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# Dysfunction of natural killer cells promotes immune escape and disease progression in endometriosis

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Endometriosis (EMs) is a chronic inflammatory disorder characterized by dysregulated innate immunity, particularly impaired cytotoxic function of natural killer (NK) cells. As pivotal effectors of the innate immune response, NK cells fail to eliminate ectopic endometrial lesions due to aberrant receptor—ligand interactions, elevated levels of immunosuppressive cytokines (TGF-β, IL-6, and IL-10), and dysfunction of adhesion molecules. This compromised immune surveillance facilitates the survival and implantation of ectopic lesions, contributing to the hallmark symptoms of pain and infertility. Recent immunotherapeutic strategies, including NK cell checkpoint blockade (anti-NKG2A, anti-PD-1), IL-2-based activation, and adoptive NK cell transfer—seek to restore NK cell cytotoxicity and reestablish immune homeostasis. This review summarizes current advances in understanding NK cell dysfunction in EMs, emphasizing its central role in immune evasion and the therapeutic promise of targeting innate immune pathways.

KEYWORDS

endometriosis, natural killer cells, immune surveillance, cytotoxicity, cytokines immunotherapy

# 1 Introduction

Endometriosis (EMs) is a chronic gynecological disorder characterized by low cure rates and high recurrence, affecting approximately 10% to 15% of women of reproductive age (1). Epidemiological studies indicate that up to 70% of affected individuals experience chronic pelvic pain (2), while approximately 50% suffer from infertility, substantially compromising the health and quality of life of women in their reproductive years (3). Although the retrograde menstruation theory remains the most widely accepted etiology of EMs, additional contributing factors, including genetic predisposition, immune dysfunction, and chronic inflammation, have been implicated in its pathogenesis (4, 5). Nevertheless, the precise molecular and cellular mechanisms underlying disease onset remain elusive. Increasingly, EMs is recognized as a multifactorial immune-mediated

disorder, in which dysregulation of fundamental immunological processes plays a pivotal role in disease initiation and progression (6).

Emerging evidence indicates that nearly all immune cell types in women with EMs exhibit functional abnormalities (7, 8). The disease microenvironment is characterized by aberrant immune cell infiltration, macrophage activation, impaired cytotoxicity of natural killer (NK) cells, and dysregulated expression of proinflammatory and regulatory cytokines (9). Ectopic endometrial cells that survive and proliferate in the peritoneal cavity possess the ability to evade immune surveillance and clearance by resident immune cells, particularly macrophages and NK cells. Mounting evidence now supports a strong association between EMs pathogenesis and impaired NK cell cytotoxicity (10). This review summarizes current progress in understanding the regulatory mechanisms governing NK cell cytotoxicity in EMs, elucidates how ectopic endometrial cells escape NK cell-mediated immune surveillance, and discusses recent advances in NK cell–targeted immunotherapeutic strategies.

# 2 Phenotypes and functions of NK cells

## 2.1 NK cell phenotypes

Natural killer (NK) cells are large granular lymphocytes defined by the $CD3^-CD56^+CD16^{+/-}CD57^{+/-}$ immunophenotype. They constitute a central arm of innate immune surveillance, endowed with the capacity to detect and lyse virally infected, malignant, or stressed cells without prior sensitization (11, 12). Beyond their cytolytic role, NK cells can also recognize subsets of normal cells, thereby participating in a broad spectrum of immunological processes, including antigen presentation, regulation of autoimmunity, orchestration of inflammatory responses, modulation of transplant rejection, and maintenance of pregnancy (13). Based on surface expression of CD56 and CD16, NK cells are divided into two major subsets: $CD56^{dim}CD16^+$ and $CD56^{bright}CD16^-$ NK cells (14). The $CD56^{dim}CD16^+$ subset constitutes approximately 90% of circulating NK cells and is highly cytotoxic. In contrast, $CD56^{bright}CD16^-$ NK cells primarily regulate immune responses via cytokine secretion, such as IFN-$\gamma$ and TNF-$\alpha$. Upon appropriate stimulation, $CD56^{bright}CD16^-$ NK cells can convert into $CD56^{dim}CD16^+$ NK cells, concomitantly enhancing their cytolytic activity (15). NK cell phenotypic and functional properties are further shaped by their tissue microenvironment. In the endometrium during the menstrual cycle, and in the decidua during pregnancy, NK cells predominantly exhibit the $CD56^{bright}CD16^-$ phenotype. These cells originate from $CD34^+$ progenitors and are involved in spiral artery remodeling, placental development, and maintenance of gestation (16, 17).

## 2.2 NK cell functions

Natural killer (NK) cells exert cytotoxic effects primarily through the exocytosis of cytolytic granules and the induction of apoptosis via Fas ligand (FasL)–mediated signaling (18). Target cell recognition is orchestrated by adhesion molecules in concert with an array of activating and inhibitory receptors, including killer immunoglobulin-like receptors (KIRs), leukocyte immunoglobulin-like receptors (LILRs), and members of the natural killer group 2 (NKG2) receptor family (19). The dynamic equilibrium between these activating and inhibitory cues ultimately dictates the magnitude of NK cell cytotoxicity. In endometriosis (EMs), NK cytotoxic activity has traditionally been evaluated using K562 leukemia cells as targets. Multiple studies have reported diminished lytic capacity of NK cells isolated from both the peripheral blood (20) and peritoneal fluid (21) of patients with EMs. However, because K562 cells lack major histocompatibility complex (MHC) class I molecules, they are intrinsically susceptible to NK-mediated lysis (22), raising concerns about their relevance in modeling EMs-specific immune interactions. A more physiologically relevant approach would be to assess NK cytotoxicity against ectopic endometrial epithelial or stromal cells. Nonetheless, technical challenges, particularly the limited availability of clinical samples and the difficulties in establishing primary cultures, have constrained such investigations. To date, only a small number of studies have employed autologous endometrial cells as targets, and the existing evidence remains insufficient to definitively establish whether NK cell cytotoxicity is reduced within the eutopic endometrium of EMs patients (23).

# 3 Role of NK cells in EMs

## 3.1 NK cell levels in EMs

Most investigations on NK cells in endometriosis (EMs) have examined peripheral blood and peritoneal fluid. Most report no marked differences in the proportions of $CD56^+$ and/or $CD16^+$ NK cells between EMs patients and healthy controls (24). Some describe reduced $CD16^+CD57^+$ or $CD16^+CD56^-$ subsets (24), whereas others note increased $CD56^-$ or $CD56^-CD16^+$ populations (25). Data on NK cells in eutopic versus ectopic endometrial tissue remain scarce. Drury et al. (26) observed that uterine NK (uNK) cell numbers rise from the proliferative to the late secretory phase, peaking before menstruation, in both EMs and non-EMs cases; however, NK cell frequencies were consistently lower in ectopic lesions. Conversely, in women with unexplained recurrent miscarriage or infertility, $NKp46^+/CD56^-$ cells are elevated in the endometrium (27). Furthermore, $CD56^-$ or $CD16^+$ NK cell counts in ectopic endometrial tissue are generally lower than those in eutopic endometrium of healthy controls. These cells in ectopic lesions also fail to exhibit typical phenotypic and functional profiles seen in uterine NK cells (26).

Recent evidence indicates that distinct NK cell subsets differentially contribute to immune dysregulation in EMs (10). CD56$^-$/CD16$^+$ NK cells, representing a more differentiated phenotype with potent antibody-dependent cytotoxic potential, are enriched in the peritoneal fluid of EMs patients, yet display functional exhaustion, marked by attenuated degranulation capacity and diminished cytokine release (27–30). Conversely, CD56$^+$/CD16$^-$ NK cells, typically classified as immature, are relatively expanded in the peripheral circulation and secrete elevated levels of immunoregulatory mediators such as IL-10 and TGF-β, potentially reinforcing local immunosuppression (5, 31). This reciprocal alteration in subset distribution between peripheral blood and peritoneal fluid reflects a phenotypic shift from cytotoxic to immunoregulatory dominance, thereby facilitating lesion persistence and undermining immune surveillance in EMs. Collectively, these findings implicate aberrant NK cell subset composition and functional impairment as central mechanisms driving the loss of NK cytotoxicity in EMs (32).

## 3.2 Role of NK cells in EMs pathogenesis

NK cells are essential components of the innate immune system, forming the first line of defense against pathogens. By eliminating misplaced endometrial cells, they help prevent ectopic implantation. Dysfunctional NK activity or impaired cytotoxicity may contribute to EMs onset. Dorien FO et al. (33) found aberrant expression of NK cell receptors and altered cytokine production by NK cells in the pelvic environment of EMs patients, further implicating their role in disease etiology. He J et al. (34) discovered that sterile alpha motif domain-containing protein 9 (SAMD9) and Ral guanine nucleotide dissociation stimulator-like 2 (RGL2) are significantly upregulated in patients experiencing pelvic pain associated with EMs. Additionally, expression of lysophosphatidic acid receptor 1 (LPAR1) is elevated in ectopic stromal and glandular epithelial cells (34). These findings indicate that NK cells contribute to EMs pathogenesis, particularly in pain phenotypes. Suppression of NK cytotoxic function may exacerbate lesion persistence and pain progression in affected individuals.

## 3.3 Expression of NK cell receptors and ligands in EMs

In endometriosis (EMs), impaired NK cytotoxicity is closely linked to dysregulated activating–inhibitory receptor balance (35). Reduced expression of the activating receptor NKG2D limits NK recognition of ectopic endometrial cells and attenuates perforin/granzyme release, facilitating lesion immune evasion (36). While ULBP-2 levels remain unchanged, the non-classical MHC molecules MICA and MICB are markedly upregulated and correlate with disease severity (37), suggesting potential interference with NK cytotoxicity that warrants further validation. Human leukocyte antigen G (HLA-G), a ligand for inhibitory receptors LILRB1 and KIR2DL4 (38), is aberrantly expressed in both eutopic and ectopic endometrium, with menstrual cycle–dependent variation (39). Elevated soluble HLA-G (sHLA-G) in peritoneal fluid—but not serum—of EMs patients further implicates this axis in NK suppression (39), though its mechanistic role remains unclear (40). Peritoneal NK cells in EMs also exhibit increased expression of the inhibitory receptor NKG2A, which binds HLA-E (41). This interaction dampens degranulation and IFN-γ secretion, paralleling immune escape pathways seen in cancer and supporting lesion persistence (42). Aberrant upregulation of the inhibitory receptor NKG2A on peritoneal NK cells enhances binding to HLA-E on ectopic endometrial cells, amplifying inhibitory signaling and suppressing degranulation, IFN-γ secretion, and overall cytotoxic capacity (32). Adhesion molecule dysregulation further compromises NK function. Effective recognition and stable immunological synapse formation require leukocyte function antigen-1 (LFA-1) on NK cells engaging intercellular adhesion molecule-1 (ICAM-1) on target cells (43, 44). In EMs, ectopic endometrial cells secrete soluble ICAM-1 (sICAM-1), which binds LFA-1 and competitively blocks membrane ICAM-1 interactions, thereby preventing synapse stabilization (45). This disruption reduces perforin/granzyme release and degranulation, weakening cytotoxicity and enabling lesion immune escape. Consistently elevated sICAM-1 levels in peritoneal fluid, together with *in vitro* evidence of NK inhibition (46, 47), identify sICAM-1 as a critical mediator of NK cell dysfunction and lesion survival.

## 3.4 The role of cytokines in regulating NK cell cytotoxicity in EMs patients

Peritoneal fluid and ectopic endometrial tissue from patients with EMs are enriched in immunosuppressive cytokines, which may disrupt normal immune surveillance (5). Consistent with this milieu, peritoneal fluid, serum, and conditioned supernatants from cultured ectopic endometrium suppress NK-cell cytotoxicity (36, 48). Transforming TGF-β emerges as a central mediator: intraperitoneal TGF-β reduces NK-cell killing and downmodulates the activating receptor NKG2D (36), implicating this pathway in EMs pathogenesis. Additional interleukins further constrain NK function (49). IL-6 signals through JAK/STAT3 to repress transcription of perforin and granzyme B while skewing NK cells toward an anti-inflammatory state with diminished interferon-γ production (48). IL-10, a potent immunosuppressive cytokine, exerts potent immunosuppressive effects by engaging the STAT3/STAT5 signaling axis, while enhancing the expression of inhibitory checkpoints such as NKG2A and PD−1. Collectively, these effects shift NK cells from a cytotoxic to a functionally exhausted phenotype (5). Moreover, elevated IL-12 p40 subunit in the peritoneal fluid may antagonize the activity of the IL-12 heterodimer, thereby impairing NK activation (23). Similarly, IL-15 attenuates NK effector programs by lowering granzyme B and interferon-γ output and reducing expression of stimulatory receptors such as NKG2D and NKp44 (50). Collectively, these cytokine-driven signals establish an immunosuppressive peritoneal niche that dampens NK-cell cytotoxicity and fosters the persistence of ectopic lesions (Figure 1).

**FIGURE 1**
Functions of NK cells in endometriosis progression.
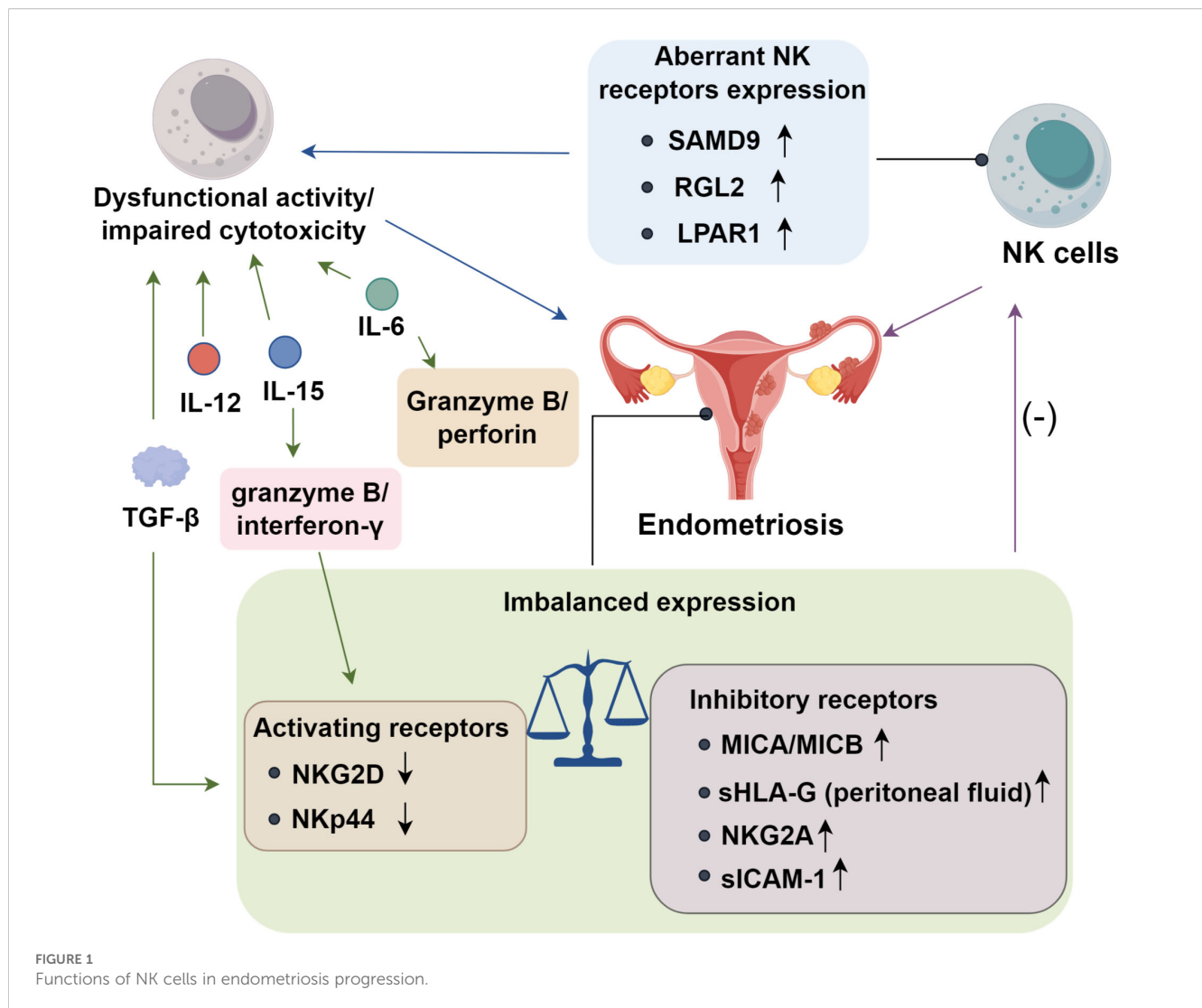
# 4 NK cell−based immunotherapy for EMs

## 4.1 Cytokine-based strategies

Ectopic endometrial cells in EMs exhibit hallmark features of apoptosis resistance, enhanced adhesion, and invasive capacity, often accompanied by localized angiogenesis during lesion initiation and progression (51). Due to phenotypic similarities with tumor cells, the decline in NK cell cytotoxicity in EMs may represent a form of immune escape, drawing parallels with cancer immune evasion. The modulation of NK cell activity in EMs involves intricate interactions between various activating and inhibitory receptors and their ligands. The downregulation of activating receptors and upregulation of inhibitory ones may be mediated by local immunosuppressive cytokines. Therefore, targeting these inhibitory factors represents a potential strategy to restore NK cell cytotoxicity.

IL-2 is a prototypical NK-stimulatory cytokine capable of reversing NK cell suppression. IL-2 stimulation leads to the generation of lymphokine-activated killer (LAK) cells, which exhibit high cytotoxicity against drug-resistant tumor cells, suggesting potential application in cancer immunotherapy (52). Notably, LAK cells have demonstrated cytotoxicity toward various target cells, including endometrial cells from EMs patients (53). In rat models of EMs, IL-2 administration enhances intrauterine immune activation and leads to failure of ectopic implantation (22). Cytokine combinations based on IL−15 and IL−2 have garnered attention. IL-15 sustains NK cell proliferation and survival without expanding regulatory T cells that are typically induced by IL-2 (54, 55). IL-21 synergizes with IL-15 to further augment NK cytotoxicity and cytokine secretion. Preclinical studies in various immune-mediated disorders indicate that such cytokine combinations can markedly enhance NK effector functions (56, 57), suggesting their potential translational value in EMs. These findings suggest that cytokine stimulation therapy may offer a viable avenue for immunotherapy in EMs.

## 4.2 Programmed death-1/programmed death ligand-1 pathway

The programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) checkpoint axis is a prominent focus in NK cell–based immunotherapy (58). PD-1 and PD-L1 expression have been detected in ectopic endometrial tissues (59, 60). In cancer immunotherapy, monoclonal antibodies targeting PD-1 and PD-L1 have yielded promising outcomes. However, such interventions may also trigger extensive adverse effects across multiple tissues and organs (61). Nonetheless, targeting the PD-1/PD-L1 axis remains a promising immunotherapeutic direction for EMs. Elevated expression of the inhibitory receptor NKG2A (which recognizes HLA-E molecules) has been observed in Ems (55). HLA-E is commonly expressed in various tumor types, and clinical trials have shown favorable responses to anti-NKG2A antibodies in certain cancers (62). Although the functional role of NKG2A in EMs remains to be fully elucidated, other checkpoint pathways, including those mediated by KIR2DL1 (binding HLA-C2) and LILRB1 (binding HLA-G), may also serve as potential immunotherapeutic targets. Importantly, the balance between activating and inhibitory signals is essential for optimal NK cell function. Excessive NK activation could risk collateral tissue damage, underscoring the necessity for cautious selection and precise application of NK-based immunotherapy for EMs.

## 4.3 Adoptive NK cell transfer and CAR–NK therapy

Adoptive transfer of NK cells seeks to reconstitute cytotoxic activity within the peritoneal cavity and can be executed with autologous, haploidentical, cord-blood, peripheral-blood, or induced pluripotent stem cell (iPSC)–derived NK products (63). Moreover, the development of chimeric antigen receptor NK cells (CAR-NK) allows for redirection of NK cells against specific targets (64). Recent CAR-NK designs frequently incorporate "armoring" with membrane-bound or secreted IL-15 to improve *in-vivo* persistence and metabolic fitness; genome editing to remove intracellular checkpoints such as CISH further augments IL-15 signaling and antitumor function (65). iPSC-derived NK platforms also introduce a high-affinity, non-cleavable CD16 (hnCD16) to sustain ADCC and enable combination with tumor-targeting antibodies (66). To enhance homing to diseased tissues, NK or CAR-NK cells can be retargeted with chemokine receptors (CXCR1/CXCR4), which improves trafficking in preclinical models (67–69). Collectively, these modifications address the historical challenges of NK persistence, trafficking, and serial killing in solid-tissue settings (70, 71).

The first-in-human, cord-blood–derived anti-CD19/IL-15 CAR-NK trial demonstrated rapid responses in 8/11 patients (73%) with minimal CRS/neurotoxicity and detectable persistence up to 12 months (72). An iPSC-derived CAR-NK product (FT596; includes CD19 CAR, IL-15 receptor fusion, and hnCD16) showed tolerability and objective responses in a Phase 1 study, supporting feasibility of standardized "off-the-shelf" CAR-NK therapy (73). Additional early-phase programs (NKG2D-ligand–targeted and CD19-targeted allogeneic CAR-NK) are progressing with preliminary activity and acceptable safety in Phase 1 settings (74). At present, clinical trial testing CAR-NK specifically for EMs is limited. However, studies highlight adoptive NK-based approaches under evaluation for severe EMs, and preclinical data support that exogenous NK cells can infiltrate peritoneal/ovarian lesions and may be delivered via routes including intraperitoneal administration (55, 75, 76). Key hurdles include identifying lesion-restricted antigens to avoid off-target cytotoxicity, improving trafficking and retention within ectopic implants (chemokine-receptor retargeting), and mitigating the immunosuppressive peritoneal milieu (TGF-β, IL-6, IL-10), potentially via IL-15 armoring or combination checkpoint blockade (77). Given the accumulating safety data and modular engineering options (78–80), CAR-NK strategies merit staged translation in EMs once lesion-specific targets and homing cues are defined.

## 5 Conclusion

In summary, NK cell dysfunction is a central immune defect in endometriosis, driven by microenvironmental immunosuppression and ectopic cell immune evasion through altered receptor-ligand interactions, adhesion molecule aberrations, and cytokine-mediated suppression, which collectively impair cytotoxic clearance of ectopic lesions. While emerging immunotherapies targeting NK cells—such as checkpoint blockade, cytokine stimulation, and adoptive cell therapy—hold translational potential, challenges remain in optimizing specificity and safety to avoid systemic autoimmunity.

However, several obstacles need to be addressed before NK cell–based immunotherapy can be widely applied in EMs. Antigenic heterogeneity of ectopic lesions complicates the identification of reliable NK cell targets; the limited trafficking and retention of NK cells within peritoneal and pelvic lesions may reduce therapeutic efficacy; and systemic activation of NK cells carries a risk of off-target cytotoxicity and tissue damage. These considerations highlight the importance of carefully designed, patient-tailored approaches and combination strategies. Future research must prioritize human studies, biomarker-driven patient stratification, and combinatorial approaches integrating NK-targeted agents with existing hormonal or surgical therapies to improve clinical outcomes for pain and infertility in EMs.

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## Conflict of interest

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