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Osteopontin as a marker of endometriosis — the current state of knowledge

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ABSTRACT

Endometriosis is a disease affecting mainly women of childbearing age, where ectopic endometrial lesions occur outside the uterine cavity. Its main symptoms are chronic pain, infertility and dysmenorrhea. These symptoms significantly reduce the quality of life of patients suffering from this disease. Despite advanced research, the exact etiopathogenesis of endometriosis is still unknown and various theories explaining its origin are postulated in the course of research.
Osteopontin is a protein originally discovered in the bone matrix and then in various tissues and organs of the body such as the kidneys, lungs, reproductive organs, vascular epithelial cells or some cancer cells. It is involved in processes such as cell adhesion and migration, angiogenesis and the promotion of tumor cell metastasis.
These processes play a role in the pathogenesis of endometriosis, hence intensive research on the role of osteopontin in the development of this disease is an interesting research direction.

Keywords: endometriosis; osteopontin; gene expression; SPP1

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INTRODUCTION

Endometriosis

Endometriosis is a disease affecting women of reproductive age, manifested by multiple symptoms, including chronic pelvic pain, menstrual cycle disorders, dyspareunia (painful intercourse) and fertility problems [1]. It involves the presence of active endometrial tissue outside the uterine cavity. Most often, these lesions are located in the ovaries, pouch of Douglas, uterine ligaments and the peritoneum of the small pelvis, but there are also rare locations, such as lungs or lymph nodes, or a caesarean section scar [2].

Endometriosis is not only specific symptoms, but also a chronic disease with long-term consequences, such as infertility [3], adverse psychological effects for both the woman and her partner [4, 5], a decrease in the quality of life and high costs associated with diagnostics and treatment.

The exact incidence of endometriosis is unknown. It is estimated, that it affects 2–10% of women in the general population [6]. Endometriosis is diagnosed in approximately 33% of women suffering from chronic pelvic pain and in as many as 20–50% of infertile women [7, 8].

Currently, one of the most commonly used classification of endometriosis is the revised Classification of Endometriosis of the American Society for Reproductive Medicine (rASRM) scale (Tab. 1, 2) [9]. It is a 4-stage scale that assesses the severity of endometriosis on the basis of the size of the foci, the depth of their infiltration and the presence of endometrial cysts and adhesions within the reproductive organ.

Endometriosis is a disease in which symptoms significantly reduce the quality of life [10]. Chronic pelvic pain independent of the cycle day, painful menstruation (dysmenorrhea), pain during intercourse (dyspareunia), spotting after intercourse, pain during urination (dysuria) or pain during defecation (dyschezia), often with bleeding from the lower gastrointestinal tract are one of the most common symptoms of endometriosis [10]. A serious problem in patients suffering from endometriosis is reduced fertility or infertility [10]. Interestingly, there is no linear correlation between the severity of the disease and symptoms, additionally some patients remain asymptomatic [11]. However, there is a relationship between the location of endometrial

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Table 1. Revised Classification of Endometriosis of the American Society for Reproductive Medicine [9]

Location	Endometriosis	Size of lesions		
		< 1 cm	1–3 cm	> 3 cm
Peritoneum	Superficial	1	2	4
	Deep	2	4	6
Right ovary	Superficial	1	2	4
	Deep	4	16	20
Left ovary	Superficial	1	2	4
	Deep	4	16	20
Posterior Cul--de-sac obliteration	**Partial**		**Complete**	
	4		40	
	Adhesions	**Degree of enclosure**		
		< 1/3	1/3–2/3	> 2/3
Right ovary	Filmy	1	2	4
	Dense	4	8	16
Left ovary	Filmy	1	2	4
	Dense	4	8	16
Right fallopian tube	Filmy	1	2	4
	Dense	4*	8*	16
Left fallopian tube	Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16

Table 2. Clinical advancement of endometriosis according to revised Classification of Endometriosis of the American Society for Reproductive Medicine (rASRM) [9]

Clinical advancement of endometriosis according to rASRM	Amount of points
I (Minimal)	1–5
II (Mild)	6–15
III (Moderate)	16–40
IV (Severe)	> 40

foci and clinical symptoms. Deep infiltrating endometriosis (DIE) lesions located within the utero-rectal septum, sacrouterine ligaments and pouch of Douglas are mainly manifested as dyspareunia and dyschezia [12]. Endometriosis in the pelvic organs such as the large intestine, rectum, ureters or bladder may be responsible for symptoms such as dysuria, dyschezia, or even hematuria or bleeding from the lower gastrointestinal tract. Numerous implants in the pelvic peritoneum correlate with dysmenorrhea [12].

The etiopathogenesis of endometriosis is unknown; today there are several established theories attempting to explain the mechanism of the disease. These include: Sampson's implantation theory [13], the theory of the spread of endometrial cells through the lymphatic and circulatory systems [14] or the Meyer's theory of metaplasia [15]. Additionally, immunological and genetic factors as well as endometrial disorders related to the increased ability of endometrial stromal and epithelial cells to proliferate, which facilitate the survival of endometrial tissue outside the uterine cavity, are taken into account [16]. As can be seen from the above examples, the complexity of the process of the formation and spread of endometriosis, its numerous forms, the ability to evolve, dependence on locoregional conditions as well as on the immune and hormonal condition of the whole organism make the explanation of the etiopathogenesis of endometriosis extremely difficult and still not fully understood.

In the diagnostic process of endometriosis, the basic diagnostic tool used in clinical practice is a properly collected medical history. Symptoms such as dysmenorrhea, pain during intercourse, pelvic pain unrelated to the menstrual cycle and fertility disorders are characteristic of endometriosis. In the detection of endometriosis, diagnostic techniques are used, such as gynecological speculum examination combined with a bimanual examination and transvaginal or transrectal ultrasound examination. The gold standard used in diagnostics is laparoscopy [17].

The search for a highly sensitive and specific marker of endometriosis are going on for many years, but so far, no satisfactory results have been obtained in this direction. Currently, the main areas of interest in current research are the search for markers in plasma, urine, uterine fluid or menstrual blood [17]. The minimally invasive procedures also include the collection of pelvic fluid and endometrial biopsy, which showed some differences in the activity of many factors compared to the healthy control group [18].

Osteopontin

Osteopontin is a phosphorylated glycoprotein encoded by the SPP1 gene with a molecular weight ranging from 44 to 70 kDa, originally isolated from the bone matrix. In the course of further studies, the expression of osteopontin on cells such as NK cells, dendritic cells, macrophages, and bone matrix cells was discovered [19].

It consists of about 300 amino acids, has the ability to bind calcium, and also contains integrin-binding domains, which allows it to bind to many integrin receptors, and thus participate in numerous biological processes, such as adhesion, migration and cell activation.

Cellular secretion of osteopontin is believed to be modified by many different factors, such as vitamin D, interferon, and glucocorticoids. TNF-α and IL-1β affect the expression and transcription of the osteopontin gene, also taking part in its synthesis [20].

Due to its biological functions, osteopontin is involved in neoplastic processes, including those in the organs of the

female reproductive system. It is believed to be a marker of ovarian epithelial carcinoma [21], endometrial carcinoma [22], and cervical squamous cell carcinoma [23].

It has been proven that this protein plays a role in the processes of angiogenesis [24], cell adhesion, apoptosis and in the development of the inflammatory process [25]. These processes are identical to the phenomena occurring during the development of endometriosis, hence the direction of research on the relationship between the development of endometriosis and the role of osteopontin seems to be interesting.

THE CURRENT STATE OF KNOWLEDGE

Due to the biological processes in which osteopontin is involved and their similarity to the processes involved in the pathogenesis of endometriosis, osteopontin is considered as a factor contributing to the development of the disease. There are also studies that say that osteopontin may be considered a marker of endometriosis.

Di Amico et al. [26] found an increased expression of the osteopontin gene in samples of endometriosis lesions from women suffering from it.

It has also been shown that osteopontin regulates the migration of stromal cells in the event of the development of endometriosis [27], and its serum levels are elevated in patients with this disease [28].

Osteopontin has been shown to be involved in cell adhesion and migration. It induces the invasion of endometrial cells into the stroma, thus promoting the formation of endometriotic implants. These phenomena are counted into the mechanisms taking part in promotion of the survival of endometriotic implants in the peritoneal environment outside the uterine cavity [29].

There are scientific studies that have shown an increased expression of osteopontin on the eutopic endometrium in women with this disease [30]. This observation seems to be a link between the theory of retrograde menstruation and the phenomenon of cell adhesion and could explain the situation of endometriosis only in some women in a situation where retrograde blood flow to the peritoneal cavity during menstruation takes place in about 90% of women.

Scientific research has shown that angiogenesis may play an important role in the pathogenesis of endometriosis. In endometriotic implants neovascularization occurs, which allows them to survive outside the uterine cavity. Vascular endothelial growth factor (VEGF) is considered to be the most potent factor involved in this process [31].

Importantly, there are reports that osteopontin can induce VEGF synthesis, thus increasing angiogenesis [32].

The study by SiHyun et al. [33] showed that the mRNA expression of the osteopontin gene in the eutopic endometrium and the level of osteopontin in the blood serum of patients are significantly higher in women suffering from endometriosis, which, according to the authors, may justify the use of osteopontin as a non-invasive disease marker. The same conclusions were drawn in the work of Yang et al. [34] also in this study, osteopontin is presented as a promising disease marker, and the authors confirmed their theses both in an animal model and in a group of patients with endometriosis.

The influence of the expression of the osteopontin gene on the functioning of various genetic signal pathways in which this protein is involved also seems interesting.

The analysis of microarrays in several studies showed an increased expression of the osteopontin gene both in endometrial tissues [35] and in the eutopic endometrium of women with endometriosis [34].

The altered expression of the OPN gene changes the activity of various signaling pathways involved in cellular processes. For example, activation of the PI3K/AKT pathway (phosphatidylinositol 3 kinase) and the secondary upregulation of uPA (urokinase plasminogen activator) may promote endometrial cell migration in patients with endometriosis, similarly to ovarian and lung cancers or head and neck cancers [35]. In addition, other authors have shown that increased expression of the osteopontin gene by affecting the expression of matrix metalloproteinase 9 (MMP 9) promotes the adhesion of endometrial cells to the stroma, and this phenomenon is additionally influenced by female sex hormones — estrogens [34].

CONCLUSIONS

Endometriosis is a disease of unknown and complicated etiopathogenesis. Therefore, we are not able to cure the source of the disease, and the available therapeutic methods focus mainly on controlling its symptoms. At the present moment, there are also no specific markers of the disease, and is still the gold standard laparoscopy, which is an invasive procedure.

An obstacle to the use of osteopontin as a marker of endometriosis is its association with numerous disease processes that may coexist with endometriosis and thus lead to false-positive results.

Hence, research on osteopontin, which is involved in biological processes that may affect the development of endometriosis, seems to be promising when it comes to unraveling the mystery of the mechanisms of origin and treatment of this difficult disease entity.

Article information and declarations

Conflict of interest

The study received no financial support. The authors have nothing to disclose.

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