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Review

Endometrial Organoids in PCOS: A Translational Tool for Gynecologic Precision Medicine

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Abstract

Background: Polycystic ovary syndrome (PCOS) is among the most common endocrine disorders affecting women of reproductive age and is closely linked to endometrial dysfunction and fertility challenges. Gaining a clearer understanding of these changes is essential for improving clinical care and outcomes. Objective: This mini-review highlights recent developments in using endometrium-derived epithelial organoids to model PCOS-related conditions, with a focus on their translational and clinical significance. **Methods:** A focused review of recent literature was conducted on PCOS-specific endometrial organoids and their application in disease modeling, drug testing, and tissue engineering. Emphasis was placed on studies highlighting molecular characterization and regenerative strategies. Results: Organoids derived from PCOS endometrium have shed light on hormonal imbalances, gene expression shifts, and cellular dysfunctions linked to the condition. These 3D models effectively mimic endometrial pathology and are being used to explore potential treatments. Additionally, efforts to integrate organoids with biomaterials are paving the way for regenerative solutions. Conclusion: Endometrial organoids represent a powerful and clinically meaningful platform for studying PCOS-related endometrial changes. Their growing role in personalized and regenerative medicine holds significant promise for tackling infertility and other reproductive health issues in PCOS.

Keywords: PCOS; endometrial organoids; tissue engineering; epithelial organoids; endometrial dysfunction

Introduction

One of the most common endocrine conditions affecting women of reproductive age is polycystic ovary syndrome (PCOS), which is characterized by polycystic ovarian morphology, hyperandrogenism, and ovulatory failure (1). Because of progesterone resistance and prolonged estrogen exposure, the endometrium in PCOS women has unique pathological characteristics, such as impaired decidualization, altered receptivity patterns, and increased proliferative activity. Traditional two-dimensional cell culture models have proven inadequate for studying the complex cellular interactions and hormonal responses characteristic of PCOS endometrium (2-4).

A paradigm change in reproductive biology research has been made possible by the emergence of three-dimensional organoid technology, which has made it possible to create physiologically accurate models that recapitulate tissue architecture and function (5-6). Endometrial epithelial organoids created from PCOS patients provide special chances to investigate disease-specific processes while preserving the pathogenic characteristics of the original tissue (7). These models show great promise for diagnosing endometrial malfunction, identifying therapeutic approaches, and creating individualized treatment plans.

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PCOS Endometrial Pathophysiology and Organoid Development

Cellular and Molecular Alterations in PCOS Endometrium

Comprehensive cellular atlases of the PCOS endometrium have been found by single-cell RNA sequencing studies (3, 8), which show notable changes in the composition of cells and patterns of gene expression. Compared to healthy controls, PCOS women's proliferative phase endometrium has lower populations of stromal cells and higher proportions of epithelial cells. Cell-type-specific disease signatures that impact metabolic processes, hormone responsiveness, and inflammatory pathways accompany these compositional changes (8,9).

Through androgen receptor-mediated signaling, hyperandrogenism, a defining feature of PCOS, directly affects the cellular activity of the endometrium (10, 11). Overproduction of androgens can raise the risk of endometrial cancer in PCOS patients by promoting cellular proliferation and dysregulating gene expression patterns. Organoid systems obtained from patients can be used to adequately replicate the distinct endometrial microenvironment created by prolonged exposure to increased androgen levels (12).

Establishment of PCOS Endometrial Organoids

The successful establishment of PCOS-derived endometrial epithelial organoids marks a significant technological breakthrough in the study of reproductive biology (7). Enzymatic dissociation techniques are used to generate these organoids from endometrial biopsies taken during the proliferative phase of the menstrual cycle, which are then cultured in three dimensions in extracellular matrix scaffolds (6, 7, 13). The organoids exhibit hormone response comparable to original tissue and preserve the integrity of the proliferative basolateral epithelial membrane (15).

When compared to control organoids, PCOS organoids show unique traits such as differential gene expression patterns linked to inflammation and receptivity and changed responses to sex hormone exposure (7). Importantly, these models maintain disease-specific traits even after several passes, which makes them useful tools for therapeutic screening applications and longitudinal studies.

Tissue Engineering Applications and Therapeutic Potential

Bioengineering Approaches for Endometrial Repair

New treatment options for endometrial dysfunction have been made possible by the combination of tissue engineering techniques with organoid technology. In order to create complex three-dimensional structures that more closely resemble natural tissue architecture, vascularized endometrial organoids were created by co-culturing epithelial organoids with endometrial stromal cells and human umbilical vein endothelial cells (16, 17). These engineered structures show improved therapeutic potential for endometrial regeneration and repair.

By making it possible to precisely control hormone gradients and cellular microenvironments, organ-on-chip technologies and microfluidic devices have significantly advanced the field (18-20). These platforms enable drug response studies under physiologically appropriate settings and dynamic simulation of menstrual cycle stages. The pathophysiology of PCOS has been better understood because to research on the bidirectional endocrine crosstalk between the ovary and endometrium made possible by the development of dual reproductive organ-on-chip systems (18-20).

Drug Screening and Personalized Medicine

Patient-derived PCOS organoids serve effective tools for drugs screening and the creation of tailored treatment strategies. These models have been used to assess how metformin therapy affects the endometrium of PCOS, showing decreased expression of androgen receptors and restoration of normal

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gene expression patterns (11). Rapid evaluation of medicinal substances and the discovery of new therapy targets are made possible by high-throughput screening techniques employing organoid models. Studying treatment responses in a variety of patient groups is made possible by the capacity to create organoid biobanks from PCOS patients (3, 7, 11). After thawing, cryopreserved organoids retain their characteristics (21). This method makes it easier to create precision medicine plans that are specific to each patient's characteristics and disease manifestations. The following table provides a comparative overview of various PCOS endometrial organoid models, outlining their culture systems, distinguishing features, and specific applications in drug screening and personalized medicine, along with their respective advantages and limitations.

Table 1. Comparison of PCOS Endometrial Organoid Models and Applications (3, 7, 12, 17, 18-20).

Model Type	**Culture System**	**Key Features**	**Applications**	**Advantages**	**Limitations**
Scaffold-free organoids	Matrigel-embedded	Epithelial-stromal organization, hormone responsiveness	Androgen response studies, cancer risk assessment	Physiological architecture, long-term culture	Limited vascularization
Epithelial organoids	3D Matrigel culture	Pure epithelial population, disease-specific signatures	Hormone response screening, biomarker discovery	Disease trait retention, high reproducibility	Lacks stromal interactions
Vascularized organoids	Co-culture system	Epithelial-stromal-endothelial integration	Therapeutic screening, regenerative applications	Enhanced physiological relevance	Technical complexity
Microfluidic models	Organ-on-chip platform	Dynamic hormone exposure, controlled gradients	Cycle modeling, drug testing	Precise control, real-time monitoring	Limited throughput

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Assembloid systems	Multi-cellular co-culture	Epithelial-stromal interactions, implantation modeling	Fertility research, therapeutic development	Comprehensive cellular interactions	Variable reproducibility

Challenges and Future Directions

Technical and Methodological Considerations

Despite significant advances, several challenges remain in PCOS organoid research and clinical translation . Standardization of culture protocols, matrix compositions, and assessment methods is critical for ensuring reproducibility across laboratories (7, 22). The replacement of animal-derived matrices with synthetic alternatives represents an important step toward clinical applications. Therapeutic screening applications have trouble with organoid heterogeneity and batch-to-batch variability (23). For therapeutic screening applications, organoid heterogeneity and batch-to-batch variability present challenges. To create robust quality standards, advanced quality control techniques are required, such as multi-omics characterisation and standardized functional assays. For clinical applications, automating organoid culture procedures may aid increase scalability and decrease variability (7, 12, 24).

Clinical Translation and Regulatory Considerations

Integration of organoid data with clinical parameters, biomarker profiles, and treatment responses will be essential for establishing the clinical relevance of these models (25). Regulatory frameworks for organoid-based drug screening and personalized medicine approaches are still evolving and require continued development. Future directions involve establishing multi-center collaborative networks for organoid research, integrating artificial intelligence for pattern recognition and drug discovery, and creating more sophisticated co-culture systems with immune cells (25). Studying causal links and creating focused therapeutic treatments are made possible by the combination of gene editing techniques with organoid technology.

Conclusions

An innovative technique for understanding endometrial dysfunction and creating individualized treatment plans is PCOS endometrium-derived epithelial organoids. These models offer platforms for examining hormone responses, inflammatory processes, and therapeutic treatments in addition to successfully capturing disease-specific molecular fingerprints. Regenerative medicine and sophisticated drug screening platforms are among the many potential uses for organoid technology that have been made possible by its integration with tissue engineering techniques. The ongoing development of PCOS organoid models has great potential for advancing our knowledge of endometrial pathophysiology and creating more effective treatments for affected women, even though standardization and clinical translation still present difficulties. The development of cooperative research networks and organoid biobanks will accelerate the shift to personalized medicine strategies for PCOS treatment. To take full advantage of the therapeutic potential of this technology, future research should concentrate on increasing model complexity, refining standardization processes, and confirming clinical applications.

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