

Natural Killer Cells and Endometriosis: A Complex Relationship with Therapeutic Implications

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Abstract

Objective: Endometriosis is a benign disease, that includes a condition in which uterine endometrial cells grow in areas other than the uterus and cause periodic bleeding in these areas. Various hypotheses have been proposed regarding the causes of these conditions, but until now researchers have not reached a definitive hypothesis. The important point is the involvement of different immune cells in the processes related to these conditions, like natural killer (NK) cells. These cells, with their high inherent capabilities, can accurately diagnose endometriosis sites and have a very high impact on the treatment of these conditions. Therefore, the therapeutic combination of NK cells with endometriosis is a new approach in gynecology.

Results: In this article, collect the latest data regarding the relationship between endometriosis pathology and its treatment with NK cells. Also, the factors involved and susceptible in this relationship were studied to obtain the best approach in this regard.

Conclusion: NK cells are one of the most important cells involved in the pathogenesis of endometriosis. Considering the key role of these cells and related factors, it is possible to design a new approach in this regard and provide better treatment of endometriosis.

Keywords

Endometriosis, Killer Cells, Natural, Interleukins, Combined Modality Therapy.

Introduction

Endometriosis is a prevalent benign gynecological condition affecting approximately 10-15% of women of reproductive age worldwide [1]. Characterized by the ectopic growth of endometrial-like tissue outside the uterine cavity, this condition can manifest in various locations within the pelvic cavity [2]. The unpredictable nature of the lesion site often results in a broad spectrum of clinical manifestations. Chronic pelvic pain, dysmenorrhea, and infertility are commonly reported symptoms, significantly impacting patients' quality of life. The American Society for Reproductive Medicine (ASRM) established a clinical staging system for endometriosis in 1997, known as the revised American Fertility Society (rAFS) classification. This widely adopted system categorizes endometriosis based on lesion location, number, size, depth, and adhesion formation, assigning stages from I (minimal) to IV (severe).

Current therapeutic modalities for endometriosis primarily target symptom management, fertility preservation, and disease recurrence prevention. Surgical and pharmacological interventions, although commonly employed, exhibit limited efficacy due to an incomplete comprehension of the disease's pathogenesis [2, 3]. Surgical management of endometriosis-associated pelvic pain is a viable option, yet its effectiveness is compromised by factors including a substantial postoperative recurrence rate (40 to 50 percent within 5 years) and potential complications such as diminished ovarian reserve [4, 5]. Pharmacological management primarily relies on hormonal agents, analgesics, and nonsteroidal anti-inflammatory drugs (NSAIDs), which can alleviate symptoms but rarely achieve disease eradication. Moreover, these treatments often induce adverse effects and may compromise fertility [6]. Collectively, these limitations underscore the urgent need for innovative treatment strategies.

The pathogenesis of endometriosis is intricately linked to immune dysregulation, with natural killer (NK) cells and other immune cells contributing to a chronic inflammatory microenvironment. Initial studies by Oosterlynck et al. reported a reduction in NK cell activity among women with endometriosis, a finding subsequently corroborated by others. Decreased NK cell cytotoxicity against autologous endometrial cells, observed both peripherally and within the peritoneal cavity, correlates with disease severity [7, 8]. The underlying mechanisms for this NK cell dysfunction include downregulation of NK cell cytotoxicity, potentially due to elevated inhibitory cytokine levels or increased expression of inhibitory NK cell receptors within the peritoneal fluid [7, 9]. Given the pivotal role of immune dysregulation in endometriosis, immunotherapy emerges as a promising therapeutic approach. By modulating and augmenting the immune response against endometrial lesions, immunotherapy aims to harness the body's innate defense mechanisms to combat this disease [10-12].

In this article, various factors affecting natural killer cells have been briefly discussed, the effects of each on these cells have been stated, and the necessary investigations have been carried out for different treatment approaches. In the end, the latest approaches based on natural killer cells in the treatment of endometriosis have been discussed.

The main section

Among other types of patients, women's diseases are of great importance due to the ability of fertility in this gender and overall human survival. In addition, women's health, as half of the world's population, has been neglected in some cases for various reasons and has not been given the importance it should have. Among the various diseases that affect this segment of society, endometriosis is one of the most important diseases, and due to its unknown etiological nature, a definitive treatment has not yet been described for it. The pathogenesis of endometriosis remains complex and multifactorial. While numerous pathological factors contribute to disease development, emerging evidence suggests a genetic component. Twin studies have demonstrated a higher concordance rate for endometriosis in monozygotic twins compared to dizygotic twins, supporting a genetic predisposition [13]. Comprehensive genomic analysis holds promise for identifying specific genes associated with endometriosis susceptibility [14]. The predominant etiological theory of endometriosis posits a retrograde menstrual dissemination of endometrial tissue. As proposed by Sampson, endometrial fragments, propelled by uterine contractions during menstruation, ascend through the fallopian tubes into the pelvic cavity. Subsequent implantation and growth of this ectopic endometrial tissue can induce a localized inflammatory response [15]. This inflammatory process involves the recruitment of innate immune cells, including neutrophils, macrophages, T cells, and NK cells [3].

NK cells, a critical component of the innate immune system, exhibit functional heterogeneity. The CD56brightCD16⁻ NK cell subset primarily produces cytokines, while the CD56dimCD16⁺ subset mediates cytotoxic effector functions [16]. In the context of endometriosis, a decline in the cytotoxic activity of CD56dimCD16⁺ NK cells within both peripheral blood and peritoneal fluid has been reported [7, 17, 18]. This functional impairment compromises the immune system's ability to eliminate ectopic endometrial tissue, facilitating disease progression. The diminished NK cell cytotoxicity in endometriosis patients is hypothesized to be influenced by a complex interplay of cytokines within

the peritoneal environment, including transforming growth factor-beta (TGF- β), interleukin-6 (IL-6), and IL-15 [19]. The critical role of NK cells in endometriosis pathogenesis underscores the potential of immunotherapy as a promising therapeutic avenue.

NK cells are crucial for immune surveillance against ectopic endometrial tissue following retrograde menstruation. An imbalance in the expression of NK cell receptors is implicated in endometriosis pathogenesis. Specifically, a reduction in activating receptors (KARs) such as NKP46, NKP30, and NKG2D, and their cognate ligands MICA, MICB, ULBP-2, and ULBP-3, coupled with an increase in inhibitory receptors (KIRs) including CD158a+, KIR2DL1, CD94/NKG2A, PD-1, NKB1, and EB6, and their corresponding inhibitory ligands PD-L1, HLA-E, HLA-G, and HLA-I within the peritoneal fluid of endometriosis patients, contributes to diminished NK cell cytotoxicity. This functional impairment facilitates the survival and implantation of ectopic endometrial cells, ultimately driving disease progression. [7, 20-24].

Preclinical studies have demonstrated the potential of immune modulators in enhancing NK cell function and mitigating endometriosis. Oral probiotics have shown efficacy in activating abdominal NK cells and reducing endometriosis development [25]. Similarly, Helixor A, a mistletoe extract, directly stimulates NK cell cytotoxicity and inhibits endometriosis progression [26]. Loratadine, an antihistamine with immunomodulatory properties, has been shown to stimulate macrophage and T cell activity, enhance NK cell cytotoxicity, and promote B cell proliferation [27, 28]. These findings suggest that targeting the immune system, particularly NK cell function, may offer novel therapeutic strategies for endometriosis management.

Conversely, the upregulation of inhibitory receptors on NK cells within the endometriotic microenvironment contributes to immune escape. Therapeutic strategies targeting these inhibitory receptors, such as KIR2DL1, LILRB1/2, and NKG2A, through the use of monoclonal antibodies, offer potential methods for restoring NK cell function [29].

NK cells exert a multifaceted impact on endometriosis, extending beyond their well-established cytotoxic functions. Through the secretion and modulation of a diverse array of soluble mediators, NK cells indirectly influence disease progression. These immunoregulatory molecules represent potential therapeutic targets to augment NK cell anti-endometriotic efficacy. The precise nature of these mediators and their functional implications will be comprehensively explored in subsequent sections “Figure 1”.

- a) **Tumor necrosis factor-alpha (TNF- α):** TNF- α , a core pro-inflammatory cytokine predominantly produced by activated macrophages and NK cells, plays a fundamental role in the pathogenesis of endometriosis. This cytokine orchestrates a pro-inflammatory cascade, stimulating the production of additional pro-inflammatory mediators such as IL-1 and IL-6 [28, 30].

Several therapeutic agents targeting TNF- α have been investigated. Pentoxifylline, an immunomodulatory drug, reduces TNF- α production and attenuates inflammatory responses. [31]. Etanercept, a TNF- α inhibitor, effectively neutralizes the cytokine and has demonstrated clinical efficacy in managing autoimmune diseases.[32]. Additionally, recombinant human TNF binding protein-1 (r-hTBP-1) inhibits TNF- α activity and has been explored as a potential treatment for endometriosis. These therapeutic approaches underscore the critical role of TNF- α in endometriosis pathogenesis and the potential benefits of TNF- α inhibition [33-35].

- b) **TGF- β 1:** TGF- β 1 is significantly overexpressed in endometriosis, with elevated levels detected in endometriosis tissues, peritoneal fluid, and the endometrial peritoneum compared to controls. This upregulation is associated with impaired immune cell function, particularly NK cells, within the peritoneal cavity, and promotes the survival, adhesion, and invasion of ectopic endometrial cells [36].

Emerging evidence implicates platelets and TGF- β 1 in modulating NK cell function within the endometriosis microenvironment. Guo et al. demonstrated that platelet-derived TGF- β 1 suppresses NK cell cytotoxicity by downregulating NKG2D expression, a critical activating receptor. Neutralization of TGF- β 1 reversed this effect, highlighting its critical role in NK cell dysfunction [37].

Expanding on these findings, Du et al. elucidated additional mechanisms by which platelets impair NK cell function in an endometriosis mouse model. Platelet depletion enhanced NK cell activity, characterized by

increased activating receptor expression (NKG2D, NKp46) and decreased inhibitory receptor expression (KIR2DL1). Furthermore, platelets downregulated NKG2D ligand expression on target cells, limiting NK cell recognition and elimination. These findings collectively underscore the complex interplay among platelets, NK cells, and the endometriotic microenvironment in driving disease pathogenesis.[38, 39].

- c) **IL-6:** Previous investigations have highlighted the role of chemokines within the peritoneal fluid of women with endometriosis in suppressing NK cell cytolytic activity. Specifically, elevated levels of IL-6 have been associated with decreased expression of Src homology region 2-containing protein tyrosine phosphatase-2 (SHP-2), a principal regulator of NK cell function [19]. Consequently, the production of cytotoxic effector molecules, such as granzyme B and perforin, is impaired, leading to reduced NK cell cytotoxicity.
- d) **IL-10:** Yang et al. demonstrated the detrimental impact of the endometriotic microenvironment on NK cell function through a co-culture model involving NK cells, macrophages, and endometrial stromal cells (ESCs) [40]. This study revealed a significant reduction in NK cell cytotoxicity, associated with decreased expression of activating receptors and interferon- γ (IFN- γ), while concurrently observing increased secretion of immunosuppressive cytokines, including IL-10 and TGF- β . These findings highlight the pivotal role of IL-10 in the impairment of NK cell function within the context of endometriosis.
- e) **IL-12:** IL-12 is implicated as a key cytokine in the complex pathophysiology of endometriosis. It has been shown to stimulate the production of other inflammatory cytokines, promote leukocyte aggregation, and enhance NK cell cytotoxicity [41]. Preclinical studies utilizing murine models of endometriosis have demonstrated the efficacy of IL-12 in inhibiting lesion development and augmenting NK cell activity [42, 43]. Preclinical studies have demonstrated that probiotic interventions, such as the administration of *Lactobacillus gasseri* OLL2809, can effectively augment NK cell function and reduce endometrial lesion burden [44]. This probiotic strain stimulates IL-12 production.
- f) **IL-15:** Elevated IL-15 secretion by ESCs within a co-culture system has been shown to reduce granzyme B, IFN- γ , and NKG2D expression in NK cells, further compromising their cytotoxic capacity and facilitating immune escape of ectopic endometrial tissue [45].
- g) **Complement System Inhibition:** The complement system, a critical component of innate immunity, is involved in pathogen elimination and host defense. However, dysregulation of this system has been implicated in various pathological conditions, including endometriosis. Targeting complement component C3 has emerged as a potential therapeutic strategy [46]. Liu et al. proposed a role for the complement receptor 3 (CR3) in the impaired tumor surveillance capacity of NK cells, suggesting that iC3b/CR3 signaling negatively regulates NK cell activity [47]. Given the widespread expression of CR3 on NK cells [48] and the inhibitory effects of the iC3b/CR3 axis, coupled with elevated iC3b levels in the peritoneal fluid of women with endometriosis, it is plausible that this signaling pathway contributes to the dysfunction of uterine NK cells in this disease, potentially hindering their ability to eliminate endometrial cells. While systemic complement activation, as evidenced by increased serum levels of C3c, C4, and sC5b-9, occurs in EM, the peritoneal cavity exhibits particularly high concentrations of iC3b [46, 49].
- h) **Cyclooxygenase-2 (COX-2):** COX-2 is a key enzyme implicated in endometriosis pathogenesis. Regulated by hormonal fluctuations and hypoxic conditions, COX-2 expression is elevated within both epithelial and stromal cells of ectopic endometrial lesions. This upregulation contributes to a cascade of pathological events, including increased cell proliferation, invasion, angiogenesis, and apoptosis resistance, ultimately promoting disease progression [50]. The intricate interplay between COX-2 and NK cell function within the endometriosis microenvironment highlights potential therapeutic methods. COX-2, upregulated in ectopic endometrial tissue, contributes to a pro-inflammatory milieu that may indirectly suppress NK cell activity. By inhibiting COX-2, it is postulated that the functional capacity of NK cells could be enhanced, thereby augmenting the body's natural defense against ectopic endometrial tissue. While traditional NSAIDs such as naproxen and diclofenac possess COX-2 inhibitory properties, newer, more selective COX-2 inhibitors like celecoxib, glycyrrhizin, and puerarin offer potential therapeutic advantages. However, to date, the clinical efficacy of these agents specifically for endometriosis management remains to be established [51, 52].
- i) **Hormonal factors:** Hormonal factors, particularly estrogen, have been implicated in modulating NK cell function within the endometriotic microenvironment. By suppressing autophagy in ESCs via the CXCL12/CXCR4 pathway, estrogen promotes cell survival and proliferation, contributing to disease progression [53]. Furthermore, the estrogen-autophagy-STAT3-HCK axis has been implicated in NK cell dysfunction. Downregulation of HCK, a hematopoietic cellular kinase, through STAT3 signaling, leads to increased IL-8 and IL-23A production by ESCs, ultimately impairing NK cell cytotoxicity by suppressing microRNA miR185-1-3p and its target gene PTGS2 [54].
- j) **BCG Vaccination:** *Bacillus Calmette-Guerin* (BCG) vaccination, traditionally employed for tuberculosis prevention, exhibits broader immunomodulatory effects. Preclinical studies have demonstrated its potential in countering endometriosis. BCG vaccination has been shown to reduce endometrial implant formation,

enhance peritoneal immune surveillance, and activate NK cells [43, 55, 56]. By promoting a shift towards a more protective macrophage phenotype and modulating cytokine production, BCG offers a promising therapeutic avenue for endometriosis management.

Immunotherapy, specifically targeting NK cell function through strategies such as CAR-NK cell therapy, offers a promising novel approach for the treatment of various diseases, including endometriosis [57]. The pivotal role of NK cells in immune surveillance against ectopic endometrial tissue underscores the potential of these strategies to effectively combat disease progression.

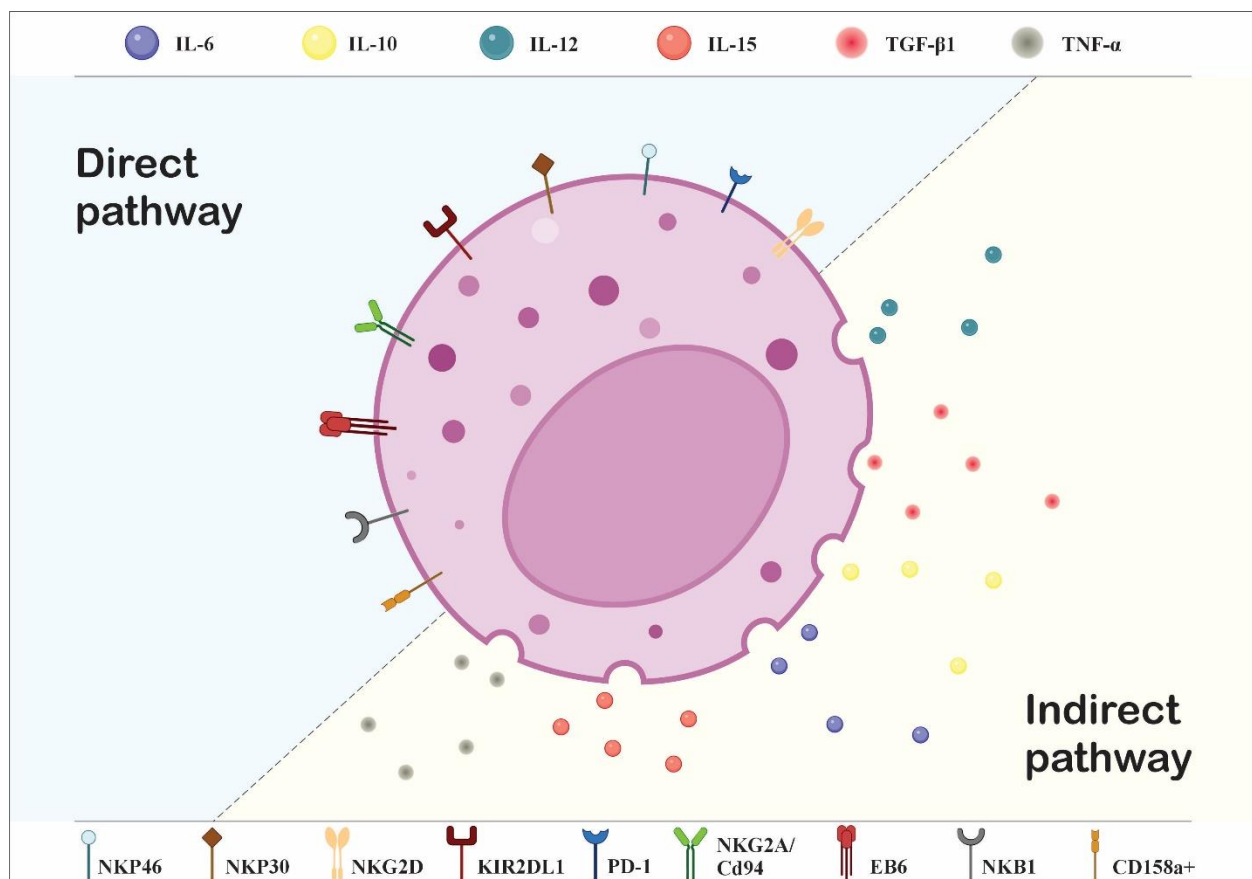


Figure (1): Endometriosis: A Complex Disease Involving Immune Dysfunction. Endometriosis, a complex disease characterized by ectopic endometrial tissue growth, involves intricate immune dysregulation. Natural killer (NK) cells, critical components of innate immunity, play a pivotal role in this process. Their functional impairment, due to altered receptor expression and cytokine imbalances, contributes significantly to disease pathogenesis and progression.

conclusion

Endometriosis is a complex disease characterized by the growth of endometrial tissue outside the uterus. Its pathogenesis involves a multitude of factors, including genetic predisposition, immune dysfunction, and hormonal influences. The immune system plays a critical role in endometriosis. NK cells, essential for immune surveillance, are impaired in endometriosis due to a complex interplay of factors, including reduced activating receptor expression, increased inhibitory receptor expression, and the influence of cytokines like IL-6, IL-10, IL-12, IL-15, TGF- β , and TNF- α . Additionally, the endometriotic microenvironment such as complement system dysregulation, elevated COX-2 expression, and hormonal influences contribute to NK cell dysfunction. Therapeutic strategies aimed at enhancing NK cell activity and modulating the endometriotic microenvironment hold promise for improving patient outcomes. This includes interventions such as the use of probiotics, immunomodulatory agents, and the potential application of immunotherapy, such as chimeric antigen receptor (CAR)-NK cell therapy, targeting specific cytokines or growth factors.

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Nomenclature:

ASRM: American Society for Reproductive Medicine, **BCG:** Bacillus Calmette-Guerin, **CAR:** chimeric antigen receptor, **COX-2:** Cyclooxygenase-2, **CR3:** complement receptor 3, **ESCs:** endometrial stromal cells, **IFN- γ :** interferon- γ , **IL:** interleukin, **KAR:** Killer Activation Receptors, **KIR:** Killer Inhibitory Receptors, **NK:** natural killer, **NSAIDs:** nonsteroidal anti-inflammatory drugs, **rAFS:** revised American Fertility Society, **r-hTBP-1:** recombinant human TNF binding protein-1, **SHP-2:** Src homology region 2-containing protein tyrosine phosphatase-2, **TGF- β 1:** transforming growth factor-beta, **TNF- α :** Tumor necrosis factor-alpha.

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