Review Article

Immunological aspects of endometriosis: a review

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Abstract: Endometriosis is a common and serious illness affecting women in their reproductive years. Despite the ongoing interest and intensive research of this crippling disease, the cause remains unknown since its first description over 150 years ago. The origins and genesis of endometriosis, despite numerous hypotheses, are still unclear. One of the possible causes of the development of endometriosis might be the immune system, despite the fact that endometriosis is generally considered to be a steroid-sensitive disease. Numerous aspects of the immune system has been found changed, from the different number of activated macrophages to different subtypes of lymphocytes and their activities, suggesting involvement of immunity. On the other hand, it is possible that immunological changes around the endometriotic lesion are only secondary to the establishment of endometriosis. In this review, we will summarize the current knowledge of immunological reactions in endometriosis.

Keywords: Endometriosis; immunology; cytokines; lymphocytes

Submitted Jun 02, 2015. Accepted for publication Jun 03, 2015.
doi: 10.3978/j.issn.2305-5839.2015.06.08
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.06.08

Lymphocytes

Despite the fact that endometriosis was first described more than 150 years ago (1), the causes are still unknown. Clearance of menstrual debris is supposed to be the result of immunocytes action. The changes in their role might result in invasion of endometrial cells and subsequently be one of the causes of endometriosis. Direct damage of the immune system by irradiation resulted in both increased prevalence of endometriosis and in increased severity (2).

When immune functions were evaluated in women with endometriosis, no differences were found in the levels of various aspects of nonspecific immunity (such as immunoglobulin levels or complement levels). However, specific T cell mediated cytotoxicity to autologous endometrial cells was strongly inhibited (3) suggesting a possible immunological basis. This low activity can be demonstrated by the addition of serum from patients with endometriosis (4), suggesting the additional role of cytokines. NK cell activity in patients with endometriosis is significantly reduced and these effects can be mediated by factors present in serum (5) or in endometrial stroma cultures-conditioned medium (6). These immunosuppressive effects are not correlated with the day of the menstrual period, estradiol, progesterone or prostaglandin E_2 level (7). Some authors suggest that this reduction of T cell-mediated cytotoxicity is based on induction of apoptosis in cytotoxic lymphocytes via the Fas-FasL pathway (8). However, the exact nature of these soluble factors is unknown (9). A hypothesis about the role of an HLA-G antigen (normally involved in maternal tolerance of the semiallogeneic fetus) in suppressed NK and cytotoxic T cell response was not confirmed by experimental data (10). The findings of highly elevated levels of killer cell inhibitory receptors (KIRs) on NK cells of patients with advanced-stage endometriosis (11) might be an explanation of the low activity of NK cells. Some authors suggested a double role—first, the low activity of NK cells might be a primary cause of endometriosis, and further development of this disease lowers their activity even further (9).

Interactions between T lymphocytes and the extracellular

matrix in women with endometriosis are well established. A study evaluating two matrix components, fibronectin and collagen IV on T lymphocyte proliferation and apoptosis showed in patients with endometriosis a general increase in the percentage of T lymphocytes in S phase suggesting activation of T cells, no apoptosis and stronger T cell proliferation when cultured with anti-CD3 antibodies and collagen IV. The contribution of this interaction to the pathogenesis of endometriosis has been suggested (12).

In monkey and human models of endometriosis, lymphocyte proliferative response and T cell toxicity are defective. Attempts to correct these defects in reaction against autologous endometrium by IL-2 were promising (13). Similar to cytotoxic T lymphocytes, the activity of CD^+ helper cells in the peritoneal fluid is also decreased, which might correspond to the high concentrations of IL-10 (14).

Treg lymphocytes are known to play an extremely important role in controlling and modulating numerous facets of immune responses. The finding of premenstrual rise of Tregs in endometriosis is an interesting observation (15), but without additional studies, the possible functions of this subset remain hypothetical. As these cells block the activation of the immune reactions, they might regulate the tolerance to the endometriotic tissue, but again, no substantial proof exists (9). Alternatively, an abundance of Tregs might reflect reduced progesterone responsive endometrial phenotype connected with endometriosis.

Another study focused on MUC1, which is under normal conditions present on eutopic endometrial glands, but overexpressed in ectopic lesions of ovarian endometriosis. The presence of MUC1 on normal endometrium is well established, but little is known about the role of MUC1 in ectopic lesions. Changes in MUC1 expression might promote anti-MUC1 immune response. Using MUC1 transgenic mice with Kras mice (where endometriosis can be induced), the authors developed an elegant model where they could observe MUC1-positive lesions resembling human endometriosis. Upon disease development, affected mice produced high titers of anti-MUC1 antibodies with predominance of the IgG_1 subclass. In addition, strong development of $Foxp3^+$ CD4 lymphocytes (Tregs) was observed. From these results, the authors suggested the role of Th2/Treg-dominant immune reactions in development of endometriosis (16). The same group even suggested that MUC1 can be a good vaccine candidate (17). All this makes Treg lymphocytes an interesting target for further research and possible interventions.

Macrophages

It is not surprising that significant changes accompanying endometriosis induce the changes in macrophages. These cells represent the primary defense cells residing in the peritoneal cavity and one of their main functions is to eliminate cellular debris. Macrophages react via phagocytosis, which is, at least in part, regulated through activation of matrix metalloproteinases and expression of CD36 receptor. Expression of both these components is reduced in endometriosis (18,19). The molecule responsible for this suppression was revealed to be prostaglandin E2 (18). Another important molecule is ICAM-1, released from the endometrial fragments. In soluble form, ICAM-1 reduces the availability of LFA1 expressed by lymphocytes and subsequently blocks their presentation to the NK cells (20).

In endometriosis we can observe significant changes in the peritoneal cavity, mostly in the increased number of macrophages and macrophage-derived cytokines. These increases, however, are not a result of activated macrophages, as their functional suppression was repeatedly reported (21). Subsequent studies showed lower expression of ICAM-1 by macrophages and higher expression of KIR by NK cells (22), which suggests possible role in immunotolerance to implanted tissue. Soluble ICAM-1 production was suppressed by endometrial stroma cultures-conditioned medium (6). The importance of macrophages was further implicated in studies of murine endometriotic lesions. Tie-2-expressing macrophages represent a subset of macrophages involved in promoting angiogenesis and tumor growth. In a mouse model, these macrophages infiltrated areas surrounding newly formed endometriotic blood vessels (23). When these cells are depleted, endothelial cells do not organize effectively, making this subset of macrophages a solid target for potential treatment of endometriosis.

Similarly, experiments showing deficient cellular immunity in monkeys with spontaneous endometriosis could indicate that endometrial cells can implant only in hosts with altered cell mediated immune responses (21). If this hypothesis is valid, we should be able to observe high incidence of allergic and autoimmune diseases in women with endometriosis, which was not found. On the other hand, the high risk of ovarian cancer is a well-established fact (24).

Autoimmunity

Some studies suggested a link between endometriosis and autoimmune diseases. This is particularly true about older

studies. These hypotheses were partly based on similarities such as high frequencies of myalgia and arthralgia among patients with endometriosis and systemic lupus erythromatosis (25). However, some later findings did not confirm this option (26). The idea that endometriosis might be a type of autoimmune disease is still entertained by many, despite the possibility that the increased levels of antibodies might result from inflammatory responses of stimulated macrophages responding to the ectopic endometrial tissue.

Another possibility was the finding of high levels of autoantibodies in endometriosis patients (25,27). Some studies even found higher levels of antibodies against endometrium (28). Most of these autoantibodies were directed against endometrial antigens, so it might be the result and not the cause of the disease. A detailed study showed that most of these autoantibodies are directed against carbohydrate epitopes (such as Thomsen-Friedenreich antigen), which led to several hypotheses about the involvement of autoantibodies in endometriosis (9), mostly by aberrant matrix metalloproteinase function or genetic defects in glycosylation (29).

It was also suggested that defective immune surveillance might be responsible for the development of endometriosis. In this concept, ectopic endometrial cells escape from surveillance (30). One of responsible mechanisms might be the elevated production of soluble ICAM-1 molecule, which modulated cytotoxic activity of NK cell and T lymphocytes.

The question remains why the immune system would attack ectopic endometrial tissue, as it should be recognized as self. An abnormal antibody-antigen reaction resulting in high deposits of complement and antibodies in the endometrium are known. However, the importance of anti-endometrial autoantibodies was questioned by Tanaka's study showing that these antibodies can be found not only in women with endometriosis, but also in healthy women and in men (31).

Inflammation

The idea of an association between inflammation and endometriosis is well known and is based on the elevated levels of inflammatory markers CRP and CA-125. Initial inflammatory response occurs via increased influx of cells. The subsequent acute inflammation involves local vasculature, somatic cells and immunocytes. Similarly, the fact that anti-inflammatory drugs help ameliorate numerous symptoms (32) connected with endometriosis also suggests the involvement of inflammatory activity. Some animal studies suggested effects of anti-inflammatory drugs directly on endometriotic implant growth (33). However, no mechanisms or direct proof was described (34). A detailed study of complement gene expression in various stages of endometriosis revealed that chronic inflammation in endometriosis is dominated by complement and that the classical pathway is the predominant one (35). The current medical guidelines do not recommend any assessment of the inflammatory conditions inside peritoneal cavity, however, this information might be strongly beneficial to better diagnose the conditions and the severity of the disease.

Cytokines

In endometriosis, the levels of cytokines such as GM-CSF, IL-1, IL-4, IL-6, IL-8, IL-10 and TNFα are significantly increased. In addition to cytokines, numerous growth factors (such as TGF-β, IGF-1, HGF and VEGF) are also increased (36). Many of these factors have cell-stimulating activities or are mitogenic for endometrial cells. Native endometrium produces various factors affecting the immune system (such as prostaglandins or MCP-1). Before menses, the rapid invasion of leukocytes releasing IL-8 and MCP-1 is known. Endometrial tissues express the same proinflammatory cytokines/chemokines which can trigger inflammatory reactions. However, cells in endometriosis express these factors in a changed manner. The production of these cytokines is increased in the peritoneal fluid of patients with endometriosis (37), which is by some connected to the lack of normal expression of progesterone receptors (38). The low ability of endometrium to support proliferation of autologous lymphocytes (39) might be attributed to the altered cytokine secretion, too. It is clear that these factors contribute to attachment, invasion and proliferation of endometriotic cells.

Cytokines such as IL-4 and IL-10 are upregulated in lymphocytes in women with endometriosis. In addition, elevated IL-4 expression was found in lymphocytes isolated from endometriotic tissue (40). IFN-γ shows opposite inclination (41). These results suggest changes in the Th1/Th2 balance toward Th2. Subsequent experiments showed that IL-4 increased proliferation of cultured endometriotic stromal cells and increased production of eotaxin, which is a strong chemoattractant for Th2 lymphocytes. Based on these data, a positive feedback loop of eotaxin-IL-4 cooperation in enhancing Th2 response was suggested (9).

A mouse model was used for evaluation of the possible role of IL-12 in prevention of endometriosis development.

Five daily injections of IL-12 reduced the weight and area of inoculated endometrium by 77% (32). In a human model, laparoscopic administration of IFN-α2b significantly reduced all symptoms and signs (42). Similarly effective was treatment with TNF-α (43). This is rather surprising, as both TNF-α and TNF-β are known for initiating proliferation of endometriotic stromal cells, which is involved in the initiation of this disease (44).

Further studies showed higher expression of IL-1β and COX-2 in ectopic mesenchymal stem cells derived from ovarian endometrioma. This IL-1 induced overexpression of COX-2 regulated the invasion ability of these cells (45). For a detailed description of the potential role of cytokines in endometriosis, see Herington *et al*. (46).

Conclusions

Endometriosis is now considered to be a disease of both endocrine and immune dysregulation. This endocrine-immunologic axis underlines the complexity of this gynecologic disorder. However, recognition of the direct involvement of two major physiological mechanisms brings about a change of focus which might represent an interesting advance in the understanding of this disease and new focus for further research. Vast changes in activities of numerous cells involved in immune reactions might offer new therapeutic targets with Treg lymphocytes being the most promising.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Králíčková M, Vetvicka V. Immunological aspects of endometriosis: a review. Ann Transl Med 2015. doi: 10.3978/j.issn.2305-5839.2015.06.08

