European Journal of Obstetrics & Gynecology and Reproductive Biology: X 5 (2020) 100067

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.elsevier.com/locate/eurox

Progress in understanding the relationship between long noncoding RNA and endometriosis

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ARTICLE INFO

Article history:
Received 24 February 2019
Received in revised form 5 June 2019
Accepted 10 June 2019
Available online 15 June 2019

Keywords:
Endometriosis
Non-coding RNA
lncRNAs
Early diagnosis

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.

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].

Abbreviation: EMs, Endometriosis; lncRNAs, long non-coding RNAs; ncRNAs, non-coding RNAs; snRNAs, small nuclear RNAs; piRNAs, PIWI-interacting RNAs; siRNAs, short inhibitory RNAs; NATs, natural antisense transcripts; Igf2, insulin-like growth factor 2; Igf1r, insulin-like growth factor-1 receptor; CDK6, cyclin dependent kinase 6; SRA, Steroid receptor RNA activator; SRAP, steroid receptor activator protein; HIF-1α, Hypoxia inducible factor-1alpha.

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http://dx.doi.org/10.1016/j.eurox.2019.100067

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

The authors thank Jun Xiao for helpful discussion and review of this manuscript.

References

[1] Rossi AC, Prefumo F. The effects of surgery for endometriosis on pregnancy outcomes following in vitro fertilization and embryo transfer: a systematic review and meta-analysis. Arch Gynecol Obstet 2016;294:647–55.
[2] Parkin KL, Fazleabas AT. Uterine leukocyte function and dysfunction: a hypothesis on the impact of endometriosis. Am J Reprod Immunol 2016;75:411–7.
[3] Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril 2016;106(1552):71.e2.
[4] Uche M, Fernando I, George C. Consensus on current management of endometriosis. Hum Reprod 2013;28:3162–3.
[5] Nnoaham KE, Lone H, Premila W, Thomas DH, Fiorenzo DCN, Carlo DCN, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96(366):73.e8.
[6] Steven S, Gerard D, Carmen D, Lone H, Attila B, Iris B, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod 2012;27:1292–9.
[7] Xu XX, Jia SZ, Dai Y, Zhang JJ, Li XY, Shi JH, et al. Identification of circular RNAs as a novel biomarker for ovarian endometriosis. Chin Med J 2018;131:559–66.
[8] Spizzo R, Almeida MI, Colombatti A, Calin GA. Long non-coding RNAs and cancer: a new frontier of translational research? Oncogene 2012;31:4577–87.
[9] Okazaki Y, Furuno M, Kasukawa T, Adachi J, Bono H, Kondo S, et al. Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. Nature 2002;420:563–73.
[10] Wapinski O, Chang HY. Long noncoding RNAs and human disease. Trends Cell Biol 2011;21:354–61.
[11] Flynn RA, Chang HY. Long noncoding RNAs in cell-fate programming and reprogramming. Cell Stem Cell 2014;14:752–61.
[12] Philippen LE, Dirkx E, Costa-Martins PAD, Windt LJD. Non-coding RNA in control of gene regulatory programs in cardiac development and disease. J Mol Cell Cardiol 2015;89:51–8.
[13] Ulitsky I, Bartel D. lincRNAs: genomics, evolution, and mechanisms. Cell 2013;154:26–46.
[14] Rinn JL, Chang HY. Genome regulation by long noncoding RNAs. Annu Rev Biochem 2012;81:145–66.
[15] Johnsson P, Lipovich L, Dan G, Morris KV. Evolutionary conservation of long non-coding RNAs; sequence, structure, function. Biochim Biophys Acta 2014;1840:1063–71.
[16] Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res 2012;22:1775–89.
[17] Harrow J, Frankish A, Gonzalez JM, Tapanari E, Diekhans M, Kokocinski F, et al. GENCODE: the reference human genome annotation for the ENCODE Project. Genome Res 2012;22:1760–74.
[18] Moraes F, Góes A. A decade of human genome project conclusion: scientific diffusion about our genome knowledge. Biochem Mol Biol Educ A 2016;44:215–23.
[19] Nayoung S, Robert B. Small RNAs in early mammalian development: from gametes to gastrulation. Development 2011;138:1653–61.
[20] Rolf B, Tanja V. Biological and bioinformatical approaches to study crosstalk of long-non-coding RNAs and chromatin-modifying proteins. Cell Tissue Res 2014;356:507–26.
[21] Hannon GJ, Rivas FV, Murchison EP, Steitz JA. The expanding universe of noncoding RNAs. Cold Spring Harb Symp Quant Biol 2006;71:551–64.
[22] Atianand MK, Cafferey DR, Fitzgerald KA. Immunobiology of long noncoding RNAs. Annu Rev Immunol 2017;35:177–98.
[23] Wu T, Du Y. LncRNAs: from basic research to medical application. Int J Biol Sci 2017;13:295–307.
[24] Ariel I, Weinstein D, Voutilainen R, Schneider T, Lustigyariv O, De GN, et al. Genomic imprinting and the endometrial cycle. The expression of the imprinted gene H19 in the human female reproductive organs. Diagn Mol Pathol B 1997;6:17–25.
[25] Panir K, Schjenken JE, Robertson SA, Hull ML. Non-coding RNAs in endometriosis: a narrative review. Hum Reprod Update 2018;24:497–515.
[26] Hong S, Guo W, Yan P, Ying Z, Qiong-Ni Z, Tai-Lin L, et al. H19 lncRNA mediates 17β-estradiol-induced cell proliferation in MCF-7 breast cancer cells. Oncol Rep 2015;33:3045–52.
[27] Ling Z, Fu Y, Ji-Hang Y, Sheng-Xian Y, Wei-Ping Z, Xi-Song H, et al. Epigenetic activation of the MiR-200 family contributes to H19-mediated metastasis suppression in hepatocellular carcinoma. Carcinogenesis 2013;34:577–86.
[28] Ghazal S, Mckinnon B, Zhou J, Mueller M, Men Y, Yang L, et al. H19 lncRNA alters stromal cell growth via IGF signaling in the endometrium of women with endometriosis. EMBO Mol Med 2015;7:996–1003.
[29] Wen-Long G, Ming L, Yanyan Y, Huixia Y, Qinping L, Yang B, et al. The imprinted H19 gene regulates human placental trophoblast cell proliferation via encoding miR-675 that targets Nodal Modulator 1 (NOMO1). RNA Biol 2012;9:1002–10.
[30] Andrew K, David O, Paul M, Michael K, Luisa D, Guillaume S, et al. The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r. Nat Cell Biol 2012;14:659–65.
[31] Sun PR, Jia SZ, Lin H, Leng JH, Lang JH. Genome-wide profiling of long noncoding ribonucleic acid expression patterns in ovarian endometriosis by microarray. Fertil Steril 2014;101(1038):46.e7.
[32] Zhang C, Wu W, Ye X, Ma R, Luo J, Zhu H, et al. Aberrant expression of CHL1 gene and long non-coding RNA CHL1-AS1, CHL1-AS2 in ovarian endometriosis. European journal of obstetrics, gynecology. Reprod Biol 2019;236:177–82.
[33] Tigan AS, Bellutti F, Kollmann K, Tebb G, Sexl V. CDK6—a review of the past and a glimpse into the future: from cell-cycle control to transcriptional regulation. Oncogene 2015;35:3083–91.
[34] Wang Y, Li Y, Yang Z, Liu K, Wang D. Genome-wide microarray analysis of long non-coding RNAs in eutopic secretory endometrium with endometriosis. Cell Physiol Biochem 2015;37:2231–45.
[35] Yuechao Z, Ping G, Yiru C, Nwachukwu JC, Sathish S, Chemyong K, et al. Dual suppression of estrogenic and inflammatory activities for targeting of endometriosis. Sci Transl Med 2015;7: 271ra9..
[36] Penner Carla C, Cooper Charlton, Nugent Zoann, et al. Steroid receptor RNA activator protein (SRAP) expression as a prognostic; factor in ER plus human breast tumors. J Cancer Res Clin Oncol 2013;139:1637–47.
[37] Jitao W, Fan F, Diandong Y, Shengqiang Y, Jianqiu L, Zhenli G. Investigation of key genes associated with prostate cancer using RNA-seq data. Int J Biol Markers 2014;29:e86.
[38] Foulds CE, Anna T, Weiwen L, Andrew L, Tsai SY, Ming-Jer T, et al. Research resource: expression profiling reveals unexpected targets and functions of the human steroid receptor RNA activator (SRA) gene. Mol Endocrinol 2010;24:1090–105.
[39] Lin K, Zhan H, Ma J, Xu K, Wu R, Zhou C, et al. Silencing of SRA1 regulates ER expression and attenuates the growth of stromal cells in ovarian endometriosis. Reprod Sci 2017;24:836–43.
[40] Tony G, Monika HM, Moritz E, Jeff H, Youngsoo K, Alexey R, et al. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res 2013;73:1180–9.
[41] Zhao Y, Yang Y, Trovik J, Sun K, Zhou L, Jiang P, et al. A novel wnt regulatory axis in endometrioid endometrial cancer. Cancer Res 2014;74:5103–17.
[42] Brock M, Schuoler C, Leuenberger C, Bühlmann C, Haider TJ, Vogel J, et al. Analysis of hypoxia-induced noncoding RNAs reveals metastasis-associated lung adenocarcinoma transcript 1 as an important regulator of vascular smooth muscle cell proliferation. Exp Biol Med 2017;242:487–96.
[43] Liang Z, Chen Y, Zhao Y, Xu C, Zhang A, Zhang Q, et al. miR-200c suppresses endometriosis by targeting MALAT1 in vitro and in vivo. Stem Cell Res Ther 2017;8:251.
[44] Huang J, Yang Y, Fang F, Liu K. MALAT1 modulates the autophagy of retinoblastoma cell through miR-124-mediated stx17 regulation. J Cell Biochem 2018;119:3853–63.

[45] Liu H, Zhang Z, Xiong W, Zhang L, Du Y, Liu Y, et al. Long non-coding RNA MALAT1 mediates hypoxia-induced pro-survival autophagy of endometrial stromal cells in endometriosis. J Cell Mol Med 2019;23:439–52.
[46] Li Y, Liu Y, Chen S, Chen X, Ye D, Zhou X, et al. Down-regulation of long non-coding RNA MALAT1 inhibits granulosa cell proliferation in endometriosis by up-regulating P21 via activation of the ERK/MAPK pathway. Mol Hum Reprod 2019;25:17–29.
[47] Sha L, Huang L, Luo X, Bao J, Gao L, Pan Q, et al. Long non-coding RNA LINC00261 inhibits cell growth and migration in endometriosis. J Obstet Gynaecol Res 2017;43:1563–9.
[48] Liu J, Wang Q, Zhang R, Zhang C, Lin J, Huang X. Identification of LINC01279 as a cell cycleassociated long noncoding RNA in endometriosis with GBA analysis. Mol Med Rep 2018;18:3850–8.