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Review Article

The Role of Immune System in the Development of Endometriosis: A Review

Rajita S. Jani[1], Devangi S. Munshi[1], Sanjay P. Munshi[2], Smit B. Solanki[3], Viral M. Pandya[4]

[1]Senior Resident, L.G. Hospital, Ahmedabad, [2]Professor and Head of Department, V.S. Hospital, Ahmedabad, [3]3rd Year Resident, [4]2nd Year Resident, V.S. Hospital, Ahmedabad.

Corresponding Author: Rajita S. Jani

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ABSTRACT

This review article gives an overview of the aetiology of endometriosis and sheds light on the role of immunological factors in the development ofendometriosis. Although retrograde menstruation is a common phenomenon among women of reproductive age, not all women who have retrograde menstruation develop endometriosis. The development of endometriosis is hypothesised to be a complex process, towards which multiple factors might be contributing at the same time, including the quantity and quality of endometrial cells in peritoneal fluid (PF), increased inflammatory activity in PF, increased endometrial-peritoneal adhesion and angiogenesis, reduced immune surveillance and clearance of endometrial cells, and increased production of autoantibodies against endometrial cells. Cytokines and autoantibodies upregulated during development of endometriosis may be used as markers for early diagnosis of endometriosis. Though hormone suppression is the treatment of choice for endometriosis, there is need for non-hormonal drugs, which can inhibit the development of endometriosis and alleviate pain or infertility without inhibition of ovulation. New molecules that modulate immune function should be explored for the treatment of endometriosis.

Keywords: Endometriosis, immune mechanisms

INTRODUCTION

Endometriosis is a gynaecological disorder of ectopic implantation and growth of endometrial tissue. These ectopic deposits are found at different sites, mostly in the pelvis, like ovaries, peritoneum, uterosacral ligaments, pouch of Douglas and rectovaginal septum. Endometriosis is the most common cause of pelvic pain and occurs in 13-33% of women having infertility. [1,2]

Even after multiple investigative studies, the aetiology of endometriosis remains elusive to medical science. [3] The most commonly quoted and accepted mechanism for occurrence of endometriosis is the retrograde menstruation theory. [4] This theory can explain the mechanism behind the ectopic implantation, but it fails to explain the cause behind the persistent survival of the endometrial tissues in an ectopic environment. To explain this, an immunological cause has been hypothesized, owing to the elevated levels of immune mediators like activated macrophages, cytokines, T cells and B cells, [2]

Sampson's Theory of Retrograde Menstruation

Retrograde menstruation is the reflux of menses through fallopian tube to ectopic site especially the peritoneal cavity. Although retrograde menstruation occurs in 70–90% of women [5] and83% in baboons, [6] endometriosis is diagnosed in only 10% of the former and 25% of the latter.

Thus, only a small percentage of women having retrograde menstruation actually develop the disease itself. This indicates the role of some other factors which would allow the retrograde displaced endometrial tissue to implant and develop into endometriotic lesions. It has also been observed that the quantity of cells in to the peritoneal cavity during menstruation could be higher among women who develop endometriosis. (Reviewed by D'Hooghe and Debrock [7]).

It is well known that women with short cycles and long duration of menstrual flow are more likely to develop endometriosis.[8] Furthermore, outflow obstruction of menstrual effluent, resulting in excessive retrograde menstruation has been associated with endometriosis both in humans [8,9] and in baboons. [10] It may be possible that both dysmenorrhoea (painful menstruation) and endometriosis are manifestations of outflow obstruction. [8]

Inflammatory mediators in Endometriosis

There is increased concentration of white blood cells and activated macrophages in the peritoneal fluid of patients having endometriosis. [11] The endometrial cells and activated macrophages secrete various inflammatory cytokines and growth factors resulting in the recruitment of various inflammatory cells and inflammatory mediators to the peritoneal cavity. Aberrant expression of several cytokines by activated macrophages, such as interleukin (IL)-1, IL-6, IL-8 and TNF-α in peritoneal fluid of women with endometriosis compared to controls [12] may contribute to a peritoneal microenvironment, which favours the implantation of endometrial cells and the establishment of endometriosis. [13] Cytokines like IL-8 and TNF-alpha are known to promote endometrial cell proliferation, endometrial adhesion and angiogenesis.Interleukin-8 (IL-8) promotes angiogenesis [14] and RANTES (Regulated upon activation, normal T-cell expressed and secreted) is a potent attractant and activator of macrophages, T-lymphocytes and eosinophils. [15,16] Certain studies have isolated elevated levels of TNF-αin patients with stage III/IV disease (168 pg/ml) than in women with stage 1/II disease (60.2 pg/ml) or control patients (3.3 pg/ml). [17] The increased concentration of TNF-α reflects enhanced secretory activity of the peritoneal macrophages and not just the mere increase in the number of peritoneal macrophages. [14] The levels of IL-8 and TNF-α correlate directly with the size and number of active lesions. [18]

Role of Immune system in Endometrial-Peritoneal Adhesion

Mediators affecting viability and adhesion of endometrial cells

Viability and survival of endometrial cells in peritoneal cavity is hypothesised to be dependent on the local estrogen production in eutopic/ectopic endometrium. Uncontrolled aromatase mRNA expression in endometriotic tissue [19] suggests that a local estrogenic milieuis important in the development of endometriosis. Autoantibodies recognising T-like antigens have been reported to be upregulated in endometriosis which in turn trigger the synthesis of cytokines such as IL-1, TNF-α and IL-6. These cytokines induce the expression of aromatase and 17β-hydroxysteroid dehydrogenase in endometriotic lesions. [20]

Endometriotic cells are found to be invasive in an in-vitro collagen invasion

assay, in contrast to eutopic endometrial cells, probably because they have a higher proportion of potentially invasive E-cadherin-negative epithelial cells. [21] TNF-α, IL-8 and IL-6 produced by the endometrial cells probably contribute to this adhesion process. [22, 23, 24] IL-8 has been shown to stimulate the adhesion of endometrial cells to fibronectin. [22] TNF-α has been reported to also promote endometrial stromal cell proliferation in vitro [23] and endometrial stromal cell adhesion to extracellular matrix components. [24]

Increasing Angiogenesis

Certain cytokines released from activated macrophages as well as endometriotic cells contribute to the development of endometriosis by promoting neovascularization of the endometrial cells attached to the peritoneum. [25] Vascular endothelial growth factor (VEGF) has been detected in high concentrations from women with moderate to severe endometriosis, [26-28] and is also secreted in endometriotic lesions. [26,27] VEGF is involved in the development of blood vessels that are critical in the growth and maintenance of ectopic endometrial tissue. Macrophage derived TGF-β is also suggested to contribute to angiogenesis in endometriotic implants. [25]

Role of Autoantibodies and Matrix Metalloproteinases

The invasion of extracellular matrix by endometriotic cells is influenced by Matrix Metalloproteinases (MMP) which are upregulated by TNF-α and IL-1. [29] TNF-α may also contribute to the decreased expression of endogenous tissue inhibitors of MMPs (TIMPS) under in vitro conditions. [30] Both these factors support the invasive growth of endometriotic explants. Specifically, the hemopexin domain containing MMPs are recognized by T-like autoantibodies and this might lead to dysregulation of the expression of MMPs and TIMPs in ectopic lesions, leading to increased invasiveness of these lesions in women with endometriosis. Also, the B-cell activity is altered accompanied by increased incidence of autoantibodies. [31, 32]

Relevance in Clinical Research

Diagnosis

Presently, the diagnosis of endometriosis can be made only by laparoscopy and biopsy of suspicious lesions with subsequent histological confirmation of endometrial tissue and there is no non-invasive way to diagnose this condition. Laparoscopy is minimally invasive procedure, but requires general anaesthesia and surgical skills with potential complications and procedural costs. Hence, anon-surgical diagnostic tool would be of paramount benefit to both physicians and patients. Efforts to evaluate the diagnostic value of endometrial markers for endometriosis have been hampered by the lack of easy, reliable and quantitative techniques to assess the expression levels of these markers in sample material.

Emerging proteomic techniques offer new approaches to identifying biomarkers for the early detection and follow-up of endometriosis. Aromatase P450 mRNA has been identified as a candidate diagnostic marker but low sensitivity and specificity impair its application in clinical practice (Reviewed by Brosens et al [33]). In a recent study, [34] the measurement of serum IL-6 levels and PF TNF-α levels could discriminate between patients with endometriosis and those without the disease. Endometriosis could be diagnosed if TNF-alpha levels in PF were higher than 15 pg/ml (100%sensitivity and 89% specificity) and if IL-6 levels in serum were above 2 pg/ml (90% sensitivity and 67% specificity)[34]. Potentially, the quantitation of autoantibodies against endometrial cells could also provide a novel method for the non-invasive diagnosis for endometriosis.

[35] However, more studies are needed to confirm that this approach may be clinically useful.

The role of Transvaginal Ultrasonography (TVU) and Magnetic resonance Imaging (MRI) in diagnosis and follow up of small endometriotic lesions is limited at present, but represents an interesting area of research. [33]

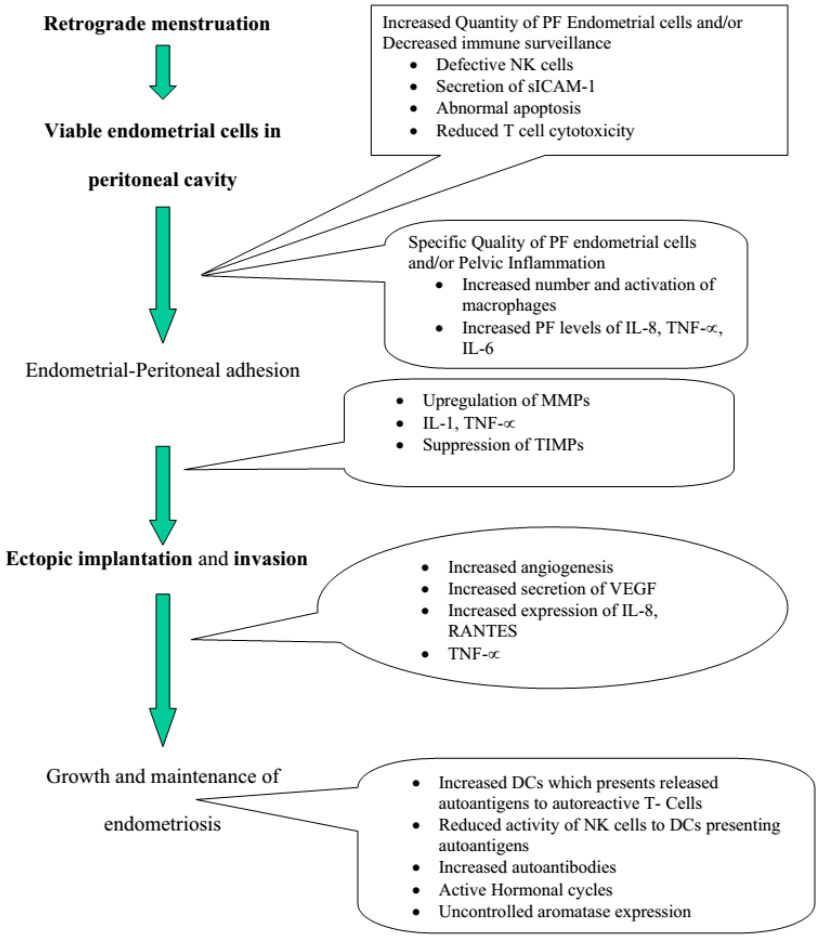

FIGURE 1. Inflammatory mediators in endometriosis

Treatment

Endometriosis causes pelvic pain and infertility and can be treated by surgery and by hormonal suppression (progestins, continuous use of oral contraceptives, danazol, GnRH agonists), as reviewed recently. [36] A drug like danazol also works as an immunosuppressive agent (reviewed by D'Hooghe and Hill [36]). Indeed, the immunologic effects of danazol have been studied in women with endometriosis and adenomyosis and include a decrease in serum immunoglobulins, [37,38] a decrease in serum C3, a rise in serum C4 levels, [38] decreased serum levels of autoantibodies against various phospholipid antigens, [37, 38] and decreased serum levels of CA125 during treatment. [39-42] Danazol inhibits peripheral

blood lymphocyte proliferation in cultures activated by T-cell mitogens but does not affect macrophage-dependent T-lymphocyte activation of B lymphocytes. [43] Danazol inhibits interleukin-1 (IL1) and TNF production by monocytes in a dose-dependent manner [44] and suppresses macrophage/monocyte-mediatedcytotoxicity of susceptible target cells in women with mild endometriosis.[45] These immunological findings may be important in the remission of endometriosis with danazol treatment and may offer an explanation of the effect of danazol in the treatment of a number of autoimmunediseases, including hereditary angioedema, [46] autoimmune hemolytic anemia, [47] systemic lupus erythematosus, and idiopathic thrombocytopenic purpura. [48, 49]

Overall, medical treatment of endometriosis is limited by cost, side effects and recurrence of endometriosis after the cessation of treatment. Therefore, there is need for new drugs that treat endometriosis-associated pain and infertility without inhibition of ovulation. Future potential targets in the treatment or management of endometriosismay be inflammatory cytokines, MMPs, adhesion and growth factors. [50] Pentoxifylline has been shown to reduce endometriotic implant growth without inducing hypoestrogenism in both humans and hamsters. In a recent study, Hornung and colleagues [51] demonstrated that Thiazolidinedione (TZD) significantly reduced leukocyte infiltration in the mouse model with endometriosis. Inhibition of TNF-alpha activity has also been a new target in the prevention and treatment of endometriosis.

Experimental endometriosis in rats was treated with recombinant human tumour necrosis factor-binding protein-1 (r-hTBP-1), a soluble form of tumour necrosis factor-α receptor type-1. [52] It was demonstrated that rhTBP-1 could reduce the size of endometriotic-like peritoneal lesions by 64%. [52] Similarly, a study carried out in baboons showed that r-hTBP-1 effectively inhibited the development of endometriosis and endometriosis-related adhesions. [53] The potential of etanercept, a soluble TNF receptor (TNFR) fusion protein, for the treatment of endometriosis is also being considered. [54]

CONCLUSION

Understanding the involvement of the immune system in the development of endometriosis may help to understand the pathogenesis and spontaneous evolution of this condition. At present, most evidence suggests that pelvic inflammation and other immunological changes are a consequence of endometriosis. The development of non-invasive diagnostic tools based on cytokines and autoantibodies could be of great benefit in the clinical management of endometriosis. Therapeutic strategies to eliminate the inflammatory reaction associated with endometriosis could lead to new treatment options for endometriosis.

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