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The Role of T Lymphocyte-Mediated Immune Imbalance in the Pathogenesis of Endometriosis

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Abstract

Endometriosis is a chronic inflammatory disease characterized by the growth of endometrial-like tissue outside the uterine cavity, affecting approximately 10% of women of reproductive age worldwide. Its pathogenesis is complex and involves multiple factors, including immune, endocrine, and inflammatory processes. Recent research has increasingly highlighted the critical role of the immune system, particularly T lymphocytes—the core effector cells of adaptive immunity—in the adhesion, invasion, proliferation, vascularization, and pain development associated with ectopic endometrial lesions. This article systematically reviews the phenotypic and functional alterations of T cells within the microenvironment of endometriosis. It focuses on various immune dysregulations, including Th1/Th2 imbalance, Th17 cells, Treg cells, and the functional exhaustion of cytotoxic T cells. By providing an in-depth understanding of the imbalance between T cell-mediated immune tolerance and inflammatory responses, this review not only offers new perspectives on the pathogenesis of endometriosis but also points the way for developing novel diagnostic biomarkers and targeted immunomodulatory therapies.

Keywords: Endometriosis, T Lymphocytes, Helper T Cells, Regulatory T Cells, Cytotoxic T Cells

1. Introduction

Endometriosis is now recognized as a systemic disease rather than a condition primarily affecting the pelvic region. It influences the metabolism of the liver and adipose tissues, triggers systemic inflammation, and alters gene expression in the brain, leading to heightened pain sensitivity and mood disorders[1]. Endometriosis is a chronic, inflammatory, hormonal, immune, systemic, and heterogeneous disease, with three distinct phenotypes: superficial, ovarian endometriotic cysts, and deep infiltrating endometriosis[2]. It affects approximately 10% of women of reproductive age[3, 4]. In recent years, its global incidence has continued to rise[5]. EMs is not merely a localized pelvic disease but a systemic chronic inflammatory condition with diverse and complex etiologies. Endometriosis may occur in the ovaries, fallopian tubes, vagina, and even in the abdomen and lungs[6]. Ectopic lesions exhibit characteristics similar to malignant tumors, including proliferation, adhesion, invasion, and migration, accompanied by estrogen-driven chronic inflammation. The disease involves extensive and heterogeneous lesions that severely impair physiological functions and quality of life, with clinical manifestations including chronic pelvic pain, dysmenorrhea, dyspareunia, menstrual irregularities, and infertility[7].

The endometrium represents a unique dynamic tissue, undergoing precisely coordinated cyclical changes under the regulation of estrogen and progesterone[8]. Throughout a woman's reproductive lifespan, the endometrium experiences approximately 400 such cyclical changes[9]. The most widely accepted theory for the development of endometriosis is the implantation theory, which posits that endometrial tissue enters the abdominal cavity via the fallopian tubes during menstruation, leading to the formation of ectopic lesions. Other factors, such as cell survival and growth, weakened immune responses, and angiogenesis, also play significant roles in disease progression[10]. Current treatments primarily rely on surgical interventions and hormonal therapy. Hormonal therapies, including combined oral contraceptive pills (COCP), progestins (oral, long-acting, implants, or intrauterine devices), and gonadotropin-releasing hormone (GnRH) agonists and antagonists, serve as first-line treatments. While they can control disease progression, they do not offer a cure and carry risks of side effects such as venous thrombosis and cancer. Surgical intervention not only fails to completely remove lesions but also involves the risk of serious complications, with postoperative recurrence rates as high as 36%[11].

T lymphocytes are among the most critical immune cells in the adaptive immune system and can be classified into various subsets based on their surface markers and functions, such as $CD4^+$ helper T cells (Th cells), $CD8^+$ cytotoxic T cells (Tc cells), regulatory T cells (Treg cells), Th17 cells, and follicular helper T cells (Tfh cells). Different T lymphocyte subsets play distinct roles in the immune imbalance observed in endometriosis (EMs), and their functional abnormalities are closely associated with the onset and progression of EMs. This article will provide a detailed elaboration on the mechanisms by which different T lymphocyte subsets contribute to the immune imbalance in EMs, aiming to offer new insights for both research into the pathogenesis of EMs and its clinical treatment.

2. Immune Imbalance in Endometriosis

The most widely accepted theory suggests that endometrial cells enter the peritoneal cavity through retrograde menstruation—a physiological process that occurs in 90% of women. These cells are typically broken down and cleared. Endometriosis is hypothesized to develop when this process is altered due to factors such as altered cell adhesion and proliferation, somatic mutations, inflammation, local steroidogenesis, neurogenesis, and immune dysregulation[3]. Transcriptomic analysis of eutopic endometrium from women with and without endometriosis supports these early observations, revealing dysregulation of genes partially involved in implantation, including those related to embryo attachment, embryo toxicity, immune dysfunction, and apoptotic responses. It has been proposed that defects in the immune system may prevent the clearance of implants on the peritoneal surface[12]. Immune system dysregulation is also considered to play a role in the pathogenesis of endometriosis[13]. The disease significantly impacts patients' quality of life and is associated with comorbid inflammatory and autoimmune conditions, including rheumatoid arthritis, psoriasis, and migraines[14]. Imbalance in the neuroendocrine-immune axis may lead to abnormal activation of hormones and cytokines, disrupting homeostasis and promoting the adhesion, implantation, and invasion of ectopic endometrial tissue, thereby facilitating the formation of ectopic lesions[14].

2.1 Dysfunction of Immune Cells

Patients with endometriosis (EMs) experience changes in both local and systemic immune functions[15]. Endometriosis is characterized by abnormal DNA methylation, histone modifications, and non-coding RNA expression, which further induce alterations in the function, quantity, and phenotype of immune cells, thereby weakening immune defense mechanisms[16]. The pelvic immune cells in EMs patients primarily include macrophages, natural killer (NK) cells, T lymphocytes, and B lymphocytes, whose functional abnormalities play a critical role in the pathogenesis of the disease[17-19].

Macrophages are the most abundant immune cells present within the pelvic cavity, and in women with endometriosis, an increase in the number of macrophages both in the peritoneal fluid (PF) and in lesions is evident[20]. In patients with endometriosis, activated macrophages fail to perform their scavenger function of clearing ectopic endometrial cells. Instead, they promote the proliferation of ectopic endometrial tissue by secreting growth factors and cytokines (such as interleukin IL-1, IL-6, IL-8, tumor necrosis factor, activation-regulated factors, normal T cell expressed and secreted factor, and vascular endothelial growth factor). Additionally, they inhibit their own clearance function, thereby driving disease progression[21]. Natural killer (NK) cells are a vital component of the innate immune system and possess potent cytotoxic activity[22]. In patients with endometriosis, the cytotoxicity of NK cells in peritoneal cells is reduced, indicating that defects in the cytotoxic function of NK cells prevent the elimination of ectopic endometrial cells and contribute to the formation of endometrial lesions[23]. The increased number and enhanced activity of B lymphocytes play a significant role in the pathogenesis of endometriosis by regulating immune cell activity and producing a large number of anti-endometrial antibodies[24]. Patients with endometriosis exhibit dysfunctional T lymphocyte effector functions, an imbalance in the proportions of helper T cell subsets (Th1/Th2/Th17), and an elevated proportion of regulatory T cells[25]. T cell subsets, including Th1, Th2, Th17, and regulatory T cells, promote disease progression by secreting various cytokines. These cytokines regulate the functions of other immune cells, facilitate the implantation and proliferation of ectopic endometrial cells, and promote angiogenesis[24].

2.2 Formation of the Immunosuppressive Microenvironment

The immune microenvironment plays a crucial role in the progression of endometriosis[26][27]. In the pelvic region of patients with EMs, there is a significant presence of immunosuppressive cells (such as Treg cells, M2 macrophages, and monocytic myeloid-derived suppressor cells M-MDSC)[28] and immunosuppressive molecules (including PD-L1, CTLA-4, IL-10, TGF-β)[29, 30]. These cells and molecules work together to suppress immune responses.

3. CD4⁺ T Cells

CD4⁺ T cells may regulate the emergence and development of ectopic endometrial cells by participating in their adhesion, proliferation, invasion, inflammatory responses, and angiogenesis[31]. Naive CD4⁺ helper T (Th) cells can differentiate into distinct effector subsets, such as Th1, Th2, Th17, regulatory T (Treg) cells, and follicular helper T (Tfh) cells[32], which modulate immune responses and inflammatory reactions by secreting various cytokines. An imbalance among T cell subsets leads to abnormal cytokine production and chronic inflammation, thereby contributing to the development of endometriosis[33].

3.1 Imbalance of Th1/Th2 Cells

Th1 cell cytokines include IFN-γ, TNF-α, TNF-β, and IL-2, which play a key role in antiviral immunity by enhancing the cytotoxic effects of CD8⁺ T cells, stimulating NK cells, and promoting cellular immunity[34]. Th2 cells produce IL-4, IL-5, and IL-13 to coordinate humoral immunity and allergic inflammatory responses[35]. Under normal physiological conditions, Th1 and Th2 cells maintain a dynamic balance, jointly sustaining the body's immune homeostasis[36]. Disruption of the Th1/Th2 balance leads to immune dysfunction, such as allergic diseases when Th2 activity predominates or autoimmune diseases when Th1 activity dominates[37].In women with endometriosis, the number of Th2 and Treg cells in peritoneal fluid increases[38], and the cytokine secretion of Th1 and Th2 cells is altered[39]. In endometriosis patients, the proportion of Th1 cells in ectopic lesions is relatively low, while the proportion of Th2 cells remains stable, indicating a bias toward Th2-mediated anti-inflammatory responses among T helper cells in the endometrial niche[33]. In women with endometriosis, polarization toward Th2 cells is observed, characterized by strong intracellular expression of IL-4 and a lack of IL-2 in lymphocytes isolated from ectopic lesions[40]. However, some studies show that the production of the Th1 cytokine IFN-γ in the peritoneum of EMS patients is significantly lower than in controls, with no significant differences found in the expression of IL-4 or IL-17a[31].

3.2 Th17 Cells

Th17 cells, along with the cytokines secreted by Th2 cells (such as IL-4 and TSLP) and IL-17a, have been described as factors promoting the development of endometriosis, as they exacerbate inflammation and stimulate endometrial cell proliferation[41]. In patients with advanced endometriosis, the number of Th17 cells in peritoneal fluid increases, which may correlate with the severity of the disease[42]. IL-17a may play a significant role in promoting angiogenesis and creating a pro-inflammatory environment in the peritoneal cavity, thereby facilitating the establishment and maintenance of endometriotic lesions [43]. A retrospective analysis found that the progression of ovarian endometriotic cysts is positively correlated with peripheral blood Th17 cell levels and the Th17/Treg ratio, and negatively correlated with peripheral blood Treg cell levels[44].

3.3 Treg Cells

In the eutopic endometrium of endometriosis patients, Tregs help suppress the immune system's recognition of ectopic endometrial cells, allowing these cells to evade immune clearance[45]. The number of Treg cells is elevated in both the eutopic and ectopic endometrium of women with endometriosis[46]. Compared to patients without endometriosis, the peritoneal lesions of those with ovarian endometriotic cysts show a significant increase in Treg cells[47]. Peritoneal fluid from EMS patients also contains elevated levels of Tregs. The accumulation of Tregs induces a type 2 immune microenvironment, accelerating the progression and fibrosis of ectopic lesions[48]. In an experimental study, peripheral natural T regulatory cells (nTregs) showed a significant decrease at intervals of 3 and 9 months, while induced T regulatory cells (iTregs) increased at 3 months. This reflects a shift toward a pro-inflammatory state, which, due to poorer regulatory effects, contributes to the persistence of endometrial lesions[49]. Activation of Tregs reduces endometrial cysts and endometriosis in patients, while depletion of Tregs exacerbates endometriosis in mice. Adoptive transfer of Tregs suppresses the progression of endometriosis and decreases the levels of helper T (Th)-cell-related and proinflammatory cytokines in mice. Tregs downregulate the mRNA expression of Th1, Th2, and Th17-related cytokines, including IFN-γ, IL-4, and IL-17, as well as the levels of the proinflammatory cytokine IL-6[50]. Evidence regarding changes in Treg proportions in the peripheral blood, peritoneal fluid, eutopic endometrium, and ectopic endometrial tissues of endometriosis patients remains inconsistent. This discrepancy may stem from variations in patient selection, particularly concerning early- or late-stage endometriosis[51].

4. CD8⁺ Cytotoxic T Cells (Tc Cells)

CD8⁺ T cells, also known as cytotoxic T cells, play a critical role in the immune system by recognizing and destroying infected or abnormal cells[47]. In peritoneal fluid from patients with endometriosis, CD8⁺ T cells exhibit reduced cytotoxic function, which may impair immune surveillance and promote the colonization of

endometriotic lesions in the peritoneal cavity[52]. An increase in $CD8^+$ T cells within the eutopic endometrium of women with endometriosis reveals a pro-inflammatory feature in the endometrial immune environment, and elevated $CD8^+$ T cell levels are associated with an increased risk of infertility in women[53]. In mouse experiments, depletion of $CD8^+$ T cells led to an increase in the weight of ectopic lesions. However, in mouse models supplemented with normal $CD8^+$ T cells, lesion weight was similar to that in normal mice. Iron overload is present in cystic fluid and lesion sites. Iron accumulation in endometriotic lesions triggers p53-mediated inhibition of xCT/GPX4, resulting in reduced $CD8^+$ T cell activity, impaired lesion clearance, and accelerated progression of endometriosis. $CD8^+$ T cells are enriched in endometriotic lesions, but their cytotoxic function is significantly diminished[54]. The reduced cytotoxicity and abnormal metabolism of $CD8^+$ T cells are induced by endometrial cells through activation of the STAT1/PDCD1 pathway, thereby promoting immune survival and facilitating the progression of endometriosis[55].

5. Discussion

Despite its high prevalence, the diagnosis of endometriosis is often delayed by several years, misdiagnosis is common, and access to effective treatment is frequently prolonged[2]. However, as confirmation typically requires surgical visualization, the true prevalence of endometriosis remains unclear. There is currently no definitive cure for endometriosis; treatment options include hormonal medications, surgical removal of lesions, or a combination of both, often accompanied by side effects and limited efficacy[56]. Current diagnostic protocols rely on a combination of clinical assessment, imaging, and surgical confirmation. While ultrasound and magnetic resonance imaging (MRI) aid in lesion localization, laparoscopic surgery with histopathological verification remains the gold standard for diagnosis[57]. This invasive approach is thus reserved for symptomatic women. Consequently, the prevalence of asymptomatic endometriosis remains unknown. Although endometriosis can initially respond positively to surgical and hormonal treatments in up to 70% of cases, most women experience symptom recurrence within two years, necessitating additional surgical interventions[58]. Regardless of the hormonal therapy used, many women continue to experience symptoms during or after treatment, or face high recurrence rates upon discontinuation. Some may also suffer from persistent pain due to surgical complications, such as adhesions[59].

The etiology of endometriosis is complex, involving immune imbalance, hormonal alterations, and inflammation[60]. Endometriosis is a multifaceted disease associated with localized and systemic abnormalities in immune responses[61]. Patients with endometriosis exhibit imbalances in immune cell subsets and the endocrine hormone-immune regulatory axis[62]. In recent years, significant progress has been made in understanding the role of T lymphocytes in the immune imbalance of EMs. Dysregulation in the quantity and subtypes of T cells, particularly Treg, Th17, and $CD8^+$ T cells, plays a critical role in the pathogenesis of endometriosis[63]. However, current research still has some limitations. Most studies focus on changes in T lymphocyte subsets in peripheral blood and peritoneal fluid, while the phenotype, function, and regulatory mechanisms of T lymphocyte subsets within the local microenvironment of ectopic endometrial lesions remain insufficiently explored. The interaction mechanisms between T lymphocyte subsets, ectopic endometrial cells, and other immune cells in the local environment require further investigation. Secondly, much of the current research on T lymphocyte subsets in EMs is correlative, lacking validation of causal relationships. While an increase in Treg cell numbers has been associated with the onset and progression of EMs, it remains unclear whether this increase is a cause or a consequence of EMs. Further validation through animal models and experimental studies is needed. The interaction mechanisms among different T lymphocyte subsets are complex, and current research predominantly focuses on the role of individual subsets, with limited exploration of synergistic or antagonistic interactions between them. Delving deeper into these interactions will contribute to a more comprehensive understanding of the immune imbalance mechanisms in EMs and provide a foundation for developing more effective immunotherapeutic strategies.

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