Progress in understanding the relationship between long noncoding RNA and endometriosis

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ABSTRACT

Endometriosis is a common gynecological disease. However, the etiology of endometriosis is still unclear, and current theories cannot fully elaborate its specific pathogenesis. Recently, some research has suggested that the occurrence and development of endometriosis may be related to genetics. Long-chain non-coding RNA (lncRNAs) is a kind of non-protein-coding RNA molecule with a length of 200-100,000 bp. With complex biological functions, lncRNAs play an important role in the normal development of individuals and the progression of various diseases, and lncRNAs have become an important field of medical research in recent years. This paper mainly illustrates the research progress on lncRNAs as they relate to endometriosis. We also provide some ideas for exploring the pathogenesis of endometriosis.
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Contents

Introduction

Endometriosis (EMs) is a disease caused by the presence, growth and infiltration of active endometrial glands and stroma in other parts of the endometrium. The incidence of endometriosis among women of childbearing age is as high as 10–15%, and 30–50% of endometriosis patients are infertile [1,2]. EMs is one of the most common diseases in obstetrics and gynecology. Although it is a benign disease, it has a series of malignant behaviors, such as proliferation, infiltration, distant metastasis and recurrence [3].

Especially in recent years, the incidence of endometriosis has shown a significant upward trend. It is estimated that there are approximately 100 million women worldwide suffering from endometriosis [4]. It not only directly affects the quality of life and fertility of patients and their partners, but it also increases health care expenditures, significantly reduces the work efficiency of patients, and causes a large economic burden to the whole society [5,6]. Therefore, studies of the pathophysiological mechanisms of endometriosis and exploration of effective diagnosis and treatment are of great significance to reduce the incidence of endometriosis and improve the quality of life of patients with endometriosis. Due to a lack of effective biological markers, the diagnosis of endometriosis is generally delayed by several years from the initial onset. Therefore, as the first step in finding effective diagnostic and therapeutic options, it is particularly important to understand the pathogenesis of the disease and to identify potential biomarkers for early screening. Although there are many theories about the etiology of endometriosis, the pathogenesis of EMs has not been clarified so far. It is generally believed that the occurrence and development of endometriosis is a complex biological process involving multiple genes and factors. With the completion of the human genome project and the rapid development of high-throughput sequencing technology, molecular diagnosis and gene therapy for gene-related diseases are promising. Through these technologies, the increased level of circular RNAs (circRNAs), such as *circ_0004712* and *circ_0002198*, has demonstrated as a potential novel biomarkers for the diagnosis of ovarian endometriosis [7]. At the same time, there has been further in-depth research on the sequence of billions of base pairs in the human genome. It has been found that most of the base pairs in the genome do not encode proteins. These base pairs can be transcribed into RNA in a developmental or tissue-specific manner, including a large number of long non-coding RNAs (lncRNAs). LncRNA is a non-coding RNA with a length of more than 200 base pairs that cannot encode proteins [8]. It lacks a specific complete open reading frame, has no protein coding function, and exists widely in various organisms [9]. LncRNA plays an important role in the process of transcription and posttranscriptional translation and regulates gene expression through a variety of mechanisms. It also plays an important role in many life activities, such as epigenetic regulation of gene expression, cell cycle regulation and regulation of cell differentiation [10]. Furthermore, as a key component of the transcriptional regulatory network, lncRNA is involved in embryonic development, lineage differentiation, gene imprinting, and disease occurrence [11,12].

Although the study of lncRNAs in endometriosis is rare, there is increasing evidence that the numerous biological functions of lncRNAs will promote the etiological study of endometriosis. A more comprehensive and in-depth study of the role of lncRNAs in endometriosis can play an important role in explaining the pathogenesis of endometriosis, early diagnosis of endometriosis, and discovery of molecular markers of endometriosis. This article reviews the relationship between lncRNAs and endometriosis.

Introduction of LncRNA

LncRNA is a non-coding RNA with a length of more than 200 base pairs that is unable to encode proteins. Like mRNA, most lncRNAs are modified by capping, tailing and binding (capped, polyadenylated, and spliced) [13,14]. Among the non-coding RNAs superfamily, lncRNAs are the most common non-coding RNAs [15]. Because of their lack of an open reading frame and biological function, lncRNAs were initially considered "transcriptional noise" in the process of gene transcription. With the development of whole gene transcriptome sequencing (RNA-seq, microarray, and tilling arrays) and the increasing depth of sequencing, tens of thousands of non-coding RNAs (ncRNAs) have been found in organisms. Recent studies have shown that only approximately 2% of mammalian genes can encode proteins, while 75% to 90% of mammalian genes are transcribed into non-coding RNA [16,17]. At present, 8801 small ncRNAs (<30 nt) and 9640 long ncRNAs (>200 nt) have been identified in the human genome [18]. Non-coding RNAs mainly function in the following: RNA modification (small nucleolar RNAs (snoRNAs)), mRNA processing (small nuclear RNAs (snRNAs)), transposon repression and maintenance of germ line stability (PIWI-interacting RNAs (piRNAs)), regulation of gene expression (miRNAs and short inhibitory RNAs (siRNAs)), and chromatin modification and silencing (long ncRNAs (lncRNAs)) [19–21]. LncRNAs account for the highest proportion of ncRNAs. There is no evidence to prove that these RNAs have direct biological functions, but most lncRNAs can regulate DNA replication, RNA transcription and protein translation through complementary pairing with microRNAs. LncRNAs are only expressed in specific cell types, and their expression level is usually lower than that of protein-coding genes. Based on its location in the genome, lncRNA can be classified into several subtypes, including i) long intergenic noncoding RNAs (lincRNAs), ii) natural antisense transcripts (NATs), and iii) intronic lncRNAs transcribed from intergenic regions of the genome by RNA polymerase II [22]. LncRNAs not only participate in the physiological process of individual growth and development but also play an important role in the pathogenesis and development of diseases [23]. Although the gene chip test is relatively fast, it is difficult to detect low abundance targets and repetitive sequences due to the limitation of the sensitivity of hybridization technology, and the false positive rate is high. Moreover, the gene chip test is only used to detect known sequences, so new RNA cannot be detected. High-throughput sequencing technology can conduct comprehensive analysis of a species' genome, which has its own advantages over gene chips, including the following: (1) the direct detection of transcript fragments can identify single nucleotides, and there is no analog fluorescence signal in gene chip hybridization, avoiding cross-reactions and background noise; (2) high-throughput and high sensitivity screening can be used to accurately count tens of thousands to hundreds of thousands of copies; (3) gene information can be directly obtained, and the size and structure of genes can be more accurately determined; (4) characteristics of known sequences can be detected, and new genetic information can be found. The birth of high-throughput sequencing is of great significance in the field of genomics research. This technology drops the cost of single base nucleic acid sequencing compared with the first sequencing technology, which is more conducive to genome detection. Based on the above advantages and the reduction of sequencing cost, high throughput sequencing has gradually become a common experimental method. It tends to replace the previous gene chip and gene expression series analysis technology and occupies a dominant position in transcriptome research technology.

Target lncRNAs/ lncRNAs as biomarkers of endometriosis diagnosis

Imprinted gene H19

H19 is a 2.3 KB lncRNA located on human chromosome 11p15.5. Its expression is mainly limited to the ovary and endometrial lining, and it is upregulated during the menstrual cycle and the proliferative period [24]. The H19 gene can be transcribed but not translated, and together with insulin-like growth factor 2 (Igf2), it forms a pair of imprinted genes [25]. H19 has a high transcription level in embryonic tissues, which decreases significantly after birth. It can be found in many kinds of cancer cells, and its

mechanism of action is very complex. H19 has different functions in different tumors. It plays an oncogenic role in liver cancer, bladder cancer, and breast cancer, while it plays an anti-oncogenic role in colon cancer [26,27].

Studies have shown that abnormal imprinting of H19 is closely related to endometriosis [28]. Ghazal [28] and other researchers detected H19 levels in the eutopic endometrium and normal endometrium of patients with endometriosis. The expression of H19 in the eutopic endometrium was significantly lower than that in normal endometrium. After knocking out the H19 gene of endometrial stromal cells, the let-7 gene was activated; then, the expression of insulin-like growth factor-1 receptor (Igf1r) was inhibited, which reduced the proliferation of endometrial stromal cells. It can be inferred that the H19/let-7/Igf1r pathway may affect the repair of the damaged endometrium in patients with endometriosis and reduce endometrial receptivity, leading to infertility [28]. In samples of endometrium at the implantation stage, the expression level of H19 in infertile women was 4 times lower than that in normal women, suggesting that H19 may play a role in the implantation of fertilized eggs [29,30].

lncRNA CHL1-AS2

In 2014, Sun et al. [31] first applied high-throughput microarray gene chip technology to compare the different expression of lncRNA and mRNA in eutopic and ectopic endometrial tissues of endometriosis patients and found that there were 948 lncRNA with transcription differences, among which the upregulation of lncRNA CHL1-AS2 was the most significant. By predicting the biological functions of differentially expressed lncRNA, it is suggested that lncRNA may be involved in the pathogenesis of endometriosis through a variety of biological pathways [31]. Subsequently, Zhang [32] and other researchers used qRT-PCR to detect the expression of lncRNA CHL1-AS2 in endometriosis patients. The results showed that the expression of lncRNA CHL1-AS2 was low in eutopic endometrium but high in ectopic lesions and adjacent tissues. Moreover, the menstrual cycle did not affect the expression ratio of lncRNA CHL1-AS2, which confirmed that the abnormal expression of lncRNA CHL1-AS2 was related to the pathogenesis of endometriosis [32].

lncRNA AC002454.1

LncRNA AC002454.1 is located on human chromosome 7:92465802-92546437. Its adjacent gene is cyclin dependent kinase 6 (CDK6), and CDK6 is an important cell cycle regulator [33]. Wang et al. [34] found that the abnormal expression of lncRNA in the eutopic endometrium of endometriosis patients during the secretory phase was closely related to regulation of the cell cycle and immune regulation. Subsequently, the expression of lncRNA AC002454.1 and CDK6 in the endometrium was detected by qRT-PCR. It was found that both genes had abnormal expression and were positively correlated in the tissue. It was speculated that lncRNA AC002454.1 could alter the cell cycle by regulating the expression of CDK6, which might be closely related to the proliferation of endometriotic cells in the secretory phase, thus participating in the progression of endometriosis [34].

Steroid receptor RNA activator

Endometriosis is an estrogen-dependent disease. Steroid receptor RNA activator (SRA) is located on human chromosome 5q31.3 and is highly conserved among species. It has five separate exons with a base length of 883 nt [35]. SRA is an auxiliary activator of steroid hormone transcription that can regulate steroid hormone receptors and is abnormally expressed in hormone-related tumors such as ovarian cancer, breast cancer, prostate cancer, etc. It is closely related to the occurrence, development and prognosis of tumors [36–38]. The SRA precursor molecule can generate lncRNA SRA and mRNA by different splicing methods. However, mRNA can translate the steroid receptor activator protein (steroid receptor activator protein, SRAP). Lin et al. found that the ratio of lncRNA SRA and SRAP in normal endometrial tissue is lower than that found in endometriosis. The SRA gene can reduce the ratio of lncRNA SRA to SRAP in the development of different diseases. It was also found that endometriosis of the ovary increased the expression of SRA and estrogen receptor alpha in the surrounding ovarian tissues and decreased the level of vascular endothelial growth factor, which may affect the progress and recurrence of ovarian endometriosis [39].

MALAT-1

MALAT1 is a newly identified lncRNA expressed in nonsmall cell lung cancer and is associated with its metastasis [40]. In recent years, a large number of studies have confirmed that the gene is closely related to the occurrence, metastasis and epithelial-mesenchymal transformation of various tumors [41,42]. Liang et al. [43] has demonstrated that miR-200c, a class of small, noncoding, single-stranded RNAs approximately 20–24 nucleotides in length, could suppress the proliferation and migration of endometrial stromal cells by downregulating MALAT1. At the same time, it has been reported that MALAT1 is involved in the regulation of autophagy [44]. The main manifestations of endometriosis are decreased apoptosis and persistent ectopic survival of dysfunctional endometrial cells. Hypoxia is an important microenvironmental factor leading to endometriosis. Liu et al. [45] found that the expression of lncRNA MALAT1 and autophagy in the ectopic endometrium of patients with endometriosis were upregulated, and the upregulated level was positively correlated with hypoxia inducible factor-1alpha (HIF-1alpha). In in vitro models, the upregulation of lncRNA MALAT1 is dependent on HIF-1 signaling; when lncRNA MALAT1 is knocked out, hypoxia-induced autophagy is also inhibited. It has been confirmed that lncRNA MALAT1 mediates hypoxia-induced autophagy and participates in the progression of endometriosis. Li et al. [46] hypothesized that lncRNA MALAT1 was mainly located in the nucleus of granulosa cells with endometriosis, while the expression of lncRNA MALAT1 was negatively correlated with the expression of P21. In the cell model, MALAT-1 gene knockout can upregulate P21 and P53 expression and phosphorylate erk1/2. Thus, MALAT-1 may regulate the proliferation of granulosa cells through P21/P53-dependent cell cycle regulation and then activate the ERK/MAPK signaling pathway to participate in the occurrence and development of endometriosis [46].

Other related lncRNA

Sha et al. [47] detected cell proliferation and migration by CCK-8 and Transwell experiments. The results showed that lncRNA LINC00261 could inhibit cell proliferation and migration and induce cell apoptosis in the CRL-7566 endometriosis cell line. It can be concluded that lncRNA LINC00261 could inhibit the growth and migration of endometriotic cells. Liu et al. [48] found that lncRNA LINC01279 was abnormally expressed in patients with endometriosis, which was closely related to cell cycle-dependent kinase-14 and CXC motif chemokine ligand-12. According to these results, lncRNA LINC01279 may be involved in the pathogenesis of endometriosis and may become one of the potential targets for the treatment of endometriosis.

Conclusions

LncRNAs play an important role in cell proliferation, differentiation and apoptosis. lncRNAs also participate in the occurrence and development of many diseases and play a role in the prognosis of diseases. The abnormal expression of many lncRNAs is closely related to the occurrence and development of endometriosis, which may participate in many biological processes such as cell proliferation, apoptosis, invasion and metastasis. The regulation mechanism of lncRNA is complex and diverse and may regulate gene expression. With the development of high-throughput sequencing and gene chip technology, the role and interaction of lncRNAs in the occurrence and development of endometriosis are attracting increasing attention. With the continuous development of in-depth research in this field, the specific role of lncRNA in the pathogenesis of endometriosis will be further revealed, and it may become a potential target for treatment or evaluation of patient prognosis, which has very important clinical value. The specific pathogenesis of endometriosis still needs more research, which will provide better programs for the diagnosis and treatment of endometriosis and improve the quality of life of women with endometriosis of childbearing age.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgement

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