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Current lncRNAs involvment in pathogenesis of endometriosis

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Introduction

Endometriosis is a steroid-dependent, reproductive disease defined as an abnormal presence of endometrial tissue outside the uterus, impacting nearly 10% of women who are of reproductive age. The condition is described by division based on histopathology and anatomical localization. According to it, three subtypes can be described: superficial endometriosis, deep infiltrating endometriosis, and ovarian endometriotic cysts.The pathogenesis of endometriosis is described as complex, with retrograde menstruation being the universally acknowledged theory. Current reports suggest that lncRNAs may influence the development and persistence of endometriosis through the modulation of inflammation, proliferation, angiogenesis, and tissue remodeling

Long non-coding RNAs (LncRNAs) are a class of molecules consisting of at least 200 nucleotides and lacking the protein-coding functionality. They are described as crucial players in cellular processes such as proliferation, differentiation, apoptosis, and metastasis. Several studies revealed that lncRNAs can function as competing endogenous RNAs (ceRNAs), interacting with microRNAs (miRNA) as a “sponge” in order to regulate cell functions and mediate cell invasion and metastasis (table 1). The mechanism of lncRNAs effects is shown in Figure 1. In this review we sum up recent advancements regarding the molecular pathogenesis of endometriosis in terms of chosen lncRNA reports.

lncRNA	miRNA	mRNA pathway in endometriosis
HOTAIR	miR-145-5p/MUC1; miR-141-3p miR-200c; miR-146a; miR-142-3p miR-200s; miR-206; miR-126-5p	miR-145-5p/MUC1; miR-141-3p miR-200c; miR-146a; miR-142-3p miR-200s; miR-206; miR-126-5p
MALAT1	miR-519b-3p; miR-761	PRRG4; HDAC1
H19	Let-7; miR-125-3p; miR-342-3p; miR-216a-5p; miR-124-3p;	IGF1R; ITGβ3; IER3; ACTA2;
UCA1	-	-
CDKN2B-AS1	miR-424-5p; miR-143-3p; miR-181a	AKT3; SMAD3
SNHG4	miR-148a-3p	c-Met

Table 1 – Association of miRNAs with particular lncRNA in endometriosis, particular sponged miRNA were presented as well as the targeted molecular pathway were given.

Results

LncRNAH19 has emerged as a significant player in the pathogenesis of various benign and malignant gynecological diseases. H19 has been also associated with various reproduction-related diseases, including endometriosis, polycystic ovary syndrome (PCOS), uterine fibroids and male factor infertility etc. H19 is determined to regulate cell proliferation and invasion in ectopic endometrium by targeting ITGB3. Elevated expression of H19 was discovered to be involved in endometriosis development. Changes in the H19/miR-216a-5p/actin alpha 2 pathway may contribute to the H19-mediated invasion and migration of ectopic endometrial cells which may be a potential underlying cause of fibrogenesis or fibrosis in patients with endometriosis.

LncRNA HOTAIR (Homeobox transcript antisense) functions as a regulatory lncRNA in various diseases acting as a miRNA sponge, influencing downstream gene transcription, regulating tumor invasion, progression, and metastasis. Higher levels of LncRNA HOTAIR in patients with aggressive since HOTAIR has an ability to modulate the invasion and migration of ESCs. Moreover, silencing LncRNA HOTAIR leads to inhibition the invasion and migration abilities of ESCs. Moreover, HOTAIR may be a key player in the maturation process of granulosa cells in patients with endometriosis since downregulation of HOTAIR suppresses the proliferation and induces apoptosis of granulosa cells in endometriosis by upregulating p21.

LncRNA UCA1 (urothelial carcinoma associated) serves as an exceedingly sensitive and specific marker unique to bladder cancer. Elevated UCA1 expression was found to be associated with factors such as lymph node metastasis, FIGO stage, and the response to chemotherapy. UCA1 was noted to be highly expressed in the eutopic endometrium of patients with endometriosis. The knockout of the UCA1 gene not only inhibits the ESCs growth but also promotes apoptosis, facilitates autophagy, and actively contributes to the onset and progression of endometriosis. Also, downregulation of lncRNA UCA1 is implicated in the pathogenesis of ovarian endometriosis, indicating its potential as a promising diagnostic and prognostic biomarker for the disease.

LncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript1) it is also known in literature as nuclear enriched abundant transcript 2 (NEAT2). An upregulated MALAT1 expression is correlated with increased cell growth, invasion, metastasis, apoptosis, defects in DNA repair mechanisms, and the promotion of tumor-associated inflammation. MALAT1 was upregulated in ectopic endometrial tissue, promoting ESCs apoptosis and suppressing proliferation, invasion of endometrial cells, modulating the pathogenesis of endometriosis. Moreover, MALAT1 was found to be downregulated in erastin-induced ferroptosis in endometriosis and was determined to reduce endometriotic-like lesions.

LncRNA CDKN2B-AS1 (cyclin-dependent kinase inhibitor 2B antisense RNA 1) recently discovered, has been demonstrated to be significantly upregulated in various cancers and may regulate cell proliferation, apoptosis, invasion, and migration. The expression level of CDKN2B-AS1 was up-regulated in both eutopic and ectopic endometrium. In ESCs overexpression of CDKN2B-AS1 facilitated cell proliferation and invasion.

LncRNA SNHG4 (small nucleolar RNA host gene 4) a member of the lncRNA SNHG family, is abnormally expressed in numerous human diseases. SNHG4 was significantly elevated expression of SNHG4 in endometriosis tissues. It promotes the aberrant growth of endometrial tissue outside the uterine cavity through the regulation of c-Met, also significant correlation between SNHG4 expression levels and endometriosis stage as well as higher expression levels of SNHG4 in the group of patients with endometriosis than in the control group was stated.

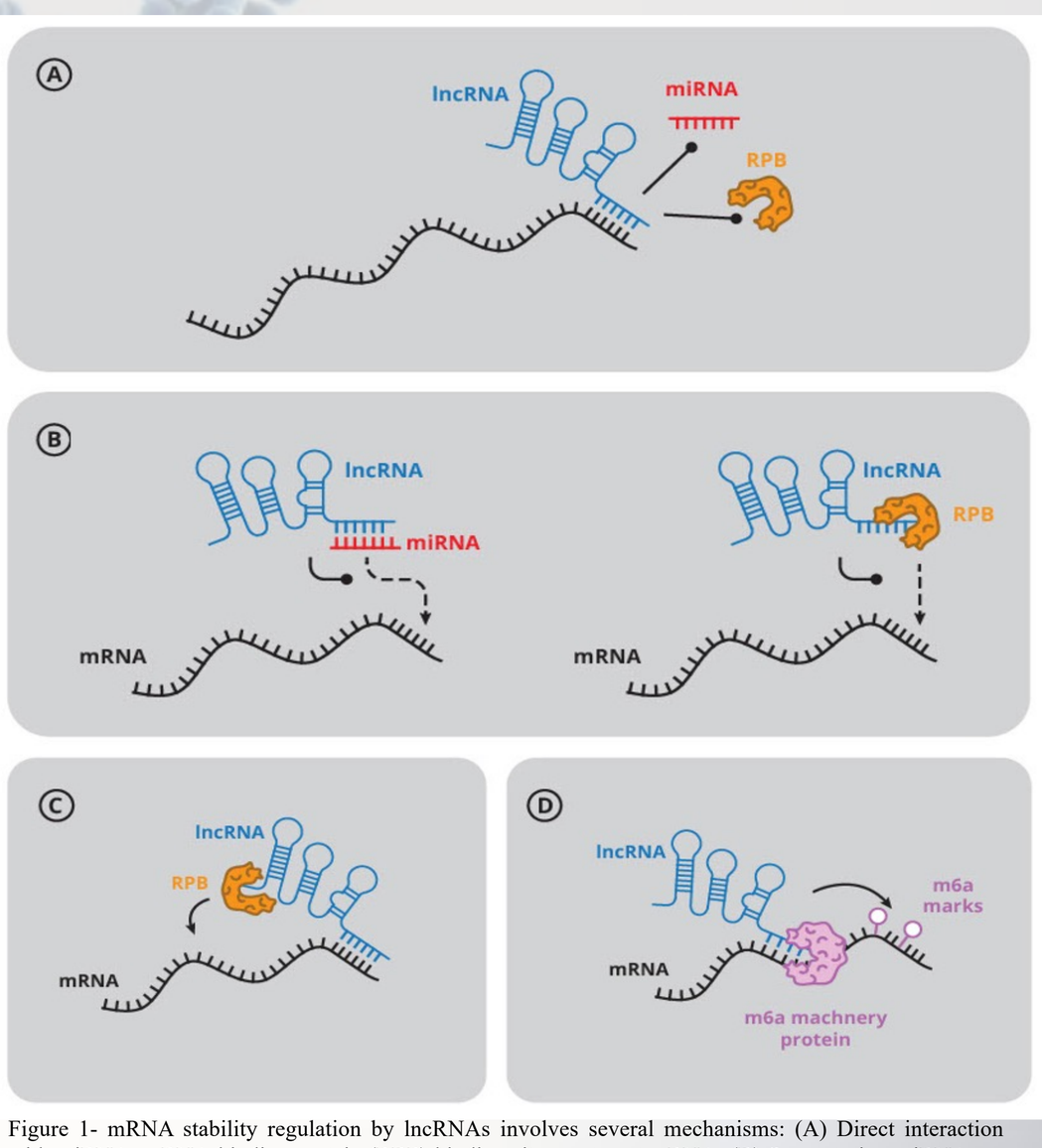

Figure 1- mRNA stability regulation by lncRNAs involves several mechanisms: (A) Direct interaction with miRNA or RNA-binding protein (RBP) binding sites on target mRNA; (B) Sequestering miRNAs or RBPs to prevent their interactions with mRNA molecules; (C) Serving as scaffolds to promote RBP-mRNA interactions; (D) Interaction with the m6A machinery, adjusting m6A levels in target mRNAs.

Conclusions

Endometriosis is a chronic disease of unknown molecular pathogenesis. Due to its debilitating nature, there is a great need for identifying diagnostic biomarkers and new therapeutic targets that may alleviate symptoms and improve quality of patients' lives. Multiple lncRNAs appear to be promising targets in studies exploring the molecular pathogenesis, as the great number of lncRNAs were found to contribute to endometriosis and ovarian cancer via various molecular pathways.