Universe Scientific Publishing

Study on Mesenchymal Stem Cell Therapy for Female Premature Ovarian Failure

Xiong Gao[1,7]*, Li Peng[2,7], Ruoling Mo[3,7], Miaowei Wang[4,7], Xing Jin[5,6,7]

1.Hunan Central South stem cell Hospital, Changsha, Hunan 410000, China
2.The Second Xiangya Hospital of Central South University, Changsha, Hunan 410000, China
3.Hainan Vocational University of Science and Technology, Haikou, Hainan 570000, China
4.Department of Rehabilitation Medicine, West China Hospital, Chengdu, Sichuan 610041, China
5.Northern Jiangsu People's Hospital, Yangzhou, Jiangsu 225000, China
6.Yangzhou Second People's Hospital, Yangzhou, Jiangsu 225001, China
7.Sehan University, Yeongam-gun, Jeollanam-do 58447, Republic of Korea

Abstract: Premature Ovarian Failure (POF) refers to ovarian dysfunction occurring in women before the age of 40, characterized by amenorrhea, infertility, and hypoestrogenic symptoms, which severely impairs patients' reproductive health and quality of life. Traditional treatments such as Hormone Replacement Therapy (HRT) can only alleviate symptoms but cannot reverse ovarian function decline. Mesenchymal Stem Cells (MSCs) have emerged as a research hotspot in regenerative therapy for POF due to their multipotent differentiation potential, immunomodulatory properties, and paracrine characteristics. This article systematically reviews the biological characteristics of MSCs derived from bone marrow, umbilical cord, adipose tissue, and menstrual blood, and deeply explores their core mechanisms in repairing ovarian function, including inhibiting cell apoptosis, regulating the immune microenvironment, promoting angiogenesis, and exerting paracrine effects. It further analyzes the efficacy differences of various transplantation routes in clinical applications and existing challenges, and prospects breakthrough directions in technologies such as biomaterial-combined transplantation and gene editing. This review provides a theoretical reference for basic research and clinical translation of MSCs-based therapy for POF.

Keywords: Mesenchymal Stem Cells; Premature Ovarian Failure; Clinical Translation; Paracrine Effects

1 Introduction

The global incidence of Premature Ovarian Failure (POF) has shown an increasing trend annually, accounting for 1%-3% of reproductive-aged women. In China, the prevalence of POF among reproductive-aged women is approximately 1.6%, with patients exhibiting a younger age distribution. The pathological essence of POF lies in the premature depletion or dysfunction of the ovarian follicle pool, leading to elevated follicle-stimulating hormone (FSH) levels (>40 IU/L) and decreased estradiol (E2) levels (<25 pg/mL). Patients often present with infertility, osteoporosis, and an increased risk of cardiovascular diseases. Etiological studies have indicated that genetic factors (e.g., FOXL2 gene mutations), autoimmune diseases (e.g., thyroiditis), iatrogenic injuries (e.g., chemotherapeutic drug cyclophosphamide), and environmental toxin exposure are major contributing factors. Although Hormone Replacement Therapy (HRT) can alleviate hypoestrogenic symptoms, long-term use may increase the risk of breast cancer and fails to reverse ovarian reserve function.

As a key subset of adult stem cells, Mesenchymal Stem Cells (MSCs) possess three core properties: self-renewal, multipotent differentiation, and immunomodulation. Since the first report in 2008 on MSCs transplantation repairing ovarian function in chemotherapy-induced POF model rats, domestic and international researchers have conducted extensive studies on cell source optimization, mechanism elucidation, and clinical translation. In recent years, with advances in single-cell sequencing, exosome omics, and other technologies, the paracrine regulatory networks and targeted homing mechanisms of MSCs have been increasingly clarified, laying a theoretical foundation for their clinical application. This article systematically elaborates on the research progress of MSCs in treating POF by integrating the latest basic research and clinical data, aiming to provide a reference for translational medicine research in this field.

2 Comparison of Sources and Biological Characteristics of Mesenchymal Stem Cells

Mesenchymal Stem Cells (MSCs) derived from different tissues exhibit significant differences in biological characteristics, which di-

rectly affect their clinical application potential.

2.1 Bone Marrow Mesenchymal Stem Cells (BMSCs)

Bone marrow mesenchymal stem cells were the first stem cell type applied in POF treatment, with strong homing ability that enables 定向 migration to damaged ovarian tissues via the SDF-1α/CXCR4 axis. However, BMSCs require acquisition through bone marrow aspiration, which is highly invasive. Additionally, their proliferative activity decreases with age: the cell proliferation rate of donors over 50 years old is 40% lower than that of younger donors. Furthermore, BMSCs have limited in vitro expansion capacity, and cell viability decreases significantly after 10 serial passages, restricting their large-scale clinical application.

2.2 Umbilical Cord Mesenchymal Stem Cells (UCMSCs)

Umbilical cord mesenchymal stem cells are derived from Wharton's jelly of neonatal umbilical cords, offering advantages of non-invasive collection and minimal ethical controversy. They exhibit excellent in vitro proliferative capacity with a population doubling time of only 28±3 hours. Moreover, UCMSCs lowly express MHC-II molecules, resulting in low immunogenicity, making them suitable for allogeneic transplantation. These cells show high expression levels of stem cell markers, with CD44 and CD90 positive rates exceeding 95%, while the hematopoietic stem cell marker CD34 has a positive rate below 2%, ensuring cell purity. Preclinical studies have demonstrated that exosomes secreted by UCMSCs can regulate the VEGF signaling pathway via miR-126-3p, significantly promoting ovarian angiogenesis.

2.3 Adipose-Derived Mesenchymal Stem Cells (ADSCs)

Adipose-derived mesenchymal stem cells can be obtained via liposuction, yielding high cell quantities (1×10^6 cells can be isolated from 100 mL of adipose tissue). ADSCs possess strong anti-inflammatory and anti-fibrotic capabilities, and can inhibit ovarian stromal fibrosis and improve the follicular microenvironment by secreting factors such as TGF-β and IL-10. Compared to BMSCs, ADSCs have more stable in vitro differentiation potential, with adipogenic and osteogenic induction efficiencies increasing by 20% and 15%, respectively, and retain stem cell characteristics after multiple passages.

2.4 Menstrual Blood Mesenchymal Stem Cells (MenSCs)

Menstrual blood mesenchymal stem cells, a newly discovered stem cell source, are obtained through non-invasive methods. They highly express CXCR4 receptors, exhibiting excellent targeted homing ability, with CXCR4+ cell proportion reaching 35%±5%. Animal experiments have confirmed that MenSCs can specifically migrate to endometrial and ovarian tissues after transplantation, promoting functional repair of the uterus-ovary axis. Furthermore, MenSCs show high expression levels of estrogen receptor (ER) and progesterone receptor (PR), enhancing their adaptability to the ovarian microenvironment, with an in vivo survival time exceeding 14 days.

3 Mechanisms of Mesenchymal Stem Cells in the Treatment of Premature Ovarian Failure

The repair of ovarian function by MSCs is the result of multi-pathway synergistic effects, with core mechanisms including paracrine effects, immunomodulation, cell differentiation, and inhibition of oxidative stress, collectively forming a cascade reaction of "damage repair-microenvironment remodeling-functional recovery."

3.1 Paracrine Effects

The paracrine effect is the primary pathway through which MSCs exert their functions. Vascular Endothelial Growth Factor (VEGF) secreted by MSCs can directly act on ovarian microvascular endothelial cells to promote angiogenesis, increasing ovarian microvessel density by 1.8-fold in POF model rats. Hepatocyte Growth Factor (HGF) inhibits granulosa cell apoptosis by phosphorylating Akt protein, reducing the follicular atresia rate by 40%. As "intercellular messengers," exosomes carry miR-21, which can target and bind to the 3'UTR region of the PTEN gene, downregulating the expression of the pro-apoptotic protein Bax. In vitro experiments have confirmed that miR-21

in UCMSCs exosomes can reduce granulosa cell apoptosis rate by 38.5% through inhibiting the PTEN/PI3K pathway, while simultaneously upregulating the expression of the anti-apoptotic protein Bcl-2. Furthermore, miR-126-3p in exosomes can enhance angiogenic capacity by activating the VEGF pathway, increasing ovarian blood flow by 52% in POF mouse models.

3.2 Immunomodulation

MSCs can inhibit macrophage polarization toward the M1 phenotype and promote their transition to the M2 phenotype by secreting anti-inflammatory factors such as IL-10 and TGF-β, thereby reducing local ovarian inflammatory factor levels. Preclinical studies have shown that UCMSCs transplantation reduces ovarian TNF-α levels by 52% and IL-6 levels by 48% in POF model mice, while increasing the proportion of Treg cells by 2.1-fold. Additionally, MSCs can inhibit excessive activation of CD4+T cells and reduce autoantibody production. In autoimmune POF models, the positive rate of anti-ovarian antibodies (AOAb) decreases from 83% to 31%, significantly improving immune dysregulation.

3.3 Cell Differentiation and Follicle Pool Protection

Induced by the ovarian microenvironment, MSCs can differentiate into granulosa-like cells, expressing specific markers such as FSHR and AMH, directly supplementing damaged follicular support cells. ADSCs induced by E2 can secrete progesterone in a dose-dependent manner in response to FSH stimulation, with progesterone levels reaching (23.5±4.2) ng/mL, approaching the function of normal granulosa cells. Moreover, MSCs can protect ovarian reserve function by inhibiting excessive activation of primordial follicles, increasing the number of primordial follicles by 35%, primary follicles by 28%, and secondary follicles by 22% in POF model mice, effectively delaying the rate of follicle pool depletion.

3.4 Inhibition of Oxidative Stress

MSCs can clear reactive oxygen species (ROS) and reduce malondialdehyde (MDA) levels by upregulating the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). Studies have confirmed that BMSCs transplantation increases ovarian SOD activity by 2.1-fold, reduces MDA levels by 45%, and enhances GSH-Px activity by 1.8-fold in POF model rats, significantly alleviating oxidative stress damage. Furthermore, MSCs can activate the Nrf2/HO-1 antioxidant pathway, further enhancing the antioxidant capacity of ovarian tissue and reducing the accumulation of lipid peroxidation products.

4 Clinical Research Progress

In recent years, clinical translation research on MSCs for POF treatment has gradually advanced, and the efficacy of MSCs from different sources and transplantation routes has been preliminarily validated.

4.1 Clinical Efficacy of MSCs from Different Sources

In the clinical application of umbilical cord MSCs, a single-arm study enrolled 32 POF patients (aged 22–38 years, disease duration 6 months–5 years) who received intravenous infusion of UCMSCs (1×10^6/kg) once monthly for 3 consecutive months, followed by a 6-month follow-up. Results showed that 56.25% (18/32) of patients restored regular menstruation; serum FSH levels decreased from 58.3±12.5 IU/L to 32.6±8.7 IU/L, and AMH levels increased from 0.12±0.05 ng/mL to 0.45±0.11 ng/mL. Among them, 2 patients achieved natural pregnancy (pregnancy rate 6.25%), with no severe adverse reactions observed.

In clinical studies of adipose-derived MSCs, 25 POF patients underwent intraovarian injection of autologous ADSCs (5×10^6 cells per ovary). At 3 months post-operation, the antral follicle count increased from 1.2±0.5 to 3.5±1.1, and E2 levels rose from 18.3±5.2 pg/mL to 45.6±10.3 pg/mL. The cumulative pregnancy rate at 6 months post-operation reached 12% (3/25), which was superior to the concurrent HRT treatment group (pregnancy rate 2.3%). Additionally, endometrial thickness in the ADSCs treatment group increased from 6.2±1.3mmto8.5±1.5 mm, improving embryo implantation conditions.

Clinical exploration of menstrual blood MSCs showed that 15 POF patients underwent uterine artery interventional transplantation of MenSCs (2×10^6 cells per session). At 3 months post-operation, the menstrual recovery rate was 66.7% (10/15), FSH levels decreased to (38.5±9.2) IU/L, and the Kupperman score for menopausal symptoms decreased from 28.3±5.6 to 12.5±3.2, significantly improving quality of life.

4.2 Relationship Between Transplantation Routes and Efficacy

Intravenous infusion is simple to perform but has low cell homing efficiency, with only approximately 0.1%–0.5% of cells engrafting in the ovary. Intraovarian injection can improve cell engraftment rate, increasing local cell concentration by 10-fold, but is more invasive and may carry risks of ovarian bleeding or adhesion. Uterine artery interventional therapy prolongs cell retention time to 72 hours through targeted delivery, with a menstrual recovery rate (72.5%) significantly higher than that of intravenous infusion (52.3%). However, it requires higher technical expertise from operators and is relatively costly.

Safety comparison of different transplantation routes showed that the incidence of adverse reactions was 6.7% in the intravenous infusion group (mainly low-grade fever), 10% in the local injection group (mainly lower abdominal pain), and 12.5% in the interventional therapy group (mainly puncture site hematoma). No serious adverse events occurred in any group, indicating that MSCs transplantation has good safety profiles.

5 Challenges and Prospects

Despite the enormous potential of MSCs in treating POF, their clinical translation still faces multiple challenges.

5.1 Key Existing Issues

Low cell survival rate and homing efficiency represent major bottlenecks. After transplantation, MSCs are vulnerable to ischemia and inflammatory microenvironments, with a survival time of less than 7 days. Only approximately 1% of cells engraft in the ovary, while most are cleared within 24 hours. The details of the mechanisms of action remain unclear; in-depth research is still needed on the target identification of functional miRNAs in exosomes and their signaling pathway regulatory networks, particularly regarding differences in paracrine profiles among MSCs from different sources and their impact on therapeutic efficacy.

Furthermore, the lack of uniform standards for cell culture, transplantation dosage, and follow-up duration makes it difficult to compare results across studies. For instance, the clinical dosage of UCMSCs ranges from 0.5×10^6/kg to 2×10^6/kg, with follow-up periods varying from 3 months to 2 years, leading to significant variations in outcomes. Long-term safety has not been fully established, requiring monitoring of cellular genetic stability and tumorigenic risk. Although no tumor formation has been observed in animal studies to date, long-term clinical follow-up data remain insufficient.

5.2 Innovative Technologies and Future Directions

In response to the above issues, innovative strategies have emerged. Combining MSCs with collagen scaffolds or hyaluronic acid hydrogels provides a three-dimensional growth microenvironment, increasing cell survival rate by 3-fold, while the sustained-release effect of hydrogels extends the duration of cellular action to over 14 days. Upregulating CXCR4 expression in MSCs via CRISPR-Cas9 technology enhances homing ability, with ovarian engraftment rate increasing by 2.5-fold in animal experiments; concurrent preconditioning of the ovarian microenvironment with CXCL12 further improves targeting efficiency.

Combined application of MSCs with low-intensity laser and growth factors can amplify repair effects. Preclinical studies have shown that this approach increases the pregnancy rate by 50% in POF model rats, with no significant differences in growth, development, or cognitive function between offspring rats and normal rats, preliminarily confirming the safety of combination therapy. In the future, integrating single-cell sequencing to screen optimal cell subpopulations and utilizing bioimaging technologies for real-time monitoring of cell distribution and therapeutic efficacy will drive MSCs therapy toward precision. Additionally, exosomes, as a cell-free therapeutic strategy, can avoid

potential risks of cell transplantation and are expected to become a core direction for next-generation treatment approaches.

References:

[1] Zou, Y. H., Ding, X. P., & Zheng, Y. F. (2025). Current status of research on stem cell application in premature ovarian failure. Chinese Journal of Birth Health and Heredity, 33(2), 471-477.

[2] Li, Y. Q., Gong, X. C., & Xing, Y. Y. (2024). Study on the therapeutic effect of exosomes derived from adipose-derived mesenchymal stem cells on premature ovarian failure. Journal of Reproductive Medicine, 33(12), 1627-1634.

[3] Liu, Y. Y., Ma, Y. Y., Huang, X. H., & Zhang, J. K. (2025). Mechanisms of mesenchymal stem cells from different sources in the treatment of premature ovarian failure. Chinese Journal of Tissue Engineering Research, 29(13), 2764-2773.

[4] Chang, M. Y. (2024). Study on the improvement effect and potential mechanisms of mesenchymal stem cells on premature ovarian failure [Master's thesis]. Xinxiang Medical University.

[5] Liu, Y. Y., He, X. L., & Tian, X. F. (2023). Research progress on mesenchymal stem cell therapy for premature ovarian failure. Fuer Jiankang Daokan (Guide of Women and Children Health), 2(18), 18-20+29.