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Progress in the Study of Endometriosis

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Abstract

Endometriosis (EMS) is a gynecological disease with a low cure rate and a high recurrence rate in women of childbearing age, with gradually worsening secondary dysmenorrhea as the main clinical manifestation and a high risk of infertility. In this paper, we summarize the progress of research on EMS and its immunological pathogenesis, as well as the immunological mechanism of EMS associated with infertility, to provide a reference for subsequent clinical management.

Keywords

Endometriosis
Immunity
Infertility

1. Introduction

Endometriosis (EMS) is a common disease in women of reproductive age due to the implantation and growth of endometrial stromal cells and glands outside the endometrial lining and fundus [1]. Its pathogenesis has not been fully elucidated, with the main theory being the implantation of refluxed menstrual blood, and other theories and pathogenic factors including the induction theory, the corpus cavernosum epithelial chemotaxis theory, immune and inflammatory causes, genetic and angiogenic factors, etc [2], and in recent years, research has focused on "in-situ endometrial determinism" proposed by Lang Jinghe, i.e. whether refluxed menstrual blood and endometrial debris can grow at the base of the uterus and in the endometrium. In recent years, research has focused on whether the refluxed menstrual blood and endometrial debris can adhere, invade, and grow "off-site," and whether the presence of the endometrium is a key factor in endometriosis. This article summarises the progress of research on EMS and its immunological pathogenesis, as well as the immunological mechanism of EMS associated with infertility, to provide references for subsequent clinical research, diagnosis, and treatment.

2. EMS and its immunological pathogenesis

The exact triggering causes of EMS remain unclear from a clinical perspective and related pathogenesis is a complex issue. The clinical view most popularly suggests that retrograde implantation of menstrual

blood is a primary factor, although immune factors are also of considerable clinical concern. The findings of the investigation into immune cells and cytokines in the peritoneal fluid of patients with this condition suggest that EMS is impacted by certain factors, including impaired function of the body's immune system [3], and the reciprocal influence and interaction between mast cells, macrophages, dendritic cells, natural killer cells, endometrial cells, and endothelial cells. Among other related cells, the cytokines they produce are the primary factors that induce the interaction between endometrial cells. This interaction determines the pathological changes, including abnormal invasion, growth, and adhesion of endometrial tissues. Clinically cited as the most critical cause of disease development, the interaction and cytokines of endometrial cells require careful consideration.

2.1. The role of mast cells in the pathogenesis of EMS

Mast cells (MCs), which play an important role in the immune-inflammatory response, possess IgE receptors on their surface with high affinity. These receptors can be activated through IgE binding, thereby leading to degranulation and release of inflammatory mediators [4]. Studies have demonstrated that MC degranulation discharges numerous inflammatory mediators that may harm nerves, cause an inflammatory reaction, and trigger neuropeptide substance generation. The discharge of these neuropeptides from sensitized sensory nerve fibers can, in turn, activate and degranulate MCs, establishing a positive feedback mechanism [5]. The article notes that TGF-β plays two key roles in the development of fibrosis: firstly, it results in the expression of fibrosis-inducing factors like COL1A1, ACTA2, MMP2, and CTGF and triggers the transformation of mesothelial cells to fibroblasts. Secondly, it may contribute to the differentiation of T cells by promoting the expression of interleukin-17 (IL-17) and interleukin-10 (IL-10), which have demonstrated links to T cell differentiation [6]. The development of fibrosis in EMS involves the TGF-β1/Smad signaling pathway, as well as various cytokines such as IL-10, leading to the formation of lesions [7].

The quantity of activated mast cells in EMS lesions significantly increases [8], whereby they contribute to the pathogenesis of EMS through the secretion of inflammatory factors. Among these factors is nerve growth factor, which is one of the products following mast cell degranulation, and it stimulates the proliferation and differentiation of B lymphocytes. The substance stimulates the release of inflammatory mediators from lymphocytes and basophils, attracts mast cells thereby promoting their degranulation, elevates the levels of substance P and calcitonin gene-related peptides, triggers nociceptors, and promotes neuronal axon outgrowth, which all contribute significantly to the development of nociceptive hypersensitivity and neuropathic pain [9].

2.2. The role of macrophages in the pathogenesis of EMS

Macrophages are a crucial component of the immune system due to their phagocytic and bactericidal effects, providing vital defense against tissue damage. Additionally, they regulate intercellular processes and regulate immune response reactions through the secretion of bioactive substances. Recent research indicates that dysfunction within the immune response in EMS may be attributed to heightened macrophage activity and quantity [10]. Ectopic endometrial glandular cells and mesenchymal stromal cells generate monocyte chemotactic protein 1 (MCP-1), a chemokine for mononuclear macrophages. The expression of MCP-1 mRNA is greater in ectopic cells compared to ectopic endometrial cells. Macrophages become recruited and activated by peritoneal fluid and foci through the higher levels of MCP-1 in EMS. Moreover, the concentration of macrophage movement inhibitory factor (MIF) significantly increases in the peritoneal fluid of EMS

patients. MIF levels were found to be significantly increased [11]. Research has established that EMS patients display significantly more macrophages in their peritoneal fluid as compared to non-EMS patients. Such a rise in macrophages can lead to enhanced chronic inflammation and inflammatory cytokines within the peritoneal fluid [12]. Macrophages in patients with EMS secrete numerous inflammatory substances, including tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), and vascular endothelial growth factor (VEGF). These substances promote the division and proliferation of ectopic endothelial cells, intercellular adhesion, and neovascularisation, which can aid the implantation and growth of ectopic endothelium.

2.3. The role of dendritic cells in the pathogenesis of EMS

Dendritic cells (DCs) originate from bone marrow hematopoietic stem cells and bear a vital antigen-presenting role, which is obligatory for initiating T cells and further plays a crucial part in EMS formation. DCs can prompt anomalies in the function and count of T cells in EMS-suffering patients, in response to various stimuli by secreting cytokines, including IL-6, IL-10, IL-12, and TGF-β, which might have an impact on EMS development. A study conducted by Lzumi *et al.* demonstrates that peritoneal DCs in ectopic lesions' endometrial tissues express high levels of mannose receptors, boosting the ability of peritoneal DCs to phagocytose dead endometrial stromal cells and, thereby, contributing to EMS development [13]. Later research by Suen *et al.* identified that plasmacytoid dendritic cells have the potential to secrete IL-10, which spurs EMS development in its early phase with its pathological angiogenic effects [14].

2.4. The role of natural killer cells in the pathogenesis of EMS

Natural killer (NK) cells play a crucial role in immune surveillance and defense, as their impaired function may cause active endometrial cells to settle in the peritoneal cavity, ultimately leading to EMS. Therefore, NK cells are regarded as the first line of defense against EMS in the peritoneal cavity. Placental protein 14 (PP14) is an immunosuppressive protein secreted by the endometrium. Studies demonstrate that PP14 levels are elevated in the peritoneal fluid of patients with EMS. This protein can inhibit the immunological activity of NK cells and has an angiogenic effect [15]. Drury *et al.* found that uterine natural killer (uNK) cells were significantly decreased in ectopic tissues compared to normal women [16]. It was hypothesized that this decrease in uNK cells may contribute to the early formation of the lesion in ectopic endometrial cells. Additionally, uNK cells were observed to be reduced in the ectopic tissue. Higher expression of lysophosphatidic acid receptor 1 was observed in the endometrial tissues of the patients. The receptor was predominantly located in the mesenchymal and glandular epithelial cells of the ectopic lesions.

3. Immunological mechanisms of combined infertility in EMS

A systematic analysis of the correlation between endometriosis and infertility verified a significant relationship between them and introduced the concept of "endometriosis-related infertility" [17]. The statement implies a direct correlation and mutual influence between infertility and EMS. The disease has an adverse impact on many aspects of the female pregnancy process, leading to various malignant consequences such as spontaneous abortion and infertility as symptoms worsen. Furthermore, infertility directly increases the risk of EMS development in females and is a risk factor for the onset of EMS [18].

It has been demonstrated that electromechanical stimulation (EMS) in combination with infertility is potentially associated with immunological factors [19]. The peritoneal fluid within the peritoneal immune environment can be influenced by macrophages, NK

cells, and T lymphocytes, which ultimately impact the outcome of pregnancy through the secretion of cytokines. Endometrial antibody deficiency can impede fertilized egg implantation and result in infertility. Macrophages can ingest spermatozoa and stimulate the release of inflammatory, growth, and VEGF factors, leading to sperm immobilization, reduced activity, and impeded sperm-egg binding. Nitric oxide produced by macrophages can impair fertilized egg implantation and embryonic development, thus macrophage proliferation and activation can impact pregnancy. Certain studies have indicated that IL-13 possesses a direct impact on the stimulation of macrophages in patients' peritoneal fluid, whereas IL-l5 is accountable for activating NK cell proliferation and is commonly over-expressed during the "implantation window" of EMS patients [20]. Further medical research has demonstrated that patients with EMS often exhibit the characteristic expression of tumor necrosis factor (TNF) in their peritoneal fluid, which can increase the risk of infertility. In both T cells and NK cells, significant embryotoxicity can occur in the human body. The combination of EMS and infertility in patients has been found to significantly elevate levels of T and NK cells in the peritoneal fluid. Additionally, this peritoneal fluid restricts the normal sperm acrosome reaction, further contributing to infertility to some extent [21].

4. Summary

In summary, the pathogenesis of EMS has not been fully elucidated. However, numerous studies indicate that macrophages, T-cells, mast cells, and other immune cells in the abdominal cavity contribute significantly to the onset and progression of EMS. Additionally, some of the inflammatory factors produced by these immune cells can stimulate the division and proliferation of endometrial cells, promote intercellular adhesion and neovascularization, and facilitate ectopic endometrium implantation. A thorough investigation into the function of immune cells and their involvement in the pathogenesis of EMS could offer fresh insights into the etiology of this condition, as well as novel treatment options. Presently, there is a growing body of research focused on immune cells and their association with EMS which has led to improved comprehension of the disease's progression. Nevertheless, there remains a need for ongoing research and verification to pinpoint specific immune cells as potential targets for EMS treatment.

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Disclosure statement

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