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IMMUNE AND INFLAMMATORY MECHANISMS IN THE PATHOGENESIS OF POLYCYSTIC OVARY SYNDROME (PCOS): CURRENT EVIDENCE AND THERAPEUTIC PERSPECTIVES

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Abstract: Polycystic Ovary Syndrome (PCOS) is a complex endocrine and metabolic disorder affecting up to 15% of reproductive-aged women. Classical mechanisms such as hyperandrogenism and insulin resistance do not fully explain its heterogeneity. Recent research increasingly highlights immune dysregulation and chronic low-grade inflammation (LGCI) as central contributors to PCOS development. This review synthesizes recent findings (2022–2025) focusing on inflammatory cytokines, immune cell infiltration, ovarian microenvironment changes, and activation of molecular pathways including the NLRP3 inflammasome. We discuss how these immunometabolic changes interact with reproductive and endocrine dysfunction, and explore therapeutic strategies targeting inflammation. Future directions and research gaps are also addressed.

Keywords: Polycystic ovary syndrome; inflammation; immune response; NLRP3 inflammasome; granulosa cells; metabolic dysfunction.

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders worldwide. While the traditional understanding of PCOS centers on hyperandrogenism, ovarian dysfunction, and metabolic disturbances, recent evidence suggests a significant contribution of immune dysregulation and chronic low-grade inflammation. Increasing data from transcriptomics, molecular biology, and clinical biomarkers indicate that PCOS may be understood as an immunometabolic disorder.

This review synthesizes updated evidence from 2022–2025 examining immune cell alterations, inflammatory mediators, ovarian microenvironment changes, molecular signaling pathways, and therapeutic implications. Low-Grade Chronic Inflammation in PCOS. PCOS is consistently associated with systemic LGCI, reflected by elevated inflammatory markers even in non-obese phenotypes.

Studies show increased levels of:

C-reactive protein (CRP),Interleukin-6 (IL-6),Tumor necrosis factor-alpha (TNF-α),Interleukin-18 (IL-18).These cytokines correlate with insulin resistance, central adiposity, and androgen excess. Some authors propose that LGCI represents the "common soil" linking metabolic, endocrine, and reproductive abnormalities. Recent analyses indicate that inflammation impairs follicular development by altering granulosa cell responsiveness, increasing oxidative stress, and inducing subclinical damage to reproductive tissues.

Immune Cell Infiltration and Ovarian Microenvironment Changes.Transcriptomic and immunohistochemical studies from 2023–2025 demonstrate that PCOS is associated with local immune activation at the ovarian level.

Key findings: Increased infiltration of macrophages (especially pro-inflammatory M1 subtype),Altered regulatory T-cell (Treg) activity. Decreased NK-cell regulatory balance,Upregulation of granulosa-cell inflammatory genes (SPI1, HSPB1, MNDA, ITGAX)

These changes impair folliculogenesis and oocyte quality even in lean PCOS phenotypes, suggesting that immune pathways, rather than adiposity, might be the primary cause of ovarian dysfunction in some patients.

Molecular Mechanisms: Focus on the NLRP3 Inflammasome.One of the major breakthroughs of the last few years is recognition of the NLRP3 inflammasome as a key pathogenic mediator in PCOS.

NLRP3 activation leads to: ↑ IL-1β and IL-18 secretion,↑ caspase-1 activation, ↑ oxidative stress,↓ insulin sensitivity

Disrupted ovarian steroidogenesis: Granulosa cell apoptosis

NLRP3 was shown to be significantly upregulated in granulosa cells of women with PCOS, both in vivo and in vitro. Obesity exacerbates inflammasome activation by downregulating AMPK signaling, creating a vicious immunometabolic cycle. Androgen–Immune–Metabolic Interactions.Hyperandrogenism interacts with immune pathways in a bidirectional manner.

Androgens may: Increase inflammatory cytokine expression, alter immune cell subsets,promote oxidative stress and disrupt ovarian microcirculation. Meanwhile, immune dysregulation worsens androgen excess by modifying steroidogenic enzyme expression. These processes synergize with metabolic imbalance (e.g., insulin resistance), creating a self-reinforcing pathogenic loop.

Therapeutic Approaches Targeting Immune Pathways:

Anti-inflammatory pharmacologic strategies

Emerging interventions include: NLRP3 inflammasome inhibitors (experimental), IL-1β/IL-6 pathway modulators, AMPK-activating compounds, Omega-3 fatty acids , Vitamin D supplementation

Lifestyle and nutritional interventions : Dietary patterns with anti-inflammatory properties (Mediterranean diet, high-fiber diets) have shown reductions in CRP and improved metabolic parameters.

Precision medicine approaches:Transcriptomic and immunophenotyping technologies may enable stratification of PCOS patients by immune profile, potentially guiding targeted therapy.

Key inflammatory biomarkers associated with PCOS, biomarker Role in PCOS Clinical relevance CRP Marker of LGCI associated with metabolic risk and IL-6 Promotes insulin resistance Identified in lean and obese PCOS TNF-α impairs insulin signaling this correlates with hyperandrogenism. IL-18 NLRP3-dependent cytokine linked with ovarian dysfunction. Caspase-1 Inflammasome effector enzyme Increased in granulosa cells MCP-1Chemokine for monocyte recruitment Suggests ovarian immune infiltration.

Limitations and Knowledge Gaps:Heterogeneity of PCOS phenotypes makes it difficult to build a unified immune model. Most data are cross-sectional, limiting causal interpretation. Clinical trials of anti-inflammatory agents in PCOS are scarce. Non-obese and adolescent PCOS populations remain understudied. Future research should prioritize longitudinal designs and molecular phenotypin

Conclusion

PCOS is increasingly recognized as an immunometabolic disorder characterized by chronic low-grade inflammation, immune cell dysregulation, and activation of molecular pathways such as the NLRP3 inflammasome. These processes contribute to insulin resistance, hyperandrogenism, and ovarian dysfunction.Targeting immune pathways holds promise for future disease-modifying therapies, especially in the context of precision medicine approaches.

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