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# Mesenchymal Stem Cell-Derived Exosomes for the Treatment of Premature Ovarian Insufficiency: Mechanism, Application and Clinical Translation Prospects

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**Abstract:** Premature ovarian insufficiency (POI) refers to a reproductive endocrine disease in which ovarian function is impaired in women before the age of 40, which seriously affects the quality of life of patients and increases their psychological and socioeconomic burden. At present, there are still certain limitations in the treatment of premature ovarian insufficiency, and none of them can fundamentally restore the patient's ovarian function. This forces people to find more effective ways to treat POI so that patients can achieve clinical pregnancy after effective treatment. Mesenchymal stem cells (MSCs) are a type of multipotent stem cells capable of self-renewal and multidirectional differentiation. A large number of studies have shown that exosomes (Exo) secreted by mesenchymal stem cells can regulate the ovarian microenvironment through multiple mechanisms and play an important role in improving the ovarian function of POI mice. In this review, we mainly discuss the biogenesis of Exo, the characteristics of MSCs-derived Exo, their role in the treatment of POI, and related preclinical studies, so as to provide some new ideas for the clinical application of MSCs-derived Exo in the treatment of POI.

**Keywords:** Premature Ovarian Insufficiency; Mesenchymal Stem Cells; Exosomes; Preclinical Research.

## 1. Introduction

Premature ovarian insufficiency (POI) is a common gynecological endocrine disease characterized by elevated gonadotropin levels and decreased estrogen levels in women under 40 years old[1-3]. The cause of POI is mainly related to premature exhaustion of primordial follicles caused by genetic defects, infection, autoimmunity, chemotherapy damage and other factors, of which autoimmune factors account for 4% to 30%[3-5]. The latest data shows that the prevalence of POI is as high as 3.5%-3.7%[6, 7]. Most patients with POI are accompanied by symptoms such as menstrual disorders, perimenopausal syndrome and infertility. It is difficult for POI patients to restore their fertility to a certain extent. Only about 5% of POI patients achieve clinical pregnancy after the disease remits naturally[8]. With the increasing number of infertility patients, fertility preservation has become another key goal in the treatment of POI. Currently, the main methods for preserving fertility include oocyte freezing, embryo freezing, ovarian tissue freezing and ovarian transplantation, as well as the use of gonadotropin-releasing hormone agonists[9].

Mesenchymal stem cells (MSCs) are a type of multipotent stem cell that can self-renew and multidirectionally differentiate. MSCs have abundant tissue sources and can be obtained from umbilical cord, amniotic membrane, bone marrow, fat, brain, lung and pancreas. MSCs treatment has also become a hot topic in the field of reproductive medicine[10]. In recent years, stem cell therapy has been used as a potential treatment modality to heal injured tissues or organs and restore normal function[11]. How MSCs rescue damaged organs and tissue damage is still unclear. Studies have shown that stem cell transplantation can promote follicle regeneration. In a mouse model of chemotherapy-induced POI, MSCs transplantation can significantly increase the number of ovarian follicles and serum estradiol concentration, leading to long-term maintenance of fertility. This research result suggests that MSCs can help repair ovarian structure and improve ovarian function[12]. It is worth noting that MSCs can produce heterogeneous cell-derived membrane structures composed of exosomes (Exo) with a diameter of 30-150nm, which are mainly derived from the endosomal system. These Exo can interact with a variety of receptor cells, thereby affecting normal cell homeostasis and disease progression[13, 14]. Because Exo can carry many substances such as proteins, microRNA, lipids and cytokines, Exo is also considered to be an important paracrine mediator between MSCs and their target cells[13]. Several studies have shown that transplantation of Exo derived from human umbilical cord mesenchymal stem cells (hUCMSCs) in chemotherapy-induced POI mouse models can restore ovarian function by promoting angiogenesis, attenuating ovarian granulosa cells (GCs) apoptosis, and inhibiting follicular atresia[15-17].

In this review, we start from the characteristics of MSCs-derived Exo, the role of MSCs-derived Exo in treating POI, and the preclinical studies of MSCs and their derived Exo in treating POI, hoping to provide a new theoretical basis for the "cell-free" treatment of POI.

## 2. Biogenesis of MSCs-derived Exo

The formation of Exo is a continuous process. During the

maturation of intracellular multivesicular bodies (MVBs), the plasma membrane is double-invaginated, the endoplasmic reticulum is classified and fused, and the Golgi complex is processed to form intraluminal vesicles (ILVs). Finally, MVBs fuse with the plasma membrane and are secreted into membrane vesicles outside the cell [18]. Under a transmission electron microscope, Exo are teacup-shaped particles of varying sizes[19]. Exo contain remnants of the endosomal sorting complexes required for transport (ESCRT) pathway. The classical ESCRT pathway can cross-talk with synthetic proteins and the ESCRT accessory protein ALG-2 interacting protein X (ALIX; also known as programmed cell death 6 interacting protein) [20]. Recent studies have shown that the active form of the ESCRT-associated protein ALIX efficiently recruits ESCRT-III proteins to endosomes and that this ALIX- and ESCRT-III-dependent pathway promotes the sorting and delivery of tetramer proteins to Exosomes[21]. Exo formation can also be independent of the ESCRT pathway, for example, the tetraspanins CD81, CD82, and CD9 are directly involved in the sorting of various cargoes of Exo[22]. Studies have reported that active RAB31 is phosphorylated by epidermal growth factor receptor (EGFR), can bind to floating proteins in lipid raft microdomains, and drive EGFR into MVBs to form ILVs, independent of the ESCRT pathway[22]. Despite the progress made in the identification of proteins involved in Exo biogenesis, the exact mechanisms by which these proteins contribute to Exo biogenesis remain to be fully elucidated.

# 3. Characteristics of MSCs-derived Exo

MSCs-derived Exo have similar biological functions to MSCs, such as repair of damaged tissues, inhibition of inflammatory response, and regulation of the immune system. Exo, as secretory vesicles involved in intercellular communication, can not only transport a variety of substances, but also be secreted by all types of cells. They are widely present in body fluids such as saliva, blood, urine and breast milk. Studies have shown that MSCs produce more Exo than other cells[23]. However, MSCs-derived Exo have no difference in morphological characteristics, isolation and storage methods from Exo from other sources[19, 24]. In terms of Exo identification, in addition to common surface markers such as CD9 and CD81, Exo derived from MSCs also express some adhesion molecules on the MSCs membrane, including CD29, CD44, CD73 and CD90[25]. The results of Bi et al. showed that the proteomics of Exo from MSCs from different tissues were different and their miRNA profiles were also different. The proteins of Exo from embryonic stem cells (human embryonic stem cells Exosomes, hESC-Exo) were enriched in developmental regulation and cell cycle function, while Exo from hUCMSCs (hUCMSCs Exosomes, hUCMSCs-Exo) were rich in proteins regulating the activity of natural killer cells and complement system. The proteins of Exo from human induced pluripotent stem cells (human-induced pluripotent stem cells Exosomes, hiPSC-Exo) played a leading role in regulating the developmental process and maintaining pluripotency. There were 16, 27, and 61 unique miRNAs in hESC-Exo, hiPSC-Exo, and hUCMSCs-Exo, respectively, and 70 common miRNAs[26]. It is worth noting that similar results were obtained in another secretome study on Exo from MSCs from different tissues[27]. It has been reported that miRNAs derived from MSCs-derived Exo are mainly present in precursor form, and a large number of miRNA companion strands have been found in MSCs-derived Exo[28]. In addition, a comparative analysis of miRNAs in MSCs-derived Exo and miRNAs in MSCs revealed that 106 miRNAs in MSCs were not detected in MSCs-derived Exo, indicating that the packaging of miRNAs into Exo is not random but a regulated process[29]. However, the specific mechanisms of this selective packaging of miRNAs remain largely unknown. A study showed that mouse bone marrow mesenchymal stem cell-derived Exo (BMSCs-Exo) was used as a dexamethasone delivery vehicle for the treatment of autoimmune hepatitis. Dexamethasone-loaded Exo can accumulate in the liver in large quantities and can be effectively internalized into macrophages, which has a significant inhibitory effect on macrophages[25]. MSCs-derived Exo have become promising candidates for the treatment of various human diseases due to their small size, long circulation half-life, low immunogenicity, strong penetration ability and ideal biocompatibility.

# 4. Mechanism of Action of MSCs-Derived Exo in POI

(1) Inhibition of GCs apoptosis

BMSCs-Exo-carried miR-644-5p inhibits GCs apoptosis by targeting cellular p53[30]. The study by Yang et al. showed that BMSCs-Exo can inhibit GCs apoptosis by improving the expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN) [31]. Interestingly, circLRRC8A carried by BMSCs-Exo can inhibit hydrogen peroxide (H2O2)-induced GCs senescence by inducing nuclear factor erythroid 2-like 1 (NFE2L1) expression through acting as a negative regulator of miR-125a-3p[32]. In the cisplatin-induced chemotherapy POI model, both BMSCs-Exo and hUCMSCs-Exo can protect GCs from apoptosis by upregulating the expression of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and downregulating the expression of the pro-apoptotic protein cleaved caspase-3 (c-caspase-3) [12, 30]. Recently, Park et al. showed that pretreatment with BMSCs-Exo could inhibit chemotherapy-induced apoptosis and fibrosis, maintain ovarian steroidogenic capacity and prevent chemotherapy-induced GCs damage by upregulating gene expression of steroidogenic factors, and ultimately preserve the fertility of mice[33]. In the cisplatin-induced POI model constructed by QU et al., hUCMSCs-Exo restored the structure and function of the damaged ovary by promoting angiogenesis and attenuating GCs apoptosis through overexpression of miR-126-3p[17]. The results of Li et al. showed that hUCMSCs-Exo can also improve GCs damage caused by cyclophosphamide (CTX) by promoting the development of follicles and the proliferation of GCs by regulating the levels of Yes-associated protein (YAP), TEA domain transcription factors (TEAD) and transcription coactivator (TAZ) in the Hippo signaling pathway, as well as inhibiting the levels of macrophage stimulating 1 (MST1) and large tumor suppressor kinase 1/2 (LATS1/2), thereby restoring ovarian function[34]. In addition, hUCMSCs-Exo transplantation promoted ovarian hormone levels and primary follicle development in CTX-induced POI mice and reduced GCs apoptosis[35].Human amniotic fluid stem cell-derived Exo carrying miR-369-3p downregulates the expression of YAF2, which can regulate the PDCD5/P53 signaling pathway to attenuate GCs apoptosis [36]. hiPSC-Exo promoted GCs proliferation and attenuated cyclophosphamide-induced GCs

apoptosis in the POI mouse model by upregulating NRF2 protein levels in GCs and promoting the expression of oxidative stress-related proteins SOD 1 and GCLC[37].

(2) Promote follicle development

The study by Yang et al. showed that BMSCs-Exo could significantly restore the estrous cycle of POI rats, increase the number of basal follicles and antral follicles, and regulate the level of reproductive hormones[31]. hUCMSCs-Exo promotes follicle development by regulating the Hippo signaling pathway, increasing the levels of YAP, TEAD, and TAZ, and inhibiting the levels of MST1 and LATS1[34]. In addition, hUCMSCs-Exo activated dormant primordial follicles by specifically enriching in oocytes; the recruitment of these primordial follicles was closely related to the stimulation of oocyte phosphatidylinositol 3-kinase (PI3K) and mTOR signaling pathways by Exo-carried miR-146a-5p/miR-21-5p[38]. Exo derived from menstrual blood-derived endometrial stem cells (MenSCs) can promote the proliferation of GCs in primordial and primary follicles and promote follicular development by increasing the expression of deleted in azoospermia like (DAZL) and forkhead box L2 (FOXL2) [39]. circBRCA 1 is decreased in the serum and GCs of POI patients and is associated with decreased ovarian reserve function. It can improve estrous cycle disorders and reproductive hormone levels in POI rats and reduce the number of atretic follicles[40].

(3) Improving the ovarian microenvironment

hUCMSCs-Exo transplantation promoted the ovarian hormone level and primary follicle development of POI mice induced by CTX, and reduced GCs apoptosis; the main manifestations were the reduction of reactive oxygen species (ROS) generation, free iron ion and lipid peroxidation levels in GCs, among which the iron death marker protein nuclear factor-erythroid 2 related factor 2 (Nrf2), cystine/glutamate antiporter (solute carrier family 7 Member 11, SLC7A11) and glutathione peroxidase 4 (GPX4) were also reduced to varying degrees[41]. hUCMSCs-Exo reduce GCs damage by transporting therapeutic proteins, nucleic acids, and lipids and preventing the formation of oxidative stress-induced ROS and DNA damage[39, 42]. Ding et al. found that miR-17-5p was highly expressed in hUCMSCs-Exo, and hUCMSCs-Exo delivered miR-17-5p to inhibit the expression of sirtuins 7 (SIRT7) to inhibit ROS accumulation, thereby repairing ovarian dysfunction[43]. hUCMSCs-Exo circBRCA 1 reduces ROS damage by directly absorbing miR-642a-5p to upregulate FOXO 1 expression in GCs[40]. Human amniotic mesenchymal stem cell-derived Exosomes (hAMSC-Exo) can enhance the activity of GCs in POI and inhibit the oxidative stress regulator SIRT4, while Exo miR-320a can be delivered to oocytes and GCs to regulate SIRT4, thereby reducing ROS levels and improving ovarian damage[43]. Clonal mesenchymal stem cells (cMSCs) and their secreted Exotypes promote angiogenesis by upregulating the expression levels of VEGF and IGF-1 in the POI mouse model established by CTX[44]. The above results show that MSCs-Exo can repair damaged ovarian tissue through anti-inflammatory, antioxidant and angiogenic effects.

(4) Regulating immune balance

PU et al. constructed a chemotherapy-induced POI rat model by intraperitoneal injection of CTX and busulfan, and used KEGG to analyze the DEGs between experimental rats. The results showed that the ovarian tissue damage in POI rats can inhibit the TNF signaling pathway and IL-mediated signaling pathway through hUCMSC-Exo transplantation to play an anti-inflammatory role, thereby improving ovarian function; the GnRH signaling pathway affects the growth, development and ovulation of follicles through hormone secretion; and the immune regulation, cell viability, inflammation regulation, fibrosis and metabolism signaling pathways improve the local microenvironment of ovarian tissue in POI rats[15]. MSC-Exo can induce T lymphocyte apoptosis, stimulate monocytes to secrete IL-10 and TGF-β, and induce the development of Tregs. MSCs play an important role in immune regulation.

# 5. Preclinical Studies of MSCs and Their Derived Exo for the Treatment of POI

In the context of treating POI with MSCs and their derived Exo, although clinical trials in this area are still limited, existing evidence shows that MSCs transplantation has great potential in restoring ovarian function in patients with POI.

Among the completed clinical trials, the clinical trial published by Igboeli et al. (http://www.Clinicaltrials.gov, (NCT02696889)) showed that after autologous BMSCs (5-15× 106) were implanted in the unilateral ovary of POI patients, the menopausal symptoms observed in the preoperative evaluation of both patients were improved during the 1-year follow-up, and menstruation was restored within 7 months after BMSCs implantation. In addition, the study did not report any complications or safety issues during the treatment and observation period[45]. The work of Mashayekhi and colleagues is noteworthy (http://www. Clinicaltrials. gov, (NCT02603744)). Nine subjects who received different doses ($5\times10^6$, $10\times10^6$, $15\times10^6$) of autologous ADMSCs unilaterally orthotopically injected into the ovary also did not experience any early side effects and secondary complications during the 1-year follow-up. In addition, there were no significant differences in ovarian volume, AMH, and basal antral follicle number between subjects in each cell group during the follow-up period ($p > 0.05$); interestingly, after transplantation of $5\times10^6$ doses of ADSCs, some variables showed good results[46]. In addition, a Phase I/II clinical trial of unilateral intraovarian injection of mesenchymal stem cells derived from menstrual blood, registered in the Iranian Clinical Trial Registry (Trial Registration Number: IRCT20180619040147N2), with an actual number of 31 participants (stem cell treatment group (n=15) and control group (n=16)), showed that cell therapy using autologous menstrual blood mesenchymal stromal cells for infertile women with ovarian dysfunction can improve ovarian dysfunction. Compared with the control group, the number and quality of oocytes, fertilization rate, embryo quality, pregnancy rate and live birth rate were significantly increased; and in the follow-up one year after treatment, 4 of the 15 participants in the MSCs group conceived naturally within 3 months after cell injection, while no natural conception occurred in the control group ($P = 0.04$) [47]. Unfortunately, the results of most completed clinical trials have not yet been published. It is worth noting that one clinical trial on MSCs-derived Exo transplantation for the treatment of POI has been registered. However, the biosafety and effectiveness of MSCs and MSC-derived Exo-related applications still need to be tested through long-term testing and in vivo models. Currently, there is still an urgent need for larger-scale, multi-center and long-term studies to safeguard the transplantation of MSCs and Exo-derived Exo for the

treatment of clinical diseases.

# 6. Conclusion and Future Perspectives

This study systematically reviewed the latest research progress of MSCs-derived Exo in the treatment of POI, and further emphasized the potential of MSCs-derived Exo in the treatment of POI in clinical applications, providing a new direction for improving ovarian function and pregnancy outcomes in POI patients. Existing studies have shown that the cell-free therapeutic properties of MSCs-derived Exo can effectively circumvent the immune rejection and tumorigenic risks of traditional stem cell transplantation. At the same time, the miRNA, proteins and cytokines they carry can intervene in the pathological process of POI through a multi-target mechanism of action, providing an innovative treatment strategy for improving patients' ovarian reserve function and reproductive outcomes. Currently, many clinical trials of MSCs and their Exo for the treatment of POI have preliminarily verified their safety, but in-depth exploration is still needed in terms of molecular mechanism analysis, dose optimization and long-term efficacy evaluation.

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