The Role of miRNA in Endometriosis

miRNA'ların Endometriosiz'deki Rolü

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ABSTRACT

Endometriosis is characterized by the presence of endometrial gland and stroma outside of the endometrial cavity. Not only the complex nature of disease limits the identification of the pathogenic mechanisms of endometriosis but the lack of simple diagnostic procedure is the major limitation. So identification of a simple clinical tool for the diagnosis of endometriosis has become a high priority research objective. MicroRNAs (miRNAs), a class of small noncoding RNA molecules, have been recognized as key post-transcriptional regulators those may associate with endometriosis. In the present paper, we aimed to review the studies which focused on the prognosis and diagnosis of the endometriosis and miRNAs. As studies on the role of miRNAs in the pathogenesis of endometriosis increase in the literature, new ideas can be put forward for early diagnosis, prevention and treatment of the endometriosis.

Keywords: miRNA, endometriosis, biomarker, pathogenesis

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ÖZET

Endometriozis, uterus, pelvik periton, yumurtalıklar ve rektovajinal septum dışındaki endometriyum benzeri implantasyon dokusudur ve nadir durumlarda diyafram, plevra ve perikardiyumda pelvik ağrıya neden olabilir. Endometriozise katkıda bulunan genetik ve epigenetik faktörleri içeren çeşitli nedenler vardır. Epigenetik faktörler arasında, mikro RNA'lar (miRNA'lar), endometriozisin patogenezinde ve tanısında geniş çapta araştırılmıştır. Bu çalışmada, endometriozis ve spesifik miRNA'ların prognozu ve tanısını birleştiren çalışmaları gözden geçirmeyi amaçladık. Bu çalışmanın, araştırmacılara bu fenomenler arasındaki bu ilişkiye odaklanmaları ve endometriozis teşhisi için yeni miRNA biyobelirteçleri bulmaları için rehberlik edeceğini düşünmekteyiz.

Anahtar Sözcükler: miRNA, endometriozis, biyobelirteç, patogenez

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INTRODUCTION

Endometriosis is an estrogen-dependent and progesterone-resistant inflammatory disease in the reproductive timespan of women. It is characterized by the presence of endometrial gland and stroma outside of the endometrial cavity (1). Although there are different types of clinical manifestations, pelvic pain and infertility are the most common ones. Moreover, susceptibility to development of epithelial ovarian cancer increases as a result of endometriosis (2-4).

During the reproductive age, endometrium as a dynamic tissue undergoes specific cyclic changes under the control of ovarian steroids. It is well documented that the ovarian steroids may enroll a central role in the pathogenesis of several uterine disorders, including endometriosis. Although the importance of ovarian steroids in phenotypic presentation of endometriosis was previously reported, the growing body of evidence confirms the network between the genetic profile, hormonal activity, menstrual cyclicity, inflammation status, and immunological factors (4,5).

Familial tendency for endometriosis have previously been reported. Women with endometriosis have a ten-fold increased risk of endometriosis in their first-degree relatives (6) Moreover, the data about monozygotic twins reveal that a 3 to 15 times higher risk in the first-degree relatives of women with endometriosis compared to those in the general population. All these knowledge may suggest the heritability of endometriosis regarding that approximately 50% of endometriosis observed in the population is due to genetic factors (7).

Genome-wide association studies (GWAS) and meta-analyses have revealed the identification of several loci that are associated with increased risk of endometriosis. Although these studies provide new insights to the pathogenic mechanisms contributing to the disease, the functional consequences and disease mechanisms are still controversial (8).

Not only the complex nature of disease limits the identification of the pathogenic mechanisms of endometriosis but the lack of simple diagnostic procedure is a major limitation. The current, the gold standard for diagnosis of the disease depends on laparoscopic investigation, followed by histopathological examination. Thus, identification of a simple clinical tool for the diagnosis of endometriosis has become a high priority research objective (9).

Identification of genetic background of a disease is remarkably critical for the diagnosis and treatment (10). In addition to gene-phenotype relationships, non-coding RNAs have widely been associated with diverse diseases including endometriosis. The present study aims to review the studies that combine non-coding RNAs, particularly micro RNAs (miRNAs) and endometriosis. This study is expected to guide the researchers to understand the nature of the endometriosis and develop novel diagnostic systems by focusing on the miRNAs.

Remembering the basic nature of multifactorial disease can be beneficial in which susceptibility gene(s) interacts with the environment to produce the phenotype. With this point of view epigenetic mechanisms becomes the center of attention. In addition to this knowledge, endometriosis known as a persistent disease with substantial gene dysregulation. Therefore, cellular memory which can be sustained by epigenetic mechanisms has a major impact in constitution of a unique cell identity for endometriotic cells (10).

The overexpression of DNA Methyltransferase 1 (DNMT1), DNMT3A, and DNMT3B genes in endometriotic tissues was reported by Wu et al. This report was the first evidence that demonstrated endometriosis as an epigenetic disease (10). Consistent with this finding, several studies provide further evidence for epigenetic changes in endometriosis. Therefore, understanding the epigenetic mechanisms involving in endometriosis may be a promising tool for the management of endometriosis (11).

Epigenetics

Epigenetics refers to reversible and heritable changes in gene expression without any change in nucleotide sequence of the genome. DNA and RNA mediated epigenetic mechanisms can switch genes on or off by the way the tissue specific gene expression profile is maintained. Hence multiple cellular responses such as development, cellular fate commitment and adaptation to the environment can be modulated as well (12).

DNA mediated epigenetic mechanisms; are mostly devoted for the control at transcriptional level through the accessibility of RNA polymerase to the promoter. It can be implemented via methylation of the DNA, histone modifications and chromatin remodeling.

RNA mediated epigenetics is a new emerging field of epigenetics. A diverse classes of RNA, ranging from small to long non-coding RNAs, have emerged as key regulators of gene expression, genome stability and defense against foreign genetic elements.

The results of the Human Genome Project indicated that 1.5% of the human genome contains protein-coding genes. However, Encyclopedia of DNA elements (ENCODE) and the Functional Annotation of the Mammalian Genome (FANTOM) are the other two large scale projects reported that vast majority of the transcribed genome is non-coding RNA (ncRNA). On the basis of their size, ncRNAs can be classified as short (<200 nucleotides) and long non-coding RNAs (lncRNAs; >200). The miRNAs, circular RNAs (circRNAs), piwiRNA are the members of the former group while long non coding RNA (lncRNAs) is the member of the later group and as a whole they enroll in RNA mediated epigenetic mechanisms as heterochromatin formation, histone modification, DNA methylation targeting, and gene silencing (12).

The discovery of the first miRNA in 1993 revolutionized the field of Medical Biology. Especially in recent years, the importance of the miRNAs has increased due to the studies in different fields (13, 14). Studies conducted after its discovery have shown that miRNAs play a critical role in human development by participating in various biological processes, and their abnormal expression is associated with several diseases including endometriosis (15-18). miRNAs may enroll in both inhibition and progression of the disease (19-21). Before giving the association of miRNAs and the endometriosis, explaining the biogenesis and action of the miRNAs could be fundamental to make the subject comprehensive.

Biogenesis and action of miRNA

miRNAs are the non-coding RNAs responsible for mainly translational repression. Their roles have been well documented in both physiological and pathophysiological conditions. Recent studies have linked specific miRNAs to biological processes including developmental stages and progression of diverse diseases (22-24).

miRNA-producing sequence would be located in the exonic, intronic or intergenic regions. RNA polymerase II and even limitedly III are responsible for the transcription of the miRNAs.

In the biogenesis of miRNA the steps are as follows (Fig.1)

1. In the nucleus.: miRNAs are transcribed by RNA PolyII to produce pri-miRNAs (hairpin structures), which are cleaved by the nuclease Drosha to generate pre-miRNA.
2. Transport from nucleus to cytoplasm: It is transported via exportin-5 and Ran-GTP to the cytoplasm for further processing by Dicer to form mature miRNAs
3. Binding of the miRNA my suppress the transcription mainly in3 ways as; translational suppression, degradation of mRNA or deadanylation of mRNA.

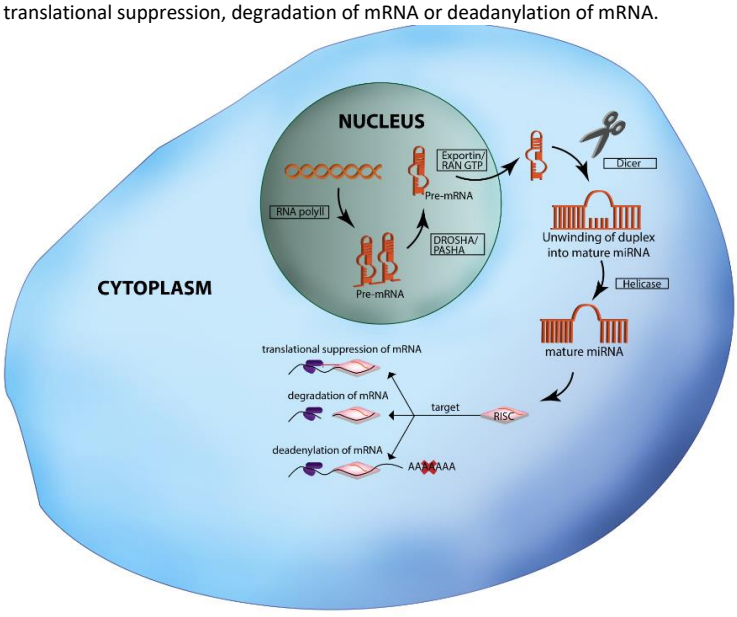

Figure 1: Biogenesis and Action of miRNA

Endometriosis and miRNAs

Many theories including implantation theory, metaplasia theory and stem cell theory were recommended for the pathogenesis of the endometriosis (22). In addition to these current theories, recent studies have shown more evidence of the role of miRNAs in the initiation and progression of the endometriosis (11,23,24). Various studies speculated that dysregulation of miRNAs may have an important role in pathogenesis of endometriosis (25). As a result of their review on this topic, Agrawal et al. stated that miR-17-5p/20a, miR-200, miR-199a, miR-143 and miR-145 have important roles in the pathogenesis of the endometriosis. miR-17-5p/20a plays a role on the pathogenesis of the endometriosis through hypoxia inducible factor (HIF)1A, vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), Ne-trin-4 (NTN4) and B-cell lymphoma 2 (BCL2) (26-29). miR-17-5p/20a increases VEGF (angiogenetic) while reducing NTN4 (anti-angiogenetic) and consequently induces abnormal angiogenesis in endometriotic foci (29, 30). The miR-200 family arrange transcription factors affecting epithelial mesenchymal transition (EMT) which is critical for the development of endometriosis and down-regulation of miR-200b might induce EMT and invasive growth of endometriosis. (31). miR-199a reduces invasion of endometrial stromal cell with suppression of the IKKβ/NF-κB pathway and interleukin-8 expression (32). Therefore, it is thought that down-regulated miR-199a in endometriosis might be associated with the pathogenesis of the endometriosis. Similar to miR-199a, overexpression of miR-145 reduces adhesion and invasion of endometrial stromal cell (Table 1).

Table 1: Endometriosis and miRNAs

Pathogenesis	Diagnostic markers	Treatment agents
miR-17-5p/20a	hsa-miR-125b-5p	miR- Let-7b
miR-200	hsa-miR-28-5p	miR-142-3p
miR-199a	hsa-miR-29a-3p	
miR-143	miR-17-5p	
miR-145	miR-20a-5p	
	miR-199a-3p	
	miR-143-3p	
	miR-451a	
	miR-3613-5p	
	miR-342-3p	
	miR-150-5p	

In addition, circRNAs which are a type of non-coding RNAs play important roles in the pathogenesis of endometriosis via regulation of miRNAs. Jiang et al. showed eight significantly and differentially expressed circRNAs in eutopic endometrium compared to the ectopic endometrium. In addition, they showed the effects of hsa_circ_0008433 on behaviors of the endometrial stromal cells with the target miRNAs. As a result, they speculated that specific circRNAs and miRNAs may have an active role on the pathogenesis of the endometriosis (33).

miRNAs as diagnostic markers for endometriosis

Endometriosis is only diagnosed by histopathological examinations (34). Only a preliminary diagnosis can be made using a physical examination and imaging methods such as ultrasonography and magnetic resonance imaging (MRI) (35). Therefore, a more easily accessible and non-invasive accurate diagnostic method is needed to allow early diagnosis of endometriosis without the use of histopathological examinations. Despite of many studies covering endometriosis-related miRNAs in the literature and although no single miRNA or biomarker miRNA panels show sufficient specificity and sensitivity for this pathology, the obtained data are promising and studies in recent years suggest that miRNAs can be used as potential biomarkers for the endometriosis (26).

miRNAs were thought to be only intracellular at first; however, in 2018, Chim et al. showed by subsequent studies that miRNAs with placental origin in the plasma, serum, tears, saliva, urine, breast milk, peritoneal fluid, cerebrospinal fluid, seminal fluid, synovial fluid, pleural fluid, bronchial lavage and follicular fluid which were identified (36,37). After that, studies began to be conducted to question whether miRNAs can be used in non-invasive diagnosis of certain diseases including the endometriosis. Nevertheless, although there were many studies for circulating miRNAs that can be used for non-invasive diagnosis, no single miRNA or any miRNA panels seems not to meet the criteria as diagnostic biomarkers (26, 38).

Vanhie et al. proposed three miRNAs for non-invasive diagnosis of the endometriosis; however, only the hsa-miR-125b-5p, hsa-miR-28-5p and hsa-miR-29a-3p had diagnostic power with an acceptable sensitivity (78%) but poor specificity (37%). Zafari et al. (38,39) proposed miR199b-3p, 224-5p and Let-7d-3p for non-invasive diagnosis of the endometriosis and this three miRNAs had the highest accuracy with high sensitivity (96%) and specificity (100%). In retrospective cohort study, Papari et al. (40) identified miR-17-5p, miR-20a-5p, miR-199a-3p, miR-143-3p, and Let-7b-5p for non-invasive diagnosis of the endometriosis and these miRNAs had high sensitivity (96%) and specificity (79%) with positive and negative predictive value of 0.80 and 0.96, respectively. In a case control study, Cosar et al. (41) found the highest accuracy by combining miR-125b-5p, miR-451a and miR-3613-5p for non-invasive diagnosis of the endometriosis. In addition, they showed that miR-125b-5p had the greatest potential as a single diagnostic marker (41). In a prospective study, Moustafa et al. (42) found significantly higher expression of miR-125b-5p, miR-150-5p, miR-342-3p and miR-451a and significantly lower expression of miR-3613-5p and let-7b in the endometriosis patient. In addition, they showed the highest accuracy by combining miR-125b-5p, miR-150-5p, miR-342-3p, miR-451a, miR-3613-5p and Let-7b (42).

Despite lots of studies with similar and different miRNAs in the literature, we are at the beginning of this issue and further studies are still needed.

miRNAs for treatment of endometriosis

In the literature, there were many studies about microRNAs proposed as treatment agents for some chronic diseases and cancers (43-46). In recent years, considering the role of miRNAs in the endometriosis pathogenesis, the scientists have been evaluated whether miRNAs can be used to treat the endometriosis.

Accordingly, in the murine model study carried out by Sahin et al. (47), microRNA Let-7B (loss of it), which plays a role in the pathogenesis of the endometriosis, was tested to treat the endometriosis. As a result, they showed that local treatment of endometriosis with Let-7b is a promising therapy without systemic hormonal side effects.

In another study, Ma et al. (20) investigated whether mir-142-3p, which is decreased in endometriotic foci and negatively correlated with KLF9 and VEGFA expression, could be used to treat endometriosis. They showed that miR-142-3p significantly decreased the growing of endometriotic foci. Moreover, in an *in vitro* study, Börschel et al. (48) showed that miR-142-3p reduces the invasion of endometrial tissue and speculated that miR-142-3p-based drugs might be used for the treatment of the endometriosis.

CONCLUSION

miRNAs appear to play a role in the pathogenesis of the endometriosis. Current data point out that alterations of a delicately balanced miRNA gene expression may cause detrimental effects in the development of the endometriosis. Thus, altered epigenetic profiles may serve as the diagnostic markers and/or treatment and prognostic prediction of the endometriosis. As studies on the role of miRNAs in the pathogenesis of endometriosis increase in the literature, new ideas can be put forward for early diagnosis, prevention and treatment of the endometriosis.

Conflict of interest

No conflict of interest was declared by the authors.

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