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Progress on macrophage's proinflammatory products as markers of acute endometriosis

Alicja Ziętek, Konrad Futyma*, Łukasz Nowakowski, Marek Gogacz, Tomasz Rechberger

2nd Department of Gynecology, Medical University of Lublin, ul. Jaczewskiego 8, 20-954 Lublin, Poland

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ABSTRACT

To provide the review of the macrophage activity products as pathophysiological markers of endometriosis by literature survey (PubMed, Cochrane). Immunoreactive cells and several of their synthesis products concentrations are elevated in the serum and peritoneal fluid in patients with endometriosis. The enhanced reactive proteins contributed to local inflammation and aggregation of endometriotic lesions. Immune response and immune surveillance of tissue play an important role in pathogenesis of endometriosis. Activated macrophages in peritoneal environment secrete immunoreactive cytokines which are responsible for inflammatory cascade of reactions. The immunoreactive cytokines should be a target not only as a disease marker but also as a part of therapeutic protocol.

1. Introduction

Endometriosis is characterized by hormone depending persistence and growth of endometrial tissue at ectopic sites, mostly pelvic peritoneum and organs: ovaries, rectum, urinary bladder. It affects 10%–15% of women of reproductive age and is associated with pelvic pain, dysmenorrhea, dyspareunia and infertility. Despite the fact that it is considered as one of the most frequently encountered gynecological disorders, the pathogenesis of endometriosis still remains poorly understood.

Four most popular theories were proposed to explain the pathogenesis and pathophysiology of endometriosis. However, none of them can particularly explore all the determining factors.

In 1927, Sampson postulated the retrograde menstruation theory, according to which the endometrial shed elements could pass along the fallopian tubes and reach the peritoneal cavity[1]. Considering the gravity, the menstruation blood would thus reach, especially the ovaries, the Douglas pouch, uterosacral ligaments, rectum and urinary bladder. Another popular etiological theory of endometriosis is the celomic metaplasia. The fact of metaplasia of undifferentiated tissue could possibly explain the existence of endometriosis in distant sites. Dinelescu *et al*. came up with the hypothesis that activation of *K-ras* gene may be responsible for the metaplastic process[2]. There is also a hypothesis that the remnants of Mullerian ducts could be responsible for the etiology of the disease. Nevertheless, nowadays it is considered as highly improbable. In order to explain the distant location of endometriosis, Halban postulated the theory of lymph and blood dissemination of endometrial cells[3]. According to this idea, the endometrial cells would spread around the organism through the lymph or blood vessel microclots. In 1987, Gleicher *et al*. postulated that endometriosis could be an autoimmune disease considering the presence of certain autoantibodies in serum[4]. In the study of Barrier, it was not proved that there was any correlation between co-occurrence of endometriosis and immune-mediated polyarthritis, Sjogrens syndrome or systemic lupus erythematous[5]. Several studies accentuated the role of race, uterine obstruction, life conditions in the pathogenesis of endometriosis[5,6]. Currently, more data support the immunological theory of endometriosis, according to which it is an inflammatory disorder recruiting cellular and humoral factors.

The aim of the present study is to review the literature for novel proinflammatory markers of endometriosis.

2. Materials and methods

Comprehensive searches in PubMed and Cochrane databases were conducted to identify studies published between 1995 and 2014 in English language with keywords: “macrophages”, “endometriosis”, “interleukins”, “tumor necrosis factor (TNF)”.

*Corresponding author: Konrad Futyma, 2nd Department of Gynecology, Medical University of Lublin, ul. Jaczewskiego 8, 20-954 Lublin, Poland.
Tel: +48 81 7244268
Fax: +48 81 7244849
E-mail: futymakonrad@mp.pl
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Data were extracted and initial screening of the title and abstract of all articles to exclude citations deemed irrelevant were performed.

3. Macrophages in endometriosis

Numerous studies have shown that macrophages are the most crucial inflammatory cells. The peritoneal fluid which normally appears in peritoneal cavity in the volume of 5–20 mL contains activated macrophages which determine and sustain the inflammation. Macrophages are an integral part of mononuclear phagocyte system which derives from bone marrow. After reaching the peritoneum macrophages remain in the peritoneal cavity as dendritic cells or scavenger macrophages. Among the macrophages exists a classical/inflammatory M1 population characterized with the antigen cytotoxicity, synthetizing cytokines like interleukin-12 (Il-12), and modulating ROS and nitric oxide factors. The M2 population of macrophages is responsible for enhancing the inflammatory response and also for the tissue reparation. During the acute stage of endometriosis, an increasing number of activated macrophages in the peritoneal fluid and endometriotic implants is observed. Those activated macrophages are responsible for numerous growth factors while cytokines secretion responsible for proliferation, angiogenesis, inflammatory response and clinical manifestation of the disease[7,8].

3.1. Interleukin-1

Among the secretory products of activated macrophages, interleukin-1 is an important immunomodulatory factor. Il-1 is the name standing for a group of molecules which induce the inflammation pathway and are responsible for the pro-inflammatory mechanisms. Among the Il-1 family, there are Il-1α and Il-1β which together with antagonist receptor (Il-1Ra) cooperate in responding to inflammation signals[9,10]. IL-1α and IL-1β bind to the same receptor molecule. The third ligand of this receptor (Il-1r), the interleukin 1 receptor antagonist (IL-1Ra), acts as an inhibitor of IL-1α and IL-1β signaling by competing with them for binding sites of the receptor. The most popularly known initializing factors for producing Il-1 are lipopolysaccharides (the component of bacterial wall) and the C5-complex system[9]. The immunological role of Il-1 is to stimulate macrophages for the synthesis of Il-2 with the receptor (Il-2R) and Il-6. The nature killer cells cytotoxicity is enhanced by Il-1, and lymphocyte T is enhanced for the synthesis of interferon γ. By humoral immune response, Il-1β is stimulating B lymphocytes for producing antibodies. Increasing concentration of Il-1 in the inflammation area is a chemoattractive factor for monocytes and neutrophils. These cytokines increase the expression of adhesional factors ICAM-1, VCAM-1 and selectin E on endothelial cells, to enable transmigration of immunocompetent cells, such as phagocytes, lymphocytes and others, to sites of infection. The new colonies of monocytes are recruited due to the production of M-CSF, GM-CSF and G-CSF. Vigano *et al*. suggested that Il-1β stimulated ICAM-1 dependent immune surveillance of shed endometrial cells in the peritoneal fluid environment. The Il-1 also affects the activity of the hypothalamus which leads to a rise in body temperature. That is why Il-1 is called an endogenous pyrogen. IL-1 also causes hyperalgesia. These are some frequent clinical symptoms correlated with the menstrual bleeding in the patients diagnosed with endometriosis. They often present the peritonitis symptoms which can be incorrectly interpreted as appendicitis, extrauterine pregnancy, diverticulitis, etc[5,9,11].

3.2. Interleukin-6

In endometriosis, macrophages produce significantly higher levels of Interleukin-6[12]. This is both a pro-inflammatory cytokine and an anti-inflammatory myokine, encoded by IL-6 gene. IL-6 is secreted by T cells and macrophages, in response to Il-1 stimulation (in the positive feedback) and interferones, lipopolysaccharides or TNF. Osteoblasts secrete IL-6 to stimulate osteoclast formation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. As an anti-inflammatory cytokine, IL-6 is mediated through its inhibitory effects on TNF-α and IL-1. The biological activities of Il-6 are mediated by the Il-6 receptor-system which comprises two membrane proteins, the ligand bindingα subunit (Il-6 R) and the signal transducing β subunit, gp130. Il-6 is an essential cytokine for differentiation of B lymphocytes into antibodies-producing cells and contributes to production of immune complexes in endometrial stromal tissue[12,13]. In co-operation with Il-1, this cytokine promotes the production of T cells. It also applies to have an angiogenic potential (connected to Il-3) which affects the uncontrolled growth and invasion of adjacent tissue. This phenomenon of macrophage activation products enforces vascularization and angiogenic potential which is responsible for the new endometrial lesions and widespreading of the disease[6,14]. Concerning endometriosis in the context of autoimmune diseases, Il-6 is a promoting factor for the epithelial and mesangial tissue growth so that it could be responsible for lacking of autoimmunology response of the organism. IL-6 is also an important mediator of fever and acute phase response. It is capable of crossing the blood–brain barrier and initiating synthesis of PGE2 in the hypothalamus. Endometrial stromal and epithelial cells produce Il-6 in response to hormonal and immunological activity. Il-1α and β, TNF, interferon-γ stimulates the endometrial cell protein Il-6. It is suggested that estrogen stimulates the endometrial cell proliferation by inhibiting the production of Il-6 (which is considered to be epithelial cell inhibitor). Barrier proposed that endometriotic implants were resistant to Il-6 activity due to a low expression of Il-6R on the cell surface[5]. There is no consensus between studies about the concentration of Il-6 in the peritoneal fluid.

3.3. Interleukin-8

Interleukin 8 is a chemokine and chemo attractant produced by macrophages. The oxidative stress correlated with local immunodeficiency is a triggering factor for releasing the levels of Il-8 (also named as CCX-8, chemokine 8). Il-8 not only induces the migration of neutrophils to the inflammation area, but also is responsible for phagocytosis, increase of intracellular calcium concentration and exocytosis. However, since years, many studies have postulated that Il-8 is also an angiogenic factor for the cells[15,16]. Excessive neovascularization and angiogenesis are responsible for the recruitment of a new endometriotic lesions and immune surveillance of existing one. In the clinical practice by laparoscopic views, it is always noticeable that endometrial lesions are coexisting with the web of blood vessels. Gómez-Torres *et al*. explained this fact by the local secretion of Il-8 which stimulates the adhesion of stromal endometrial cells by fibronectin[17]. Many observations have proved the elevated levels of Il-8 both in peritoneal fluid and sera in patients with endometriosis. Nevertheless, there is no compromise whether Il-8 is stimulating not only deep ovarian endometriosis (seen with the endometrial cysts) but also endometriotic lesions. By Gazvani *et al*., there was significantly high correlation between the Il-8 concentration and angiogenic pathophysiology, while Barcz and coworkers showed no connection between endometriosis and Il-8 level in serum and peritoneal fluid[15,16].

3.4. Interleukin-12

There are several studies considering interleukin-12 as an important pathophysiological factor in etiology of endometriosis. IL-12 is a heterodimeric cytokine encoded by two separate genes, p35 and p40. It is naturally produced by macrophages, dendritic cells and B lymphocytes in response to antigen stimulation. IL-12 is involved in the differentiation of T cells into Th1. It stimulates the production of interferon gamma (IFN-γ) and TNF-α by macrophages in autocrine mechanism. It also stimulates the production of NK cells and inhibits the immunosuppressive activity of Il-4. IL-12 also has an antiangiogenic activity due to IFN-γ synthesis which stimulates the inducible protein-10. IL-12 binds to the IL-12 receptor, which is a heterodimeric receptor formed by Il-12Rβ1 and IL-12Rβ2. IL-12R-β2 is considered to play a key role in IL-12 function. In the context of immunodeficiency definition, several studies were conducted to determine the role of Il-12 in pathogenesis of endometriosis. Gazvani and colleagues postulated that this cytokine was a standard constituent of peritoneal fluid in women with endometriosis. In their study, there was no correlation between stage, clinical symptoms, cycle phase or the concentration of Il-12 in the peritoneal fluid[16,18,19].

On the other hand, in the study of investigators led by Itoh, the immunoregulatory role of Il-12 in pathogenesis of endometriosis was strongly fostered. They enhanced the cytotoxic effect of the cytokine to nature killer cells and Th1 lymphocytes by adding Il-12 to cultured cells[19]. The local increase of immunological activity in peritoneal cavity attenuates the adhesional potential of endometrial stromal cells[20]. In fact, patients with the low Il-12 concentration in the peritoneal fluid are potentially more susceptible to development of endometrial superficial cells and deep endometriotic lesions.

3.5. TNF-α

Many studies indicate that some of the main endometriosis symptoms like pelvic pain, infertility, dysmenorrhea, are the effect of TNF-α activity. TNFs are the family of pleiotropic cytokines with a range of injurious effects. TNF-α is produced by macrophages, monocytes, neutrophils and activated lymphocytes. The immunomodulatory role of TNF-α is up to the receptors TNF-R1 and TNF-R2 located at the surface of immune cells[21]. The activity and functioning of TNF-α is strongly correlated with and enhanced by Il-1 and Il-6. The main activities are stimulating the inflammatory response (production of stress reactive oxidants, prostaglandin E2) and phagocytosis and chemoattractant for neutrophil cells. TNF-α is also known as a pyrogen and stimulator of an acute phase response markers, such as C-reactive protein, fibrinogen, myoglobin. In the studies of Braun *et al*., it was proved that TNF-α was a physiological cytokine present in human in both proliferative-phase and secretory-phase endometrium. The immunoreactive TNF-α which is additionally enhanced by Il-1 and progesterone has a strong effect to induce the inflammatory reaction as well as the adhesion of endometrial cells to a stroma of peritoneal cavity[22]. Gogacz and colleagues have indicated that concentration of activated macrophages producing TNF-α in the peritoneal fluid of patients with endometriosis is significantly higher than in a control groups[13]. Moreover, some scientific data have postulated that there is a correlation between the elevated concentration of TNF-α in peritoneal environment and the stage of endometriosis[23].

4. Conclusions

The peritoneal immune cells are the source of TNF-α and concomitantly they play an important role in pathogenesis of endometriosis. Clinical studies supporting the inflammatory response in pathogenesis of endometriosis still remain hypothetical and demand to be conducted. Not only many of the clinical symptoms like pelvic pain, infertility, dysmenorrhea and dyspareunia but also the laboratory tests, elevated C-reactive protein, Ca-125, ROMA and elevated white blood cells levels, seem to strongly support this theory. It seems that activated macrophages in the local peritoneal environment and their immunoreactive cytokine products are the etiological factors of the inflammatory pathway but also of the adhesional and infiltration potential of endometrial stromal cells. Elevated cytokines concentration in the serum and peritoneal fluid could be a disease marker and the prediction factor of staging and prognosis of endometriosis. Future diagnostic and treatment strategies should consider these immunoreactive markers in order to establish more precise diagnostic protocol and implicate new therapeutic strategies.

Conflict of interest statement

The authors report no conflict of interest.

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