-catenin	Associated with distant metastases, FIGO stage, and lower five-year survival.	Zhang et al. [39]
GHET1 ↑	Wnt/β-catenin/ AKT/mTOR	Associated with the growth of CC cells, migration, and EMT.	Liu et al. [24]
lncOGFRP1 ↑	β-catenin	Inhibits cell proliferation and migration.	Zhou et al. [40]
RP11-480I12.5 ↑	Wnt/β-catenin	Associated with clinical stage, tumor size, and lymph node metastasis.	Zhang et al. [41]
lncRNA-CTS ↑	SMAD/TGF	Associated with FIGO III-IV and lymph node metastasis.	Feng et al. [17]

HOXC13-AS, HOXC13 Antisense RNA; HIF1A-AS2, HIF1A Antisense RNA 2; ROR1 AS1, ROR1 Antisense RNA 1; GHET1, Gastric Carcinoma Proliferation Enhancing Transcript 1; lncOGFRP1, (Not found) RP11-480I12.5:(Not found); lncRNA-CTS:(Not found). AKT, NA; mTOR: mammalian Target of Rapamycin; SMAD/TGF: (Not found); *, High expression.

apoptosis, as well as participating in processes related to chemoresistance. It is important to emphasize that SNHG16 is described as a promising diagnostic and prognostic biomarker in cancer patients [20].

lncRNAs and the signaling pathways of Epithelial-Mesenchymal Transition

lncRNAs have been recognized as key players in the regulation of cellular signaling pathways, as they can interact with proteins, DNA, and other RNAs to modulate gene expression and influence information flow. Additionally, they can modulate mRNA stability, affecting the amount of proteins produced by genes. Through these mechanisms, lncRNAs play an important role in the precise regulation of these cellular pathways, contributing to the cellular response to external stimuli and to the proper balance of physiological processes [36]. In Table 2, we list the main pathways related to EMT.

In this review, we observed that some lncRNAs are capable of regulating certain biological pathways, such as the *Wnt*/β-catenin and *AKT*/mTOR pathways [24, 37]. These two signaling pathways play fundamental roles in EMT, as they regulate the expression of transcription factors and cell adhesion proteins, as well as modulating junctional pathways and the regulation of extracellular matrix molecules [42].

Among the lncRNAs observed regulating the aforementioned pathways, the lncRNA GHET1 stands out, which acts as an oncogene in various types of cancer. Evidence suggests that silencing this lncRNA can suppress cancer progression through the regulation of the *AKT*/mTOR and *Wnt*/β-catenin pathways. In the same study, it was observed that this lncRNA is capable of stabilizing *E2F6* mRNA through interaction with IGF2BP2 [24].

In another study, involving the lncRNA HOXC13-AS, it was observed that this lncRNA epigenetically activates the *FZD6* gene, a member of the cell surface receptor family for Wnt, thereby activating the *Wnt*/β-catenin signaling pathway, which is involved in regulating cell proliferation and EMT.

The β-catenin is maintained at low levels in the cytoplasm of epithelial cells by a complex protein degradation machinery. When the Wnt pathway is activated, β-catenin is stabilized and translocated into the nucleus, where it associates with transcription factors and activates the transcription of genes involved in EMT [43].

The lncRNAs GHET1 and HOXC13-AS exert significant influence on the *Wnt*/β-catenin and *AKT*/mTOR pathways. Both lncRNAs play a significant role in regulating these pathways, thus influencing EMT and

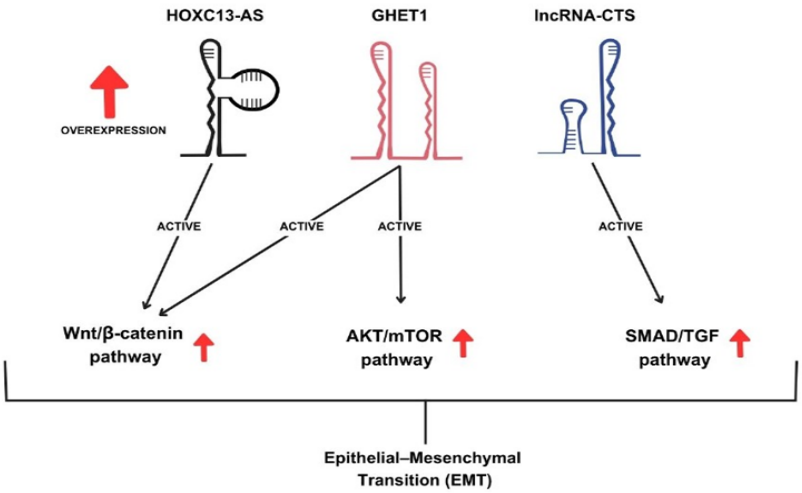

Figure 1. Interaction between lncRNAs and Signaling Pathways Involved in EMT

Table 3. lncRNAs and Transcription Factors Involved in EMT

LncRNAs	Target	Clinical finding or biological processes	Reference
SPRY4-IT1 (NF)**	*ZEB1*	Contributes to migration and invasion.	Fan et al. [16]
ZEB1-AS1 ↑	*ZEB1*	Overexpression of the lncRNA was associated with FIGO stage IIa-IIb and lymph node metastasis.	Cheng et al. [49]
HIF1A-AS2 ↑	*Vimentin, N-cadherin, E-cadherin*	Associated with cell proliferation, invasion, and migration.	Deng et al. [38]
ROR1-AS1 ↑	*N-cadherin, Vimentin*	Was associated with distant metastases, FIGO stage, and lower five-year survival.	Zhang et al. [39]
SNHG7 ↑	*E-cadherin, N-cadherin, Vimentin*	Associated with lower survival in CC patients.	Zang et al. [50]
lncOGFRP1 ↑	*Vimentin, N-cadherin, SNAIL, E-cadherin*	Inhibits cell proliferation and migration.	Zhou et al. [40]
CASC15 ↑	*E-cadherin N-cadherin*	Associated with lymph node metastases and FIGO stage.	Shan et al. [51]
SNHG3 ↑	*N-cadherin, SNAIL, vimentin, and E-cadherin*	Associated with proliferation, migration, and invasion.	Sun et al.[52]
LINC00665 (NF)**	*N-cadherin, Vimentin*	Associated with cell migration and invasion.	Xia et al. [53]

SPRY4-IT1, SPRY4 Intronic Transcript 1; ZEB1-AS1, ZEB1 Antisense RNA 1; HIF1A-AS2, HIF1A Antisense RNA 2; ROR1 AS1, ROR1 Antisense RNA 1; SNHG7, Small Nucleolar RNA Host Gene 7; lncOGFRP1, (Not found); CASC15, Cancer Susceptibility 15; SNHG3, Small Nucleolar RNA Host Gene 3; LINC00665, Long Intergenic Non-Protein Coding RNA 665; SNAIL, (Not found); *, High expression; **, Not found.

CC progression, as observed in Figure 1. These findings highlight the potential of lncRNAs as therapeutic targets and suggest their importance in understanding the mechanisms underlying the development and progression of this specific type of cancer.

The lncRNA-CTS, although poorly studied, has been found to be associated with a poor prognosis in CC, as well as being linked to increased expression of the transcription factor *ZEB2*, promoting EMT by inhibiting the action of miR-505, a microRNA that suppresses the expression of *ZEB2* [17]. In the same study, the authors observed that lncRNA-CTS activates the *SMAD*/TGF pathway through miR-505 in tissue samples and CC cell lines. The *SMAD*/TGF pathway is a cellular signaling pathway involved in a variety of biological processes, including EMT, and its activation results in increased expression of transcription factors promoting mesenchymal differentiation. In Figure 1, we can observe the interaction of this lncRNA and the aforementioned pathway [17].

lncRNAs and the regulation of transcription factors involved in EMT

It is known that lncRNAs play important roles in the regulation of gene transcription [44]. These RNAs function by binding to histone-modifying complexes, DNA-binding proteins (MBPs), including transcription factors (TFs), and even RNA polymerase II [45]. TFs act directly by binding to their binding sites on the genome or indirectly by activating another gene (such as a miR), while epigenetic mechanisms play their role by providing an activating or inhibitory context for transcription [46].

As shown in Table 3, some of the genes listed in our study also act in EMT and are called TFs, such as *ZEB1*, *E-cadherin*, Vimentin, *N-cadherin*, and *SNAIL* [47]. Together, these TFs play a critical role in regulating EMT, promoting the transition of epithelial cells to a mesenchymal phenotype, thereby contributing to cellular plasticity during embryonic development, tissue regeneration, and pathological processes such as tumor metastasis [48].

ZEB1 and *SNAIL* are transcription factors that negatively regulate the expression of *E-cadherin* and *N-cadherin*. *ZEB1* binds to the E-box response elements in the promoters of *E-cadherin* genes, thus inhibiting their expression. Consequently, *ZEB1* reduces adhesion between epithelial cells, promoting the transition to a mesenchymal phenotype. Additionally, *ZEB1* can also activate the expression of genes associated with the mesenchymal phenotype, further reinforcing the transition [54].

E-cadherin and *N-cadherin*, on the other hand, are cell adhesion molecules that play a crucial role in maintaining cohesion between epithelial cells [55]. Loss of *E-cadherin* weakens the connections between epithelial cells, allowing their dissociation and increased cellular mobility. The presence of *N-cadherin* in epithelial cells facilitates their transition to a mesenchymal phenotype and promotes cell invasion and migration [55].

Vimentin is a protein known as a marker of EMT, which can be used to identify mesenchymal cells in tissues and cell cultures [56]. This protein plays a fundamental role in maintaining cellular integrity, providing resistance against stress. Additionally, Vimentin is involved in cell cycle regulation and adhesion, further validating its role in the development and progression of human cancers [57].

In this context, in this review, we can cite some studies that demonstrate how these transcription factors are regulated by lncRNAs. For instance, the study by [49] demonstrated that the lncRNA *ZEB1*-AS1 induces the expression of the transcription factor *ZEB1*. Furthermore,[17] demonstrated through silencing assays that the negative regulation of ROR1-AS1 inhibited the levels of *N-cadherin*, vimentin, c-myc, β-catenin, and cyclin D1.

We also highlight that altered expression of SNHG7 may contribute to increased protein expression levels of *E-cadherin* and decreased protein expression of *N-cadherin* and Vimentin [50]. Additionally, the survival time of patients with high expression of lncRNA SNHG7 was notably reduced. In the last study, lncOGFRP1 was observed to be capable of inhibiting the expression of β-catenin, Vimentin, *N-cadherin*, and *SNAIL* while promoting the expression of *E-cadherin* [40].

Future perspectives and clinical applications of lncRNAs in EMT

Understanding the mechanisms of lncRNA regulation is crucial for developing targeted therapeutic approaches. One perspective of lncRNAs is the selective inhibition of pro-EMT lncRNAs, which may represent a promising therapeutic strategy to block tumor progression and metastasis. lncRNA silencing approaches, such as the use of antisense oligonucleotides, small interfering RNAs (siRNAs), or gene editing technologies, can be explored to inhibit the expression of lncRNAs associated with EMT [58].

In another study, the effect of inhibiting the expression of these lncRNAs using siRNAs was investigated, specifically si-*ZEB1*, and it was found that introducing this siRNA into HeLa cells led to a significant reduction in *ZEB1*-AS1 expression [49]. Additionally, it was also observed that another lncRNA, GHET1, was suppressed by siRNAs, resulting in inhibitory effects on the proliferation, migration, and EMT of cervical cells. It is worth noting that EMT is associated with chemotherapy resistance. Among the lncRNAs listed in this review, only SNHG16 was observed to be involved in chemoresistance [59].

Targeting lncRNAs involved in EMT, in combination with routinely employed therapies, can enhance treatment efficacy, overcome resistance, and inhibit tumor progression. In addition to being considered potential therapeutic targets, lncRNAs can also serve as biomarkers for early diagnosis, risk stratification, and monitoring the treatment response of EMT in CC. The identification of specific lncRNAs associated with EMT can provide valuable insights for the selection of personalized therapies and monitoring treatment effectiveness [15].

Over the last decade, the increasing understanding of the role of lncRNAs in EMT and the ability to target them therapeutically may lead to significant advances in cancer treatment and other diseases. However, further research is needed to translate these perspectives into effective clinical therapies.

Author Contribution Statement

Manuscript writing: All authors. Final manuscript approval: All authors.

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Conflict of Interest

The authors declare no conflicts of interest.

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