

Inflammation and endometriosis

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1. ABSTRACT

Endometriosis is defined by presence of endometrial glands and stroma outside the uterine cavity and it affects approximately 5%–10% of women of reproductive age. Although endometriosis is usually considered to be due to retrograde menstruation, the true pathogenesis of this disease remains poorly understood. Endometriosis is associated with an inflammatory response and this inflammation leads to endothelial dysfunction and might even lead to carcinogenesis. Here, we review our current understanding of the role of inflammatory processes in the pathogenesis of endometriosis.

2. INTRODUCTION

Endometriosis, defined as the growth of endometrial glands and stroma outside the uterus, affects approximately 5%–10% of women of reproductive age (1). Endometriosis can lead to severe pelvic pain and is associated with decreased fertility, early embryonic death, and miscarriage (2). According to the widely accepted theory by Sampson, its development is thought to be caused by retrograde menstruation (3). However, the pathogenesis of endometriosis remains poorly understood since its first report more than 100 years ago. Laser capture microdissection and cDNA array analysis of endometrium has identified inflammatory mediators associated with endometriosis (4). Inflammatory mediators interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α upregulate human endometrial haptoglobin production in women with endometriosis (5). Moreover, inflammation is associated with inhibited endothelial function in women with endometriosis (6). Inflammation even promotes malignant transformation of ovarian endometriosis by inducing mismatch repair

abnormalities (7). Therefore, inflammation is crucial in the pathogenesis of endometriosis, and even in carcinogenesis. In this review, we discuss the role of inflammation in endometriosis and their interaction.

3. INFLAMMATION INFLUENCES ENDOMETRIOSIS

In the past, the relationship between inflammation and endometriosis was seen in infertile women, in whom intraperitoneal inflammation was observed (8), and was thought to be partially due to retrograde menstruation (9,10). These findings suggested that inflammation may be involved in endometriosis pathogenesis. Among several inflammatory cytokines, TNF- α was studied by different researchers. Scholl and colleagues (11) found that TNF- α plays a role in endometriosis. The expression of TNF- α was increased in tissues of patients with endometriosis (12). *In vitro*, the production of TNF- α from cultured endometrial cells was regulated by urocortin 2 and urocortin 3, neuropeptides expressed by human endometrium (13). Thus, TNF- α may be a key cytokine involved in the inflammatory aspect of endometriosis. In addition, IL-16 in peritoneal fluid may be involved in the pathogenesis of endometriosis, by initiating or sustaining inflammatory responses in the peritoneal cavity (14).

Subsequent studies on the mechanism of inflammation in endometriosis patients focused on inflammatory cells. Neutrophils and macrophages, inflammatory cells involved in the primary immune response, were identified to have higher chemotactic activity in both proliferative and luteal biopsies in women with endometriosis, compared with normal

endometrium (15). On the one hand, neutrophil activation was found only to respond to activation signals in endometriosis patients with stage III and IV disease, which is associated with the proinflammatory effect of endometriotic tissue (16).

Alternatively, macrophages may be regulated by estrogens through their functional receptors (17), suggesting an association between estrogens and the immune response in endometriosis. Study of the estrogen receptor (ER) found that the ER- α expression positively correlated with the expression of inflammatory cytokines in macrophages during endometriosis (18). The G-protein-coupled ER is increasingly expressed in patients with ovarian endometriosis and with pelvic inflammatory disease (19). Moreover, gonadotropin-releasing hormone analogues used in the treatment of endometriosis were found to reduce inflammation in other studies (20–22). Inflammation itself can influence the expression of ERs in women with endometriosis, and ER- β may play an anti-inflammatory role in endometriosis (23). Thus, the role of steroids in the inflammation seen in endometriosis cannot be ignored. When stimulated by stress, the peripheral corticotropin-releasing hormone from women may promote peritoneal inflammation in endometriosis (24). In the rat model of endometriosis, the release of inflammatory mediators and deregulation of the hypothalamic-pituitary axis responses in the hippocampus occurred after stress (25). Thus, the inflammation seen in endometriosis may be associated with dysregulation of the hypothalamic-pituitary-adrenal axis.

As the role of inflammation in endometriosis became apparent, anti-inflammatory medications have been investigated in endometriosis. Mariani *et al.* (26) found that a selective vitamin D receptor agonist, elocalcitol, can inhibit the progression of endometriosis in a mouse model, by inhibiting peritoneal inflammation. LX44 can suppress endometriosis development partly by anti-inflammation in the mouse model (27). More recently, Taguchi *et al.* (28) reported the anti-inflammatory function of resveratrol in endometrial stromal cells, derived from endometriosis.

However, in contrast to findings that inflammatory cytokines were increasingly expressed in endometriosis, pre-existing peritoneal inflammation may decrease endometriosis in the mouse model (29). Inflammation was poorly related to the degree of endometriosis in an animal model (30). These findings suggest that although inflammatory mediators are upregulated and inflammatory cells are activated, pre-existing inflammation may not contribute to the development of endometriosis. Since these findings were based on an animal model, further studies in humans are needed to provide an understanding on the precise role of inflammation in endometriosis.

4. REGULATED UPON ACTIVATION, NORMAL T-CELL EXPRESSED AND SECRETED (RANTES)

RANTES, also known as chemokine (C-C motif) ligand 5 (CCL5), is a chemotactic cytokine for several inflammatory cells, including T cells, and plays an active role in recruiting leukocytes into inflammatory sites. RANTES has been identified as a natural HIV-suppressive factor secreted by activated CD8⁺ T cells and other immune cells (31). In endometriosis, the secretion of RANTES by ectopic endometriosis implants may contribute to peritoneal leukocyte recruitment in inflammation (32). In women with endometriosis, the expressions of RANTES in peritoneal fluid and in endometrial tissues are increased compared with controls (33,34). The same finding was observed in follicular fluid from endometriosis patients undergoing *in vitro* fertilization (35). In the rat model in which endometrium was autotransplanted onto peritoneal tissue, the expression of RANTES was also significantly increased (36). The same result was found in the peritoneal fluid of mice (37). These findings, based on both the human and animal models, suggest that the increased expression of RANTES locally may be involved in endometriosis. Considering the chemotactic role of RANTES for several inflammatory cells, increased secretion of RANTES may be associated with inflammation in endometriosis.

Although the precise relationship between RANTES and endometriosis is unclear, recent studies contribute a greater understanding to the role of RANTES in endometriosis. The gene encoding CCR5, the receptors for RANTES, was found to be a possible candidate gene for endometriosis (38). The secretion of RANTES can be promoted by the combination of 17- β -estradiol and dioxin in endometriosis (39). Furthermore, the endometrial stromal cells, human peritoneal mesothelial cells, and monocytes in the peritoneal cavity of endometriosis patients may promote RANTES secretion in autocrine and paracrine manners (40), suggesting that the secretion of RANTES may be the result of endometriosis. However, Wang *et al.* (41) observed that increased secretion of RANTES in the ectopic milieu promoted the onset and progression of endometriosis by recruiting macrophages, which in turn inhibit apoptosis and enhance the growth of endometrial stromal cells. These findings suggest that RANTES may be the result of endometriosis, as well as a promoter of inflammation in the pathogenesis of endometriosis. Therefore, RANTES may play a role of positive feedback for inflammation in endometriosis.

5. T CELL IMMUNE RESPONSE-RELATED INFLAMMATION IN ENDOMETRIOSIS

Endometriosis has been found to induce the expression of genes in peripheral leukocytes identified in non-gynecologic chronic inflammatory diseases (42).

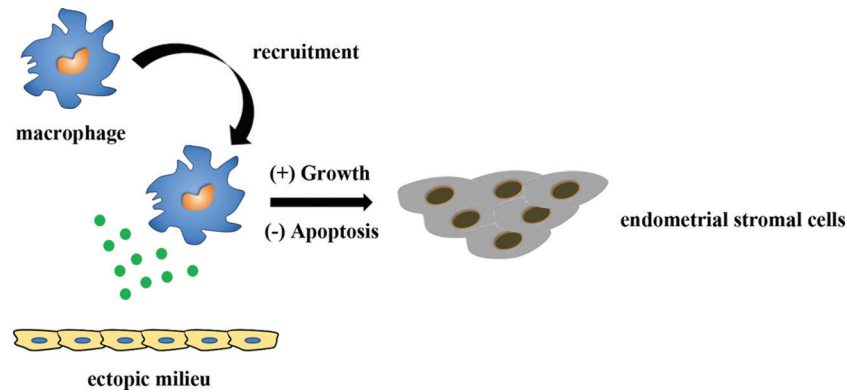


Figure 1. RANTES promotes the onset and progression of endometriosis. Increased secretion of the regulated upon activation, normal T cell expressed and secreted (RANTES) in the ectopic milieu promoted the onset and progression of endometriosis by recruiting macrophages, which in turn inhibit apoptosis and enhance the growth of endometrial stromal cells.

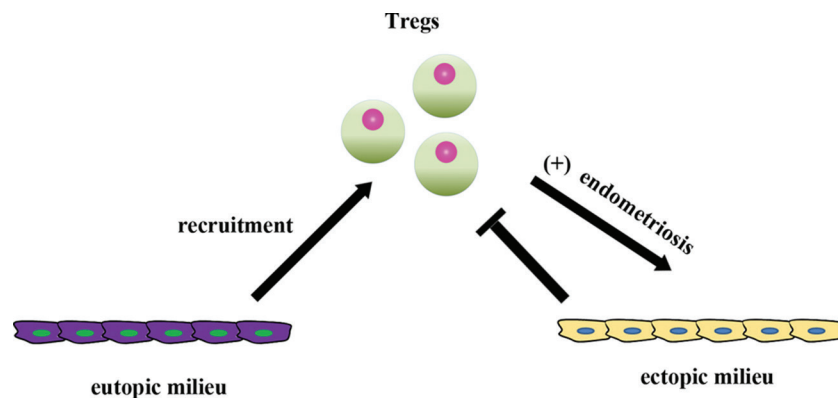


Figure 2. The regulatory T cells in the immunopathogenesis of endometriosis. The regulatory T cells (Tregs) play a complex role in the immunopathogenesis of endometriosis in that Tregs in eutopic endometrium promote the development of endometriosis, while endometriosis disrupts Treg recruitment in both eutopic and ectopic endometrium.

Recently, researchers found that endometriosis is a risk factor for the development of severe pelvic inflammatory disease (43). These findings suggest that endometriosis may contribute to pelvic inflammation. Thus, inflammation may not only be the cause but also a result of endometriosis. Moreover, the pathophysiology of endometriosis-associated infertility was found to be an immune-mediated process (44). Thus, immune-mediated inflammation should be considered in the pathogenesis of endometriosis, and may help to further clarify the complex relationship between inflammation and endometriosis. T cells have been demonstrated to one of the most important participants in endometriosis. Thus, we will discuss T cell immune response-related inflammation in endometriosis.

In previous studies, researchers found that the expression of T cells was increased in endometriosis as compared to eutopic endometrium (45). Moreover, in women with endometriosis, the activity of T-suppressor cells was decreased while T-helper cell activity was increased (46), demonstrating that the T cell-mediated

immune response was involved in endometriosis. Later, stromal T cells and T cell activation markers were found to be increasingly expressed in ectopic endometrium (47), suggesting that T cells may participate in regulating cellular processes of endometriosis tissue by secreting cytokines. Studies of endometriosis patients confirmed this by finding that T cells release differential levels of monocyte chemoattractant protein-1, RANTES, and macrophage inflammatory protein-1-alpha in response to stimulation (48). In addition, T cells participate in inflammation in endometriosis through interacting with extracellular matrix (ECM) proteins, especially with collagen IV (49, 50). T cell activation in endometriosis can be activated by dendritic cells within lesions, leading to the impairment of early lesion establishment (51).

When the number of T cells was found to increase in peritoneal fluid and peripheral blood from endometriosis patients compared with controls, an increased ratio of CD4+ T: CD8+ T was also found (52). Later, Szylo *et al.* (53) observed similar findings of an increased CD4:CD8 ratio, as well as increased IL-6

and TNF- α levels and decreased IL-10 production by lymphocytes in patients with endometriosis. Thus, the imbalance of CD4⁺ T and CD8⁺ T cells may be associated with dysregulation of inflammatory cytokine release. However, the T cell receptor beta polymorphism, which has been extensively studied in autoimmune diseases, has not been found to be associated with endometriosis (54), demonstrating that gene mutations of the T cell receptor may not be so important in T cell related-inflammation in endometriosis.

The subsets of T cells involved in immune response-related inflammation in endometriosis occur through different mechanisms. The cytotoxic T cell was expressed differently in peritoneal fluid with endometriosis, compared to without (55). In peritoneal fluid, the peritoneal T helper type 1 (Th1) immune response was reduced, which is associated with endometriosis (56). The suppression of CD4⁺ Th1 cells in endometriosis may be due to an increased expression of IL-10 and IL-12 (57). CD4⁺ T helper cells in peritoneal fluid from endometriosis patients can be regulated by leptin (58). In addition, a shift towards Th2 immune response was found in endometriosis inflammation (59). Recently, regulatory T cells (Tregs) attracted the attention of researchers. Treg is a subpopulation of T cells which modulates the immune system, maintains tolerance to self-antigens, and abrogates autoimmune disease. In the animal model of endometriosis, peripheral Tregs were decreased, which may contribute to endometriosis-associated infertility, while the increase in ectopic Treg expression may promote the development of endometriosis (60). In turn, endometriosis may disrupt Treg recruitment in both eutopic and ectopic endometrium (60). Further research found that Tregs were decreased in the peripheral blood but were increased in the peritoneal fluid of women with endometriosis, compared with controls, suggesting that Tregs participate the immunopathogenesis of endometriosis by leading to an abrogated local cellular immune response and facilitation and development of autoimmune reactions (61). Thus, several subsets of T cells are involved in the inflammatory immunopathogenesis of endometriosis. The Th1 response is decreased in endometriosis and is regulated by cytokines such as IL-10 and IL-12 or leptin. The Tregs play a complex role in the immunopathogenesis of endometriosis in that Tregs in eutopic endometrium promote the development of endometriosis, while endometriosis disrupts Treg recruitment in both eutopic and ectopic endometrium. Therefore, the T cell immune response plays a complex role in the inflammatory immunopathogenesis of endometriosis. Future research is necessary to investigate the mechanism and to provide further understanding of the pathogenesis of endometriosis.

6. CONCLUSION

In conclusion, inflammation is crucial in the pathogenesis of endometriosis. TNF- α may be a key

cytokine involved in the inflammation of endometriosis. Neutrophils and macrophages are inflammatory cells participating in inflammation, and the latter is associated with estrogen, suggesting an immune response in endometriosis. Moreover, inflammation itself can influence the expression of ERs in women with endometriosis. Since the chemotactic role of RANTES secretion is associated with inflammation in endometriosis, this plays a positive feedback role in the inflammation in endometriosis. As for T cell immune response-related inflammation, several subsets of T cells are involved in the inflammatory immunopathogenesis of endometriosis. Future studies on the mechanism of intracellular signaling would provide a further understanding on the inflammatory pathogenesis of endometriosis, which will help to identify a new therapeutic strategy.

7. ACKNOWLEDGEMENTS

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Abbreviation: IL-1beta: interleukin-1beta; TNF-alpha: tumor necrosis factor; ER: estrogen receptor; ECM: extracellular matrix; Th1: helper type 1

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