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MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) in endometriosis — review of literature

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ABSTRACT

Endometriosis is a disease of the female genital organs, the causes of which are not fully understood. Recent studies have shown that non-coding RNAs (ncRNAs) like long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) can contribute to the pathogenesis of endometriosis. Profiling of miRNA and lncRNA expression is carried out using state-of-the-art molecular biology techniques (RT-PCR, sequencing, microarray analysis). The use of the latest technologies may make it possible to establish a genetic profile, which is a promising prospect for early diagnosis of endometriosis. In the future, genetic testing may become the gold diagnostic standard and eliminate invasive laparoscopy. In the case of endometriosis, it is important to extend the research to molecular aspects, which may facilitate the diagnosis of the disease or indicate new (based for example ncRNA) treatment methods. The paper presents the latest data on the importance of miRNA/lncRNA in endometriosis.

Keywords: endometriosis; miRNA; lncRNA

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INTRODUCTION

According to the classical definition, endometriosis is the surgical detection of endometrial tissue outside the uterine cavity, however, this narrow anatomical definition turns out to be insufficient to explain the pathogenesis of endometriosis, the molecular substrate, the full spectrum of its clinical manifestations, frequent relapses and reactions to modern methods of treatment [1]. Women wait an average of 8–10 years for a diagnosis. The basic method of recognizing endometriosis is laparoscopy (called the gold standard), which consists in excision of endometrial lesions [2].

The pathogenesis of endometriosis is controversial — immune, hormonal, genetic and environmental factors are involved [3]. There is no single theory that would fully explain the emergence of endometriosis. A very popular theory is the Sampson theory. It seems that the disease may arise as a result of the phenomenon of "retrograde menstruation". During menstruation, part of the menstrual secretion enters the peritoneal cavity through the fallopian tubes. The live endometrial cells delivered in this way can inhabit the peritoneal cavity, creating ectopic lesions. However, it has been shown that 90% of women without endometriosis experience retrograde menstruation. Another theory of the cause of endometriosis is the so-called metaplasia theory, *i.e.*, the transformation of cells lining the peritoneal cavity into endometrial cells outside the uterine cavity. A malfunctioning immune system may be responsible for the causes of the disease. Weakened immunity or autoimmune diseases promote the formation of foci of endometriosis. Another theory about the causes of endometriosis speaks of a genetic predisposition. If your grandmother, mother or sister has endometriosis, you are more likely to suffer from the disease as well. As a result of changes at the level of genes that participate in the differentiation of anatomical structures of the genitourinary system, abnormal location of stem cells may occur. The above phenomenon, together with immunological changes and pro-inflammatory

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environment of the peritoneum, determines the progression of endometriosis.

In the treatment of symptomatic endometriosis, hormone therapy and analgesics are used, however, endometriosis often returns [3]. Therefore, it is important to have a comprehensive and individualized approach to the patient and to find a non-invasive diagnostic marker of the disease. In the research plans of the area associated with endometriosis is the identification of the molecular basis of this disease.

RNAs are divided into two classes: messenger RNA (mRNA), which is involved in protein synthesis, and non-coding RNA (ncRNA). First, the work focuses on the analysis of non-coding RNAs (miRNA/lncRNAs) in patients affected by endometriosis. ncRNAs are candidates for reliable laboratory biomarkers of this disease [4, 5].

RNA molecules can become desirable biomarkers in the non-invasive diagnosis of endometriosis because they are characterized by tissue specificity and high stability in biological fluids [6].

MicroRNA (miRNA)

MicroRNAs circulating in the blood have potential as useful biomarkers of endometriosis [7]. In tissues, miRNAs are stable. They are detected in the serum of patients using quantitative methods (qPCR). Mature miRNAs are single-stranded molecules of non-coding RNA with a length of about 22 nucleotides. They regulate gene expression by influencing the translation process [8]. The greatest prognostic power is given by the determination of several microRNAs, whose change in expression is observed in endometriosis.

Genes for microRNAs can occur between protein-coding sequences and function as stand-alone transcription units, or they can be in coding sequences [9]. Genes for miRNAs are found both in exons, introns, and in untranslated regions [10]. Such a transcription unit arrangement may lead to the simultaneous creation of miRNA and mRNA transcripts [9]. The miRNA genes are organized in a manner characteristic of polymerase II and III, transcribing the genes of small RNAs [9, 10].

In the process of transcription, the primary pri-miRNA transcript is created. Pri-miRNA is then treated with Drosh ribonuclease, which releases pre-miRNAs with a length of about 60–70 base pairs [9]. Exportin-5 transfers pre-miRNAs from the cell nucleus to the cytoplasm, where the resulting molecules undergo further processing by the Dicer enzyme [9–11].

The catalytic reaction results in a double-stranded miRNA-miRNA* duplex consisting of a leading strand and a lagging strand [11]. After duplex breakdown, the passenger thread is usually degraded, sometimes combining with Ago proteins to maintain miRNA functions. The leading strand, on the other hand, binds to a number of proteins, including RNA-binding proteins and the aforementioned catalytic Ago proteins (Argonaute), forming a complex miRNP (microribonuclear protein complex), called RISC (RNA-induced silencing complex) [10, 11]. The resulting complex, mainly due to Ago proteins, performs mRNA degradation or translational reprisals, and therefore negatively regulates gene expression at the post-transcriptional level [10, 11]. This is possible due to the complementarity of miRNA with target mRNA in the 3'UTR region [11]. In the case of full complementarity, mRNA degradation occurs. If complementarity is incomplete, translation is inhibited [10, 11]. It is believed that up to 30% of protein-coding genes can be regulated by the corresponding miRNAs. The microRNAs are "guardians" that take care of the proper course of processes such as cell division, proliferation, differentiation or cell apoptosis, which are of fundamental importance for the proper functioning of the body [12].

MiRNA IN ENDOMETRIOSIS

In endometriosis, there is a pool of genes regulated by miRNAs. The miRNAs dominant in endometrial cells include miRNAs from the let family. It is known that Let-7b with pleiotropic activity regulates the expression of ER α/ß, KRAS 4A/4B, Cyp19 or IL-6 [13] genes, which is important in the pathophysiology of endometriosis. The development of this disease is also influenced by the altered expression of miR449b3p [14]. In ectopic endometrium, altered levels of miR-139-5p and miR-375 expression have been detected that can regulate the expression of transcription factors HOXA9 and HOXA10 and the endothelin 1 gene (EDN1), influencing the development of endometriosis [15].

MicroRNAs in endometriosis regulate the expression of mTOR kinase (the mammalian target of rapamycin) and genes of the VEGF pathway [16].

mTOR kinase affects the regulation of cell growth, proliferation and movement, as well as translation and transcription processes. VEGF enhances the process of angiogenesis in endometriosis.

An analysis of the miRNA profile in the eutopic endometrium of women with endometriosis was performed. A pool of 667 human miRNAs in patients with endometriosis was studied. Two of the miRNA pools studied were shown to be subject to increased expression, while 13 miRNAs were characterized by reduced levels of expression in these patients.

In addition, hsa-miR-483-5p and miR-629 have been shown to have significantly reduced expression in patients with endometriosis [17]. Studies of the pool of various microRNAs in endometriosis have shown that they can have a significant impact on the development of lesions (Tab. 1).

* complementary RNA

Table 1. MicroRNA (miRNA) regulatory functions in endometriosis	
Biological process	miRNA
Hypoxic injury	miR-15b and miR-16
Tissue repair and TGFβ-regulated pathways	miR-1, miR-21, miR-141 and miR-194
Inflammation	miR-199a, miR-16, miR-302a, miR-542-3p
Cell growth, proliferation and apoptosis	miR-15b/16, miR-143, miR-145, miR-20a, miR-221 and miR-222
Extracellular matrix remodelling	miR-29c
Angiogenesis	miR-126

Recent research indicates that plasma miRNAs may be potential diagnostic markers of endometriosis [18]. The search for miRNAs as biomarkers and modeling was conducted on a group of 120 patients (38 people in the control group and 82 people with endometriosis as a study group), which was then validated in an independent group of 90 patients (30 in the control group and 60 in the study group) [19].

The researchers identified a set of 42 miRNAs that can distinguish women with endometriosis from women without endometriosis, based on genome-wide miRNA expression profiling. The method has diagnostic power for mild endometriosis, which confirmed the biological relationship between some miRNAs (such as hsa-miR-125b-5p, hsa-miR-28-5p and hsa-miR-29a-3p) and endometriosis.

A possible biological link between some miRNAs and endometriosis has therefore been confirmed, but their potential as useful biomarkers require well-designed, large cohort studies and detailed analyses.

MicroRNAs are involved in the pathogenesis of endometriosis by alleviating inflammation, proliferation, angiogenesis, and tissue remodeling [20, 21]. It has been shown that potential biomarkers of endometriosis may be miR-21, miR-29c, miR-100 and miR-143 [20, 21]. These miRNAs are regulated upwards in ectopic endometrial tissues. The target for miR-29c during the late secretory phase is c-Jun mRNA, a gene that drives proliferation, apoptosis, and invasion of endometrial cells. Increased expression of miR-100 inhibits cell proliferation, migration, and invasion in the cancer model. Lowering the expression of miR-100 stimulates metastasis. Thus, increasing the expression of miR-100 and miR-143 in endometrial tissues triggers a defense mechanism against the possibility of transformation to malignant changes in the phenotype of benign endometriosis [20, 21].

MOMENDO project (https://cordis.europa.eu/article/id/418294-molecular-cues-into-the-pathogenesis-of-endometriosis/pl) detected that miRNAs are dysregulated in endometriotic tissue, thereby contributing to the invasive development of endometriotic cells. Importantly, the experimental increase in the expression of selected microRNAs inhibited many pathogenic features of patient-taken endometriotic cells in cell culture, including their growth, invasiveness, and stem status. Using transcriptomics, it has been shown that some patients' endometriotic cells are like cancer cells; This new data can be used in personalized therapies. The positive therapeutic effects obtained in experimental preclinical models paved the way for some strategies to emerge therapeutic targets, including gamma-secretase inhibitors, microRNA-based drugs, and anti-inflammatory compounds that will be evaluated in clinical trials of endometriosis.

Abnormal expression of individual miRNAs may result from changes in the genome, abnormalities in their biogenesis, or may be related to epigenetic factors regulating gene expression. Attention is paid not only to the genetic causes of changes in miRNA expression, such as single nucleotide polymorphisms (SNPs) in miRNA genes, affecting the transcription and formation of pri-miRNAs or subsequent interactions between mature microRNAs and mRNAs, but also to the possibility of changes in the level of methylation of these genes. Therefore, not only structurally determined changes in the level of expression of miRNAs are important, but also their epigenetic regulation. Perhaps these mechanisms will become a target in the future for the development of new therapies that modulate the expression of miRNAs through changes in the level of methylation of their genes. However, the use of microRNAs in the diagnosis of endometriosis is only in the initial phase of research.

LncRNA

According to the ENCODE consortium (Encyclopedia of DNA Elements, 2012) human genetic material is transcribed in 93% (of which 39% of tranxrypts correspond to introns and UTR sequences of protein-coding genes, 1% to exons, and 54% to protein-coding genomes) [22, 23]. Before non-coding sequences were studied, they were thought to be nothing more than "junk DNA".

The first long non-coding RNAs, treated as mRNAs at the time of their discovery, were the H19 and Xist genes

(X-Inactive Specific Transcript, a transcript specific for X chromosome inactivation) [24–28].

The H19 gene was identified on chromosome 7 of mice. H19 forms a group together with the insulin-like growth factor Igf2 (Insulin Like Growth Factor 2) gene, but unlike it, it is transcribed but not translated [24].

The Xist gene belongs to a complex of genes in one of the regions of the X chromosome, called XIC (X Inactivation Center, the center of X chromosome inactivation). The Xist gene is crucial for the correct phenomenon of lionization described by geneticist Mary Lyon [28, 29]. It is the process of switching off one of the X chromosomes in women (or other female mammals), thanks to which gene expression is equalized in women and men [30]. The function of shutting down the entire chromosome is unique in the world of lncRNA.

Long non-coding RNAs have a length of more than 200 base pairs [23]. Exon regions are located within the lncRNA genes. Their large amount as a result of splicing allows the formation of diverse forms of this family. lncRNAs perform various functions, including those of clinical relevance [23]. The structure of lncRNAs is similar to protein-coding genes (PCG). However, the level of expression of lncRNA genes is much lower than PCG.

The reduced level of expression is the result of differences in thestructure of lncRNA gene promoters and amplifiers (this applies mainly to epigenetic changes in histones). The change in expression reduces the severity of the transcription process and with less stability of the lncRNA molecule from the mRNA molecule [23].

Depending on the type of lncRNA, their stability varies. Less stable are lncRNAs associated with the intron and promoter. Intergenic lncRNAs, antisense or 3'UTR end are more stable [23]. lncRNAs are specifically expressed in tissues and even cells [31, 32]. LncRNA expression may be associated with single nucleotide polymorphisms located within genes and their promoters. This may affect the pathogenesis of diseases [32]. lncRNAs due to the specificity of expression can play an important role in the regulation of processes in the organisms, as well as participate in the repair of pathological processes.

LncRNAs are common throughout the cell [33] and can therefore perform a variety of functions. lncRNAs localized in the nucleus affect chromatin, transcription, RNA processing. lncRNAs located in the cytoplasm affect mRNA stability, translation, and cellular signaling pathways. As a result of environmental changes or infection, lncRNAs can travel from one cell location to another [33]. Thanks to the flexible and dynamic structure of lncRNA (it can take on a secondary structure), the functions of these molecules are very versatile. They can change locations, especially nuclear ones, and interact with proteins [33]. lncRNAs are characterized by low sequence conservatism, which allows for variability of the structure and subsequent function and regulatory specialization of lncRNAs [34, 35]. lncRNAs can interact in two ways: cis and trans (according to Kopp F. and Mendell J) [35, 36]. The cis method means the effect of lncRNA on the expression of neighboring genes [36–39], *i.e.*, directly affecting the transcription process as an enhancer, "stopping" transcription factors, affecting chromatin looping and gene methylation [39]. The trans method involves controlling the expression of distant genes by influencing their promoters and enhancers. lncRNAs can also affect proteins that bind to these regions and, in complex with them, affect chromatin conformation and polymerase activity [39].

One of the first trans-function lncRNAs discovered were the HOTAIR (Homeobox (Hox) Transcript Antisense Intergenic RNA), intergenic RNAs antisensibly complementary to the Homeobox transcript and MALAT1, which, as it turned out in further studies, play a significant role in the development of endometriosis [40–42].

LncRNA IN ENDOMETRIOSIS

Recently, in endometriosis research, long non-coding RNAs [42] have been of interest, which tend to have a greater sequence matching and thus the specificity of the action on target genes. All stages of the transfer of genetic information from DNA to protein require the participation of non-coding RNA molecules. Their participation is particularly marked in the mechanisms leading to the inclusion or exclusion of the expression of individual genes.

Altered expression of lncRNAs in endometriosis is involved in the regulation of numerous processes include epithelial–mesenchymal transition (EMT), endometriosis cell stemness, angiogenesis, lesion establishment and growth, endometriosis cell survival, proliferation and invasion, oxidative stress, autophagy, and endometrial receptivity (Fig. 1).

In the research of Zhou et al. [43], 388 lncRNA transcripts studied were overexpressive and 188 were overexpressed, and 188 were reduced in ectopic endometrial compared to eutopic endometrial.

It is known that lncRNA expression varies in the serum of women with endometriosis, eutopic endometrial of women with endometriosis compared to healthy women, and in ectopic endometrial ovaries compared to eutopic endometrial in women with endometriosis [43].

The types of lncRNAs and their changes in endometriosis expression are presented in Table 2.

However, the clinical relevance and biological mechanism of lncRNA in the development of endometriosis remain largely unknown.

Important for endometriosis lncRNA is H19. H19 is 2–3 kb lncRNA. It is located on the human chromosome

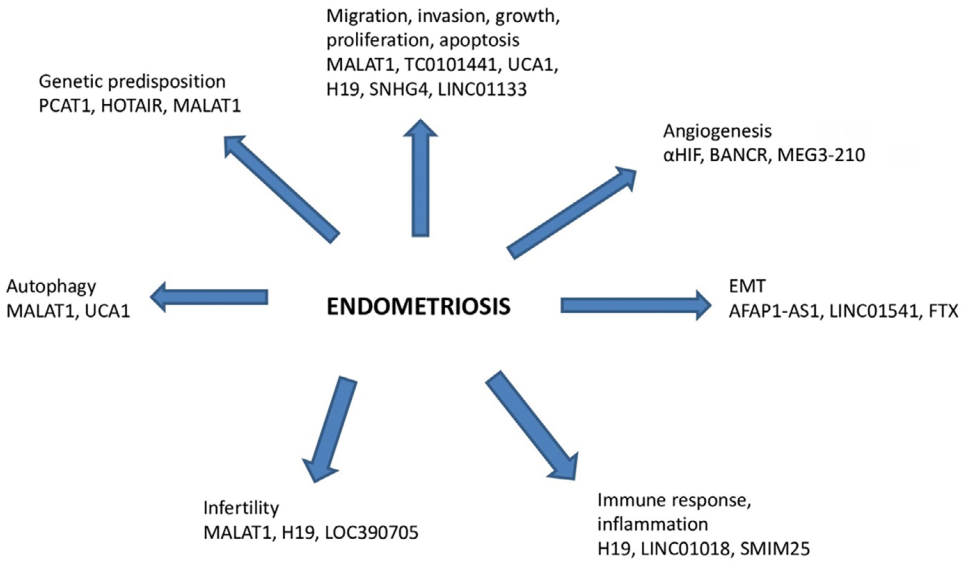

Figure 1. Scheme of phenotypic changes that occur as a result of altered lncRNA expression in endometriosis

Table 2. Differentially expressed lncRNAs in endometriosis

lncRNA			
Upregulated		**Downregulated**	
Endometriosis tissue	**Body fluids**	**Endometriosis tissue**	**Body fluids**
MALAT1 CCDC144NL-AS1 AC002454.1 TC0101441 AFAP1-AS1 H19 UCA1 SNHG4 LINC01133	TC0101441	LINC00261 LINC01541 MEG3-210 FTX UCA1 H19	MALAT1 H19 (T17) UCA1

11p15.5, which can be transcribed but not translated. Together with insulin-like growth factor 2 (IGF2), H19 forms a pair of imprinted genes [44]. A reduction in H19 lncRNA levels has been demonstrated in patients with endometriosis in the eutopic endometrium. Decreased H19 expression leads to increased let-7 activity, which in turn inhibits IGF1R (insulin-like growth factor 1 receptor). This process limits the proliferation of endometrial stroma [45].

MALAT1 is another important lncRNA in endometriosis. It was shown that miR-200c, which is regulated by MALAT1, was down-regulated in endometrial tissue inendometriosis [46]. Many studies have confirmed that the MALAT1 gene is associated with recurrence, metastasis and epithelial-mesenchymal transformation of various tumors [47, 48].

A unique pool of serum lncRNAs was detected, which was associated with the severity and progression of endometriosis. Thanks to the detected lncRNAs, it is possible to distinguish between early and severe stages of endometriosis. lncRNAs can therefore be non-invasive biomarkers for diagnosing endometriosis and act as important regulators of its development [49].

Huang et al. concluded that lowering UCA1 lncRNA levels cannot be a biomarker for the diagnosis of ovarian endometriosis. They pointed out that in most patients with endometriosis, UCA1 expression was increased in ectopic tissue compared to expression in eutopic endometrial tissue. Most importantly, at the time of discharge, serum UCA1 levels were reduced in relapsed patients compared with non-relapsed patients [50].

lncRNA TC0101441 has been identified as a potential extracellular follicular biomarker for endometriosis. Serum extracellular vesicle levels TC0101441 were

significantly higher in patients with stage 3/4 endometriosis compared to patients with stage 1/2 endometriosis and healthy subjects. This indicates the importance of circulating extracellular vesicles TC0101441 as a biomarker of endometriosis [51].

Whole-genome DNA sequencing studies identified genetic variations in lncRNA loci that may affect the pathogenesis of endometriosis. A possible mechanism is disruption of lncRNA function by single nucleotide polymorphisms. A specific variant of polymorphic may predispose patients to endometriosis. Studies of Korean patients showed that SNP rs10965235 in the CDKN2B-AS gene located on chromosome 9p21.3 is associated with severe endometriosis [52].

Another polymorphism SNP rs3820282 located in the WNT4 intron on chromosome 1p36.12 is associated with endometriosis. This polymorphism can affect the amplifier-promoter interaction, resulting in a decrease in the level of LINC00339 and an increase in the level of CDC42 [53].

Genetic changes at SNP sites rs1838169 and rs17720428 on chromosome 12q13.3 in HOTAIR are commonly detected in patientswith endometriosis [54]. These variants appear to increase lncRNA stability, resulting in reduced levels of HOTAIR-regulated HOXD10 and HOXA5 transcripts.

The SNP variant rs591291 located on chromosome 11q13.1 in the MALAT1 promoter region was associated with an increased risk of endometriosis in the Chinese population, indicating that a change in MALAT1 expression level may affect the risk of endometriosis [55]. SNP rs710886 in PCAT1 is known to be associated with an increased risk of developing endometriosis [56]. rs710886 appears to interfere with PCAT1 miR-145 sponging, affecting the expression of FASCIN1, SOX2, MSI2, SERPINE1, and JAM-A and the proliferative and invasive capacity of endometriosis stem cells. In summary, genetic variants associated with endometriosis may predispose patients to disease by disrupting the regulatory function of the lncRNA gene through various mechanisms.

In conclusion, genomic and transcriptomic studies of the whole genome showed correlations of lncRNA with endometriosis.

CONCLUSIONS

The literature data presented in the article indicate that work is still underway to search for markers of endometriosis. These studies may contribute to a better understanding of the mechanisms of this disease and the development of new treatments. Perhaps with appropriate manipulations at the molecular level (including miRNA/lncRNA), in the future some diseases, including endometriosis, can be completely eliminated.

Article information and declarations

Author contributions

TS, BS contributed to the conception of the study. HR and KS contributed significantly to manuscript preparation. TS, BS wrote the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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