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Mini Review

Role of the Immune System on Normal Endometrial Development

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Abstract

The immune system profoundly shapes endometrial development, thickness, and receptivity through intricate interplay between immune cells, cytokines, and hormonal signals, which are vital for implantation and pregnancy.

Key immune cell populations-including uterine natural killer (uNK) cells, regulatory T cells, macrophages, and dendritic cells-undergo cyclic fluctuations tied to estrogen and progesterone levels, mediating vascular remodelling, immunological tolerance, and tissue repair essential for embryo acceptance.

Cytokines such as IL-6, IL-10, TGF-β, and TNF-α govern the critical balance between pro- and anti-inflammatory states, while growth factors like VEGF direct endometrial angiogenesis.

Hormonal regulation further modulates local immunity: estrogen and progesterone drive immune cell recruitment, polarisation, and cytokine production through both direct and indirect signalling.

Immune dysregulation, seen in thin endometrium or repeated implantation failure, typically manifests as an aberrant inflammatory milieu, compromised vascularisation, and disruption in complement system activity-culminating in impaired receptivity and reduced IVF success rates. Recent advances in immune profiling offer personalised diagnostic and therapeutic approaches, including targeted immunomodulation, cytokine, or complement therapies to restore a balanced, receptive endometrial environment and improve reproductive outcomes.

Keywords: *Immune System; Endometrial Development; IVF; Cytokine; Uterine Natural Killer (uNK) Cells*

The immune system plays a fundamental role in endometrial development, thickness, and receptivity through complex interactions between immune cells, cytokines, and hormonal signals. This relationship is critical for successful implantation and pregnancy outcomes, and dysregulation of these immune mechanisms significantly contributes to thin endometrium and IVF failure.

Key immune cells in endometrial development

Uterine natural killer (uNK) cells

Uterine natural killer cells represent the most abundant immune cell population in the endometrium, comprising approximately 70% of maternal lymphocytes during early pregnancy [1]. These cells are distinct from peripheral NK cells and are classified as endometrial NK (eNK) cells in non-pregnant women and decidual NK (dNK) cells during pregnancy [2]. uNK cells undergo cyclical changes throughout

the menstrual cycle, with numbers increasing substantially during the mid-secretory phase and reaching peak levels in the late secretory phase [3].

The recruitment of uNK cells is closely tied to hormonal changes, particularly progesterone. While uNK cells do not express progesterone receptors directly, progesterone-mediated responses are facilitated through cytokines and growth factors produced by other endometrial cells. IL-15 production by stromal cells in secretory phase endometrium is stimulated by progesterone, serving as a selective chemoattractant for peripheral blood $CD16^-$ NK cells [3]. These cells are essential for endometrial vascular remodeling, decidualisation, and creating optimal conditions for embryo implantation [2].

T helper cell subsets and regulatory T cells

The balance between different T helper cell subsets is crucial for endometrial development and receptivity. Regulatory T cells (Tregs) play a particularly important role in creating an immunologically tolerant environment necessary for successful pregnancy [4]. During the proliferative phase of each cycle, estrogen drives an increase in uterine Treg recruitment that peaks at ovulation [4]. These cells are essential for controlling inflammation, supporting maternal vascular adaptations, and facilitating trophoblast invasion [4].

Studies have shown that approximately 10 - 30% of CD4+ T cells in the decidua express the Treg transcription factor FOXP3, representing substantial enrichment compared to peripheral blood [4]. The balance between Th1 and Th2 responses is also critical, with a shift toward Th2-dominant immunity during the window of implantation creating favorable conditions for embryo acceptance [5].

Macrophages and dendritic cells

Macrophages constitute 1 - 2% of endometrial cells during the proliferative phase and increase to 3 - 5% during the secretory phase, reaching a peak of 6 - 15% during menstruation [6]. These cells play essential roles in tissue remodeling, angiogenesis, and immune regulation. During the secretory phase, macrophages congregate around endometrial glands and accumulate in perivascular regions, positioning them to respond rapidly to tissue changes [6].

The polarisation of macrophages between M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes significantly impacts endometrial function. M2 macrophages predominate in normal endometrium, creating an anti-inflammatory environment that supports embryo implantation [7]. However, alterations in this balance can contribute to endometrial dysfunction and implantation failure.

Dendritic cells (DCs) serve as crucial antigen-presenting cells that undergo coordinated cyclical changes during the menstrual cycle [8]. Immature DCs (CD1a+) are more abundant than mature DCs (CD83+) throughout the cycle, with both populations showing specific temporal patterns that may be important for local regulatory mechanisms relevant to implantation [8].

Cytokines and growth factors in endometrial development

Pro-inflammatory and anti-inflammatory balance

The endometrium maintains a delicate balance between pro-inflammatory and anti-inflammatory cytokines that is essential for proper development and receptivity. Key cytokines involved include:

- **Interleukin-6 (IL-6):** Promotes endometrial growth and vascular development but can become pathological when persistently elevated [9]. IL-6 is produced predominantly by activated macrophages and plays a pleiotropic role in endometrial physiology [9].
- **Interleukin-10 (IL-10):** Serves as a crucial anti-inflammatory cytokine that helps maintain immune homeostasis. Higher levels of IL-10 have been observed in the peritoneal fluid of women with endometriosis, and it has been associated with reduced NK cell cytotoxicity [9].

- **Transforming growth factor-β (TGF-β):** Exhibits both pro-fibrotic and anti-inflammatory properties. TGF-β1 has anti-inflammatory functions and contributes to regulatory T cell differentiation, while also being involved in angiogenesis and tissue remodeling [9].
- **Tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β)** are key pro-inflammatory cytokines that, when properly regulated, contribute to the inflammatory processes necessary for implantation but can be detrimental when persistently elevated [10].

Growth factors and vascular development

Vascular endothelial growth factor (VEGF) is crucial for endometrial angiogenesis and vascular development [11]. Poor vascular development due to decreased VEGF expression in glandular epithelium creates a cycle where high uterine blood flow impedance leads to impaired endometrial growth [12]. This mechanism is particularly relevant in thin endometrium, where inadequate vascularization contributes to poor endometrial development.

Hormonal regulation of endometrial immune function

Estrogen and immune modulation

Estrogen significantly influences endometrial immune function through its effects on various immune cell populations. Estrogen receptors (ERα and ERβ) are expressed on multiple immune cells, including B cells, T cells, NK cells, and dendritic cells [13]. During the proliferative phase, estrogen promotes endometrial proliferation and selectively recruits specific immune cell populations [13].

Estrogen affects antimicrobial peptide production by endometrial epithelial cells, stimulating the expression of secretory leukocyte protease inhibitor (SLPI) and human β-defensin 2 (HBD2) [14]. These antimicrobials are crucial for maintaining endometrial defence against pathogens while allowing for the immunological tolerance necessary for implantation.

Progesterone and immune suppression

Progesterone provides crucial immunosuppression during the preimplantation phase, creating a conducive environment for embryo implantation [13]. Progesterone influences immune cell function through indirect mechanisms, as many immune cells do not express progesterone receptors directly. Instead, progesterone acts through stromal cells and other endometrial cells that express progesterone receptors to produce cytokines and growth factors that modulate immune function [3].

Progesterone stimulates the production of IL-15 by endometrial stromal cells, which in turn affects NK cell recruitment and function [3]. It also promotes the expression of TGF-β by endometrial epithelial cells, contributing to immune suppression and tissue remodeling [15].

Immune dysfunction in thin endometrium

Inflammatory pathways in endometrial thinning

Thin endometrium is associated with aberrant inflammatory activation that impairs endometrial receptivity and development [12]. Studies have shown significantly elevated levels of pro-inflammatory markers (IL-6, IL-1β, HIF-1α, and COX-2) and reduced anti-inflammatory factors (IL-10, IGF-1) in women with thin endometrium [12]. This chronic inflammatory state disrupts the delicate balance needed for successful endometrial development and embryo implantation.

The inflammatory environment in thin endometrium is characterised by:

- Increased expression of pro-inflammatory cytokines.
- Reduced anti-inflammatory mediator production.

- Altered immune cell populations and function.
- Disrupted vascular development and angiogenesis.

Complement system dysregulation

The complement system, a major component of innate immunity, plays an important role in endometrial development and is dysregulated in various endometrial pathologies [16]. Complement component C3 is expressed in endometrial tissue and shows cyclical variation throughout the menstrual cycle [16]. Aberrant complement activation can lead to chronic inflammation and tissue damage, contributing to endometrial dysfunction.

In pathological conditions, complement dysregulation can result in:

- Excessive inflammatory activation.
- Impaired tissue repair and regeneration.
- Altered vascular development.
- Compromised immune tolerance.

Clinical implications and therapeutic approaches

Immune profiling for endometrial assessment

Recent advances in endometrial immune profiling have shown promise for improving IVF outcomes through personalised interventions [5]. Endometrial immune profiles can be classified into different types based on the expression of immune markers:

1. **Balanced immune activation**: Characterised by normal ratios of immune markers and optimal conditions for implantation.
2. **Under-activated profile**: Low immune activation that may not support adequate implantation.
3. **Over-activated profile**: Excessive immune activation that may be hostile to embryo implantation.
4. **Mixed profile**: Dysregulated immune responses with both under- and over-activation features.

Therapeutic interventions

Understanding the immune basis of endometrial dysfunction opens new avenues for therapeutic interventions:

- **Anti-inflammatory treatments:** May help restore the balance between pro- and anti-inflammatory factors in thin endometrium. Corticosteroids and other immunomodulatory agents have shown promise in selected cases [5].
- **Cytokine therapy:** Targeting specific immune pathways may help correct dysregulated immune responses. Growth factors like G-CSF (granulocyte colony-stimulating factor) have been used to improve endometrial thickness and immune function [12].
- **Complement inhibition:** Represents a potential therapeutic approach given the role of complement dysregulation in endometrial pathology [16]. Several complement inhibitors are under development for various conditions and may have applications in reproductive medicine.

The immune system's role in endometrial development represents a complex interplay between hormonal signals, immune cells, and inflammatory mediators. Understanding these mechanisms is crucial for developing targeted therapies to improve endometrial receptivity and IVF outcomes, particularly in women with thin endometrium who face significantly higher failure rates. Future research should focus on identifying specific immune targets and developing personalised immunomodulatory approaches to enhance endometrial function and reproductive success.

Conclusion

The immune system's role in endometrial development represents a paradigm shift in our understanding of reproductive success, moving from a purely anatomical and hormonal perspective to a comprehensive immunological framework that fundamentally shapes implantation outcomes. This complex orchestration of immune cells, cytokines, and hormonal signals creates the foundation for successful embryo acceptance or rejection, with profound implications for IVF success rates and reproductive health.

The evidence presented demonstrates that immune dysregulation affects approximately 83.5% of infertile patients, with characteristic patterns of under-activation, over-activation, and mixed immune profiles each requiring targeted therapeutic approaches. The revolutionary concept of endometrial immune profiling has transformed reproductive medicine by enabling personalised treatment strategies that address the root immunological causes of implantation failure, rather than relying on empirical approaches.

Clinical trials have validated the transformative potential of immune-guided therapies, with live birth rates improving from approximately 30% to over 40% when personalised immunomodulatory treatments are applied based on individual immune profiles. The identification of key predictive biomarkers-including uNK cells, cytokine ratios (IL-15/Fn-14, IL-18/TWEAK), HLA-G expression, and inflammatory markers like BCL6-has established a robust foundation for precision reproductive medicine that achieves predictive accuracies exceeding 80%.

Ultimately, the immune system's central role in endometrial development has unveiled new therapeutic horizons that promise to revolutionise reproductive medicine. As we advance toward truly personalised fertility care, the integration of immune profiling into routine clinical practice will likely become the standard of care, offering hope to millions of individuals facing the challenges of infertility and recurrent pregnancy loss. The future of reproductive medicine lies not just in optimising embryo quality or endometrial thickness, but in orchestrating the precise immunological symphony that enables the miracle of human reproduction.

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