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Short Review

Immunity And Endometriosis: A Short Review.

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Abstract

Endometriosis is a prevalent disorder of the female reproductive system that frequently demonstrates malignant-like characteristics, including invasive growth and recurrence. Despite extensive investigation, the precise mechanisms underlying its pathogenesis remain incompletely elucidated. Accumulating evidence indicates that dysregulation of the immune system plays a central role in disease development and progression. Alterations in both the number and function of immune cell populations, such as macrophages, T and B lymphocytes, and natural killer (NK) cells, have been consistently documented. These findings have led to the hypothesis that immunotherapy may represent a promising novel strategy for the treatment of endometriosis.

Keywords : *Endometriosis; macrophages; immunity; NK cells; autoimmunity.*

INTRODUCTION

Endometriosis is a chronic medical condition in which tissue resembling the lining of the uterus grows outside the uterine cavity. These ectopic growths can occur on the ovaries, fallopian tubes, the outer surface of the uterus, the pelvic peritoneum, and in rare cases, in more distant organs. Beyond its well-known association with infertility, endometriosis is also linked to stress-related effects on sexual dysfunction.[1]

It is one of the leading causes of morbidity among premenopausal women. Despite decades of extensive research, the complex pathogenesis of this enigmatic disorder remains controversial. [2] The most widely accepted theory is that endometriosis develops as a result of retrograde menstruation and/or transplantation of shed endometrial fragments. When displaced endometrial cells implant on pelvic structures, they remain hormonally responsive and form the characteristic lesions of the disease. However, this explanation is incomplete: retrograde menstruation occurs in more than 90% of women, yet fewer than 10% develop endometriosis.[3]

Alternative theories have been proposed. The metastatic theory suggests that endometrial cells disseminate through lymphatic or vascular routes.[4] Another hypothesis, the stem cell theory, posits that progenitor or stem-like cells may contribute to lesion formation.[5] For a comprehensive overview of these and other proposed mechanisms, readers are referred to.[6] Increasing attention has been directed toward the immune system, even though endometriosis is generally regarded as a steroid-sensitive condition. Evidence shows multiple facets of immune dysfunction in affected women.[7] Endometriosis is not simply a gynecological disease but one in which immune dysregulation plays a central role. Normally, immune surveillance clears displaced endometrial cells. In endometriosis, however, this process is impaired, resulting in chronic inflammation, angiogenesis, and lesion survival.

MACROPHAGES

Macrophages are central immune effectors responsible for pathogen recognition, phagocytosis, and antigen presentation to T cells. Under physiological conditions, they also participate in regeneration of the endometrium,8 a process partly regulated by CD36 receptor expression and matrix metalloproteinase activation—both reduced in endometriosis.[9]

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The role of macrophages in endometriosis remains debated. Their numbers are consistently elevated in the peritoneal cavity, yet their functional activity appears suppressed.8 Reduced expression of CD3, CD36, and annexin A2 may underlie this impairment.[10] Activated macrophages release proinflammatory cytokines such as TNF-α, IL-6, IL-8, and IL-1β, promoting neutrophil recruitment, chronic inflammation, and lesion development.[11]

Lesional macrophages often display an M2-polarized phenotype,[12] associated with tissue remodeling and cancer progression.[13] Studies suggest a dynamic shift from M1 dominance in early disease to M2 predominance in later stages, indicating a role in disease progression.[14] These findings have prompted interest in macrophage-targeted therapies as a potential treatment strategy.[15]

LYMPHOCYTES

T lymphocytes represent another key immune population implicated in endometriosis. CD8+ T cells are the predominant T-cell subset in endometrial tissue, found as single intraepithelial cells, adjacent to glands, or clustered in lymphoid aggregates.[16] However, data on their activity and function remain inconsistent.[17] B lymphocytes have also been studied, though results are similarly inconclusive. While many studies report increased B-cell activation and autoantibody production, others describe unchanged or reduced B-cell counts.[18] The pathogenic significance of autoantibodies remains uncertain.

More recent research has examined regulatory lymphocyte subsets. Tregs and Bregs from women with endometriosis show altered numbers and enhanced secretion of IL-24, which may contribute to immunosuppression and ectopic tissue survival.[19] Elevated PD-1 and PD-L1 expression on circulating T and B cells has also been documented, potentially contributing to immune tolerance of endometriotic lesions.[20] Interestingly, activated Tregs appear reduced within endometriotic tissue but not in peripheral blood, suggesting a localized effect on inflammation and lesion growth.[21]

NK CELLS

NK cells normally play a critical role in immune surveillance by eliminating abnormal or misplaced cells. In endometriosis, their cytotoxic function is impaired, which may allow ectopic endometrial fragments to evade clearance and persist in the peritoneal cavity.[22]

Reduced NK cell activity has been consistently observed in patients with endometriosis and may serve as a potential diagnostic marker.[23] Mechanistically, the disease is associated with upregulation of NK inhibitory receptors (e.g., KIR2DL1, CD94/NKG2A, PD-1) and downregulation of activating receptors (e.g., NKp46, NKp30, NKG2D), leading to impaired cytotoxicity.

Beyond immune evasion, NK cells may influence stromal cell biology, local immune tolerance, and implantation processes, thereby contributing to infertility and pregnancy complications. For an in-depth review, see.[24]

CYTOKINES

Cytokine imbalance is another hallmark of endometriosis. Women with the disease exhibit elevated levels of proinflammatory and growth-related cytokines such as GM-CSF, IL-1, IL-6, IL-8, IL-10, TNF-α, IGF-1, and TGF-β.[25] These mediators promote adhesion, invasion, angiogenesis, and survival of ectopic lesions.

Despite clear associations, causality remains uncertain. For instance, elevated IL-1 production has been reported,[26] but results vary across studies. Large-scale profiling has revealed distinct cytokine expression signatures, but their mechanistic roles are poorly defined.[27], [28] At present, cytokines may be more promising as diagnostic biomarkers than as established pathogenic drivers.[29] Therapeutic strategies targeting cytokines—such as TNF inhibitors, IL-6 blockers, and chemokine antagonists—are under investigation but show variable outcomes.[30]

AUTOIMMUNITY

Endometriosis shares certain features with autoimmune disorders, including chronic inflammation, autoantibody production, and altered lymphocyte populations.[31], [32] However, available evidence does not support its classification as a true autoimmune disease. Elevated autoantibodies typically target endometrial antigens, suggesting they are a consequence rather than a cause of disease. While epidemiological links with autoimmune and allergic diseases have been suggested, they remain unconfirmed.[33] Nonetheless, immunomodulatory strategies used in autoimmunity have been proposed as potential therapeutic approaches.[34]

CONCLUSIONS

Endometriosis is increasingly viewed as a disorder of immune dysregulation. Substantial evidence indicates widespread alterations in the activity of immune cells—including macrophages, lymphocytes, NK cells—as well as in cytokine networks. However, it remains unclear whether these immune changes are causal factors or consequences of the disease.

While immunotherapy offers a promising avenue, its clinical application remains limited. Current immunomodulators have shown only modest effects.[30] Given the unsatisfactory outcomes of conventional treatments, future therapies may

combine classical hormonal approaches with novel strategies, including selective progesterone receptor modulators, aromatase inhibitors, anti-angiogenic agents, GnRH antagonists, and even gene-based interventions.[35] Continued investigation into the immunological mechanisms underlying endometriosis will be essential for developing more effective, targeted therapies.

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