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THE ROLE OF THE IMMUNE SYSTEM IN THE PATHOGENESIS OF ENDOMETRIOSIS (REVIEW OF THE LITERATURE).

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Abstract: The article provides an overview of modern theories of the development of endometriosis, provides literature data on the state of the immune system in women with endometriosis. Immune disorders occurring at the level of the ectopic endometrium, endometrioid focus, as well as in the peripheral blood and peritoneal fluid of women with various forms of genital endometriosis are considered.
Keywords: genital endometriosis, immunity, cytokines.

Endometriosis is a common chronic disease of women of reproductive age. About 10% of women suffer from it [1]. Chronic inflammatory processes and a relatively high level of estrogens are well-known signs of endometriosis, but the exact etiology of the disease remains unclear [2]. This can be explained by the complex and multifactorial nature of the disease, in which the involvement of genetic, hormonal, environmental, and immunological factors has previously been identified [3]. Currently, the most widely accepted theory for the formation of endometrial lesions is that during menstruation, endometrial cells and tissue fragments are drawn through the fallopian tubes and attach to pelvic structures, causing an inflammatory reaction, fibrosis, and pain [4].

Cytokines are responsible for the inflammatory reaction and its regulation. Activation of immune cells triggers signaling pathways that cause the release of inflammatory cytokines, which then contribute to the accumulation of multiple types of cells at the site of inflammation [5]. Studies have shown that one of the conditions for the development of endometrial lesions is immune system dysfunction, which affects the expression of certain cytokines [6]. Neutrophils and peritoneal macrophages produce biochemical factors that promote angiogenesis, growth, and invasion of endometrioid cells. Peritoneal macrophages and NK cells have limited ability to eliminate endometrial cells in the abdominal cavity during endometriosis. Imbalance between Th1/Th2 cells leads to abnormal cytokine secretion and inflammation, which continues to cause disease progression [7,8]. It is still unclear whether immune system disorders cause endometriosis, but the course of the disease can be influenced by modulating its actions [9].

According to Kao L [10], abnormal, genetically polymorphic endometrial cells can respond to local endometrial signals by proliferation rather than apoptosis. The products secreted by these cells are an additional source of cellular invasion and disease progression, as well as causing local inflammatory reactions. Functional impairments in immune cells in endometriosis may result from the same environmental toxins that cause changes in the functions of B, NK, and T cells in women with endometriosis. Populations of innate immune system cells involved in the pathophysiology of endometriosis include neutrophils, macrophages, NK cells, and dendritic cells (Figure 1).

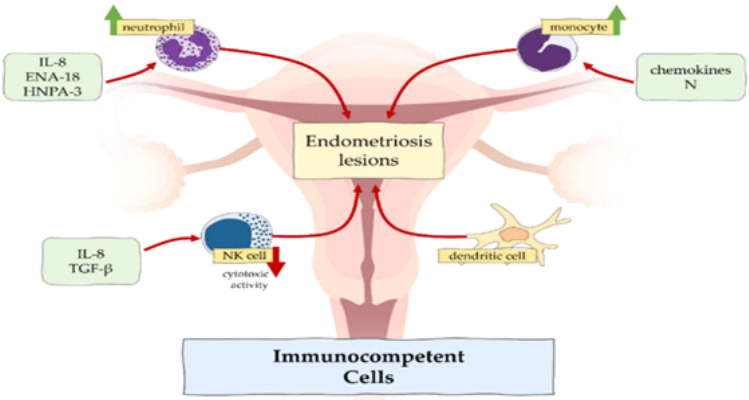

Fig. 1. The role of immunocompetent cells in endometriosis

In patients with endometriosis, there is an increased percentage of neutrophils compared to women without the disease [9]. This is likely due to increased concentrations of chemotactic factors such as IL-8 present in plasma and peritoneal fluid, epithelial neutrophil-activating peptide (ENA-78), and human neutrophil peptides 1-3 (HNP1-3) in the local environment of endometriosis [4, 13]. The role of these cells largely involves the creation of inflammation, particularly through the secretion of IL-17A, which enhances neutrophil migration, or other pro-inflammatory factors such as IL-8, VEGF, and CXCL10 [11].

Macrophages play a key role in the development of endometrial lesions and associated inflammation. However, the total number of monocytes in the peripheral blood of patients with endometriosis did not change [7,16]. In peritoneal fluid, they are the most numerous cells found in healthy individuals, so it is not surprising that their elevated levels were observed in the local conditions of endometriosis. In their presence, the development of endometrial implants occurs more intensively. The decreased expression of CD3 (cluster of differentiation 3) and annexin A2 is represented by decreased phagocytic ability. In addition, the production of inflammatory mediators by macrophages promotes implantation and proliferation of endometrial cells, leading to the development of endometrial lesions [12]. It is worth noting that Grivs et al. recently found that estradiol is a key mediator of interactions between macrophages and nerve tissue in peritoneal endometriosis [2].

NK cells, predominantly characterized by the following surface markers: CD56 dim CD16+ and CD56 Bright, act as a link between two types of immune responses - innate and adaptive. The involvement of NK cells in the pathogenesis of endometriosis was first described by Oosterlynck et al., who found that the cytotoxic activity of NK cells is lower against ectopic endometrial cells. This correlation was associated with late stages of the disease [17]. The mechanism of NK cell function inhibition in endometriosis is not clear. An abnormal expression of various activating and inhibitory receptors on their surface has been described compared to the population of these cells in healthy women [17]. It has been reported that the expression of KIR (killer immunoglobulin-like receptor) on the surface of peritumoral NK cells is increased, which may explain this phenomenon [5,9]. NK cells contribute to the balance of immune tolerance by eliminating cells that present autoantigens, so their reduced activity in endometriosis may explain the autoimmune response observed in the disease [2,14]. It has been shown that IL-6 and TGF-β in the peritoneal fluid of women with endometriosis decrease the cytolytic activity of NK cells [16]. It has been found that interaction between endometrial cells and macrophages reduces the cytotoxicity of NK cells, probably due to increased release of IL-10 and TGF-β [18]. Endometriosis has been repeatedly considered an autoimmune disease. There is a clear correlation between endometriosis and the presence of other immunological and autoimmune diseases such as rheumatoid arthritis, psoriasis, and allergies [1]. Due to the presence of autoantibodies, the role of B cells in the pathophysiology of endometriosis has also been investigated. In addition to producing antibodies, B cells also produce cytokines such as IL-6 (granulocyte-macrophage colony-stimulating factor) and IL-17, which have been shown to modulate immune cells (such as CD4+ T cells) and sustain chronic inflammation.

The link between endometriosis as a local chronic inflammatory disease and excessive cytokine secretion has been discussed repeatedly. Cytokines, as chemotactic factors, participate in the recruitment of macrophages and T-cells, mediating the inflammatory reaction that correlates with the disease (see Table 1).

Table 1. Pathogenetic role of cytokines in endometriosis.

Cytokine	Possible role
INF-c	interacts with IL-2 in regulating the balance between Th1 and Th2 cells; conflicting research results
IL-1	regulation of immune and inflammatory reactions
IL-2	the role in the pathogenesis of endometriosis is not clearly defined
IL-6	an increase in haptoglobin, which "protects" endometrial implants from immune surveillance by reducing phagocytosis
IL-8 TNF-α	They are factors that contribute to the adhesion of endometrial cells to the peritoneum and may contribute to the progression of the disease
IL-4 и IL-10	higher values of IL-4 and IL-10 in the peritoneal fluid confirm that the development of endometriosis is accompanied by activation of the Th2-type immune response
ТФР-β	may be responsible for inhibiting the activity of NK cells in the peritoneal fluid
VEGF	powerful heparin-binding angiogenic factor

The main biological activities resulting from the transmission of interferon (IFN) signals are antiviral, antiproliferative, antiangiogenic, and inhibitory activity in relation to antigen presentation. IFN also affects the regulation of genes and pro- and anti-apoptotic proteins [1]. IFN-γ is mainly produced by activated T or NK cells, and its role is to modulate the cellular immune response, which, among other things, contributes to the activation of macrophages and the development of T cells [2]. When studying peripheral blood and peritoneal fluid, Hsu et al. demonstrated a decrease in the level of IFN-γ in both fluids. However, Podgaec et al. found a higher expression of IFN-γ in the local environment of lesions, i.e. in peritoneal fluid, in patients with endometriosis compared to controls [3]. Interestingly, it was noted that IFN-γ does not affect the growth and apoptosis of cells from ectopic endometrial implants of ovarian origin [4,5]. This may indicate that endometrial cells become resistant to apoptotic signals when they enter the abdominal cavity during retrograde menstruation [6].

IL-1 is a family of pro-inflammatory cytokines that are secreted by activated peritoneal macrophages into the peritoneal fluid [7]. IL-1 performs several functions in the body, the most important of which is the regulation of immune and inflammatory reactions. It initiates the cascade of inflammatory reactions primarily through cytokines (IL-6, IL-8), B cells and antibodies, as well as the secretion of specific matrix metalloproteinases (MMP) and prostaglandins [8]. Levels of IL-1 are elevated in women with endometriosis [9]. It has been reported that changes in the function of immune cells in the peritoneal fluid and cytokine production, including IL-1, are one of the causes of infertility [10]. In advanced stages of the disease, increased levels of this cytokine are observed not only in peritoneal fluid but also in serum [7]. IL-1β plays an important role in the formation of new blood vessels in tissues surrounding endometriosis lesions by producing vascular endothelial growth factor (VEGF) and IL-6 [3,10]. It also affects the proliferation of endometrial cells and regulates the expression of ICAM-1 on the cell surface [12]. However, unlimited secretion of IL-1 can lead to tissue damage and chronic inflammation, although self-regulation of the IL-1 family has been demonstrated [17].

Interleukin 2 (IL-2) stimulates the proliferation and differentiation of B and T cells, the activation and proliferation of non-specific cytotoxic effector cells, including NK cells and lymphokine-activated killers (LAK), and participates in the activation of monocytes and macrophages [15]. The role of IL-2 in the pathogenesis of endometriosis is not clearly defined. Hsu et al. found a decrease in the concentration of IL-2 both in peripheral blood and in peritoneal fluid, more pronounced in the late stages of the disease. At the same time, they did not observe differences in the levels of IL-2 and IL-10 mRNA between the study and control groups. Similar results were presented by Hernandez-Guerrero et al., showing lower intracellular synthesis of IL-2 in the peritoneal fluid and peripheral blood of patients. [14].

Intensively and periodically produced in response to infection and tissue damage, interleukin 6 (IL-6) induces host protection by stimulating acute-phase reactions, hematopoiesis, and immune responses. Its expression is strictly controlled by transcriptional and post-transcriptional unregulated mechanisms. However, continuous IL-6 synthesis can occur in pathological conditions, including chronic inflammation and autoimmunity [17]. According to literature examples, IL-6 promotes the occurrence and development of ectopic endometrial foci, interfering with the cellular response [15]. Macrophages are the predominant cells secreting IL-6 in the peritoneal fluid []. IL-6 secreted by activated macrophages has pleiotropic effects, and one of its effects is to increase the level of haptoglobin, which "protects" endometrial implants from immune surveillance by reducing phagocytosis. This positive feedback loop thus contributes to the survival of ectopic endometrium and the development of endometriosis foci [6]. It is also worth noting that elevated levels of IL-6 inhibit the activity of NK cells in the peritoneal fluid of patients with endometriosis [9].

IL-8 and TNF-α were among cytokines with higher expression levels observed in the peritoneal fluid of women with endometriosis [15]. IL-8 is a chemotactic factor that attracts cells such as neutrophils, basophils, and T lymphocytes to the site of inflammation. It is released from monocytes, macrophages, neutrophils, and others in response to inflammation and participates in the activation of neutrophils [1]. TNF-α is produced by macrophages/monocytes in response to acute inflammation. It is responsible for several signaling pathways leading to necrosis or apoptosis [16]. Elevated levels of IL-8 in the peritoneal fluid of women with endometriosis promote higher proliferation of ovarian endometrioma stromal cells. Based on this, it was concluded that IL-8 may contribute to the development of endometriosis [3,4]. In addition, it was found that TNF-α promotes increased expression of IL-8 genes and proteins, also stimulating proliferation of stromal cells derived from endometriosis [2].

Interleukin 10 (IL-10) is a powerful anti-inflammatory cytokine, the deficiency or abnormal expression of which can amplify the inflammatory response or lead to the development of a number of autoimmune diseases [2,16]. Initially, IL-10 production was mainly attributed to Th2 lymphocytes, but further research has shown that B cells, T cells, macrophages, as well as cells not directly involved in the cellular response, such as keratinocytes and tumor cells, can be sources of IL-10 [1,7]. In general, the term "anti-inflammatory effect" includes mechanisms such as inhibition of the release of pro-inflammatory mediators, counteracting phagocytosis, decreasing antigen presentation while simultaneously enhancing regulatory T cell functions and the tolerance environment [4]. In addition, IL-10 can enhance the activation and proliferation of certain types of immune cells, including mast cells, CD8+ T cells, NK cells and B cells. The molecular mechanisms and functional consequences of such IL-10 activity remain unclear. Interleukin 4 (IL-4) is a cytokine with pleiotropic activity [5]. It participates in immunoglobulin class switching, increases the expression of MHC class II molecules in B cells, enhances CD23 expression, increases IL-4 receptor expression, and affects longer survival of T and B cells [11]. However, its main role is in the differentiation of naive T cells after antigen stimulation. As a result of this process, activated T cells can produce Th2-polarized T-helper cells [12]. With regard to endometriosis, it has been repeatedly shown that the development of the disease is accompanied

The aforementioned cytokines, promoting a Th2-type response, inhibit the cytotoxic response, the participation of which was postulated in the removal of ectopic endometrium [8]. IL-4 in ectopic endometrial implants stimulates the secretion of eotaxin, which leads to increased angiogenesis and progression of the lesion [18]. At the same time, its anti-inflammatory activity can suppress adhesion formation in the abdominal cavity. It has been shown that cells capable of producing IL-4 are present in ectopic endometrial tissues and that IL-4 has stimulating potential against endometrial stromal cells [9]. The presence of higher levels of IL-4 and IL-10 in peritoneal fluid confirms that the development of endometriosis is accompanied by the activation of a Th2-type immune response at the local level. However, the detection of higher systemic concentrations of Th1-related cytokines (IFN-gamma, IL-2) with an increase in IL-10 and a decrease in IL-4 in peripheral blood may be a manifestation of a compensatory effect that counteracts inflammation[10].

Studies in women with endometriosis have shown increased activity of TGF-β in the peritoneal fluid [16]. This is a highly pleiotropic cytokine that is involved in many processes, including angiogenesis and immunoregulation. Its isoform TGF-β1 has anti-inflammatory properties; however, TGF-β promotes the differentiation of both regulatory T cells and inflammatory Th17 cells. It can be overproduced in some autoimmune diseases [16]. Researchers suggest that TGF-β in endometriosis may be responsible for inhibiting the activity of NK cells in the peritoneal fluid [17]. This theory is consistent with the hypothesis of retrograde menstruation, according to which impaired NK cell function is the driving force behind the survival and implantation of endometrial cells in the structures of the pelvis. It is believed that angiogenesis, the process of creating new capillaries, may be involved in the pathogenesis of endometriosis. Vascular endothelial growth factor (VEGF) is a potent heparin-binding angiogenic factor [18]. Since endometriosis is characterized by high vascularization inside and around the ectopic tissue, it has been suggested that levels of the powerful angiogenic growth factor VEGF in peritoneal fluid may have strong clinical significance. Studies have shown that women diagnosed with endometriosis have higher levels of VEGF in their peritoneal fluid than healthy women. Furthermore, it has been demonstrated that the main source of VEGF is peritoneal fluid macrophages, and that antibodies to VEGF eliminate increased proliferation of endothelial cells induced by macrophage-derived media from the peritoneal cavity of women with endometriosis. Based on this, we can conclude that VEGF expression in endometriosis is regulated by estradiol and progesterone. [19].

Endometriosis is increasingly being discussed as an autoimmune disease. It turns out that immune cells such as neutrophils, macrophages, NK cells, and dendritic cells can play a special role in the angiogenesis, growth, and invasion of endometrioid cells. Immune cells secrete cytokines and defensins, which also affect the endometriosis environment. Inhibitors of immune cells are supposed to control the immune response, but in patients with endometriosis, there is a difference in the levels of these indicators compared to healthy patients.

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