Human mesenchymal stem cell treatment of premature ovarian failure: new challenges and opportunities

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Abstract
Premature ovarian failure (POF) is one of the common disorders found in women leading to 1% female infertility. Clinical features of POF are hypoestrogenism or estrogen deficiency, increased gonadotropin level, and, most importantly, amenorrhea. With the development of regenerative medicine, human mesenchymal stem cell (hMSC) therapy brings new prospects for POF. This study aimed to describe the types of MSCs currently available for POF therapy, their biological characteristics, and their mechanism of action. It reviewed the latest findings on POF to provide the theoretical basis for further investigation and clinical therapy.

Keywords: Mesenchymal stem cells, Ovarian function, Premature ovarian failure

Introduction
Premature ovarian failure (POF) is a common endocrine disease causing female infertility. It is characterized by high gonadotropin expression [follicle-stimulating hormone (FSH) ≥ 40 mIU/mL], low estradiol (E2) expression, and follicular dysplasia in women aged less than 40 years [1]. During 2007–2008, the term primary ovarian insufficiency (POI) was suggested to represent this dysfunction related to very early aging of the ovaries [2]. Causes of POF/POI are unknown and related to many complicated factors such as genetic defects [3], autoimmunity [4, 5], chemotherapy injury [6], and others; POF/POI can present as idiopathic [7]. Currently, the prevention and treatment of POF are extremely limited. The most commonly employed hormone replacement therapy cannot effectively recover ovarian function [8]. Thus, the demand for novel and effective therapeutics for POF has increased. Mesenchymal stem cells (MSCs) are highly important in regenerative medicine because of their inherent regenerative properties [9, 10]. Many reports suggested that human mesenchymal stem cell (hMSC) transplantation was a promising treatment for POF [11]. MSCs are multipotent stem cells that are easy to obtain and have poor immunogenicity [12, 13]. They can be harvested from several adult tissues, such as the bone marrow (BM), umbilical cord (UC), peripheral blood, adipose tissue (AD), placenta, and menstrual fluid [14–20]. They are an excellent source of growth factors/cytokines. In this study, the recently published data on hMSC treatment of POF were summarized, and precise mechanisms underlying the effect of stem cells on POF were explored.

Present situation in POF
The etiology of POF remains sophisticated, including X-chromosome abnormalities, autosomal genetic abnormalities, autoimmune disorder, and enzymatic defects. The POF induced by chemotherapy drugs is more prominent in young patients [21, 22]. The most common clinical treatment of POF is still hormone replacement therapy (HRT). HRT is indicated to reduce the risk of...
osteoporosis, cardiovascular diseases, and urogenital atrophy and to improve the quality of life of women with POF. However, the role of HRT in promoting fertility remains controversial. Artificial cycles can never replace natural cycles. HRT is considered unsafe in women with a history of breast cancer or ovarian cancer, and alternative measures should be employed to reduce risks and symptoms associated with POF [23, 24]. The last and the most promising measure resorted to is egg donation for most women with POF. However, egg donation resources are very scarce, and patients receiving donated eggs can never have their biological offspring. Therefore, clinicians are looking for new therapies for POF, and MSC transplantation is a promising treatment.

**Treatment of POF using human MSCs**

**Human bone marrow MSCs**

**Characteristics of human bone marrow MSCs**

Human bone marrow MSCs (hBMMSCs) have high proliferative potential and the ability to differentiate into adipocytes, chondrocytes, and osteoblasts. hBMMSCs were widely researched for treating tumors [25–27], cartilage repair [28], and myocardial infarction [29]. hBMMSCs are multipotent stem cells that can differentiate into multiple cell types, including osteoclasts, myocytes, macrophages, adipocytes, and cardiomyocytes [30]. hBMMSCs primarily derive their energy from glycolysis. The saturated fatty acid palmitate induces BMMSC apoptosis and decreases proliferation in vivo [31]. Many studies showed that hBMMSCs could regulate cytokine expression in Th1 and Th2 cells [32]. hBMMSCs or extracellular vesicle infusion decreased the expression of pro-inflammatory cytokines and chemokines [33].

**Effects and mechanisms of hBMMSCs on POF (Fig. 1)**

BMMSCs were the first stem cells used to evaluate the therapeutic ability of MSCs against chemotherapy-induced POF rat models [34]. BMMSC therapy was found to be protective against germ cell apoptosis and DNA damage in mice undergoing chemotherapy [35]. Cisplatin-induced granulosa cell (GC) apoptosis was reduced when BMMSCs migrated to GCs in vitro and the antral follicle count, E2 levels, and anti-Müllerian hormone (AMH) levels increased after 30-day BMMSC treatment [36, 37]. The new primordial follicles were formed, and FSH levels were near normal in mice with POF after BMMSC injection [38]. Moreover, BMMSCs can reactivate folliculogenesis [39]. BMMSCs homed in the stroma of injured ovaries and the levels of insulin-like growth factor-1 (IGF-1) and tumor necrosis factor-α (TNF-α) increased in ovaries [40]. Human angiogenin promotes primordial follicle survival and angiogenesis in transplanted human ovarian tissue [41]. The overexpression of miR-21 in BMMSCs could repair the ovarian function in rats with chemotherapy-induced POF, which was related to the inhibition of GC apoptosis by targeting phosphatase and tensin homolog deleted on chromosome ten (PTEN) and recombinant human programmed cell death 4 (PDCD4) [42]. Yang et al. demonstrated that BMMSC-derived exosomes could prevent ovarian follicular atresia in cyclophosphamide (CTX)-treated rats via the delivery of miR-144-5p. Moreover, miR-144-5p was related to the inhibition of GC apoptosis by
targeting PTEN [43]. The effect of BMSCs on POF was positive. However, the treatment efficacy was not sufficient for therapeutic purposes probably due to the loss of transplanted MSCs. Some scholars added simple BMSC injection to other interventions and found that they had better therapeutic effects. Heat shock pretreatment is an effective method to enhance the anti-apoptotic capacity of BMSCs and achieve a better treatment effect in POF [44]. In addition, human BMSC-exosomes resulted in further stimulation of angiogenesis via the Akt/mTOR signaling pathway [45].

**Human placenta–derived MSCs**

*Characteristics of human placenta–derived MSCs*

Human placenta–derived MSCs (hPMSCs) are a sub-population of villous stromal cells isolated from the full-term placenta. They are widely present in the villous stroma and can differentiate into osteoblasts, cardiomyocytes, smooth muscle cells, adipocytes, endodermal pancreatic islet cells, liver cells, astrocytes, and ectodermal neurons [46–48]. hPMSCs express MSC markers such as stage-specific embryonic antigen (SSEA4), CD44, CD54, CD73, CD90, CD105, CD166, and Oct4 [49]. hPMSCs have immunomodulatory, anti-apoptotic, pro-angiogenic, and anti-fibrotic properties [50–52]. hPMSCs can secrete paracrine factors to exert an antioxidative effect [53] and also secrete pro-angiogenic molecules, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), transforming growth factor-beta (TGF-β), and IGF-1 [54]. HGF secreted by hPMSCs induced lining trophoblast migration in the placental villous microenvironment [49]. Besides, exosomes of hPMSCs also played important biological roles including enhancing angiogenesis in vitro and in vivo [55].

**Effects and mechanisms of hPMSCs on POF (Fig. 2)**

HPMSC transplantation is an effective method to recover ovarian function in mice with CTX-induced POF [56]. A study by Zhang et al. [57] reported reduced levels of FSH, LH, and antizona pellucida antibody (AZP Ab) in serum and increased the levels of AMH and E2 after transplantation of hPMSCs into female BALB/c mice aged 6–8 weeks. hPMSC transplantation significantly recovered the estrus cycle in the POF group and decreased GC apoptosis. The transplantation of hPMSCs suppressed GC apoptosis induced by the endoplasmic reticulum stress inositol-requiring enzyme 1α (IRE1α) signaling pathway in mice with autoimmune-induced POF [58]. In addition, a previous study suggested that hPMSC transplantation reversed ovarian function in mice with POF and decreased the ratios of Th17/Tc17 and Th17/regulatory T (Treg) cells via the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway [59].

*Human amniotic MSCs*  

*Characteristics of human amniotic MSCs*

Amnion is a waste product of perinatal tissue sources. Therefore, the procedure to obtain human amniotic...
MSCs (hAMSCs) is noninvasive and represents an advantageous source of cells for cell therapy. hAMSCs are derived from embryonic mesoderm. They are spindle, polygon, or star shaped; the number of long spindle-shaped cells increases significantly after subculture for 3 days [67]. More than 95% of hAMSCs expressed surface markers (CD105, CD29, CD44, CD73, CD49d, and CD90) [68]. Also, cells expressed embryonic/pluripotent stem cell markers such as Oct-4 and SSEA-4 [69]. Some studies identified that hAMSCs secreted a large number of various factors, including EGF, HGF, VEGF, IGF-1, growth differentiation factor 9 (GDF-9), bFGF, and many miRNAs [70]. Compared with hPMSCs, hAMSCs had higher expression of HGF, bFGF, and IGF-1 (>thirtyfold higher) [70]. The expansion potency of hAMSCs was higher than that of adult bone marrow–derived MSCs [17]. hAMSCs had many advantages to be used as a source of allogeneic cells for regenerative medicine, such as high rates of proliferation, self-renewal, multi-differentiation capacity, immunosuppressive paracrine activity, anti-inflammatory effects, and anti-fibrotic properties [71–76]. hAMSCs might prevent age-related reductions in proliferation and differentiation potentials [77]. hAMSCs that expressed granulocyte chemotactic peptide 2 (GCP-2) and stromal cell–derived factor-1α (SDF-1α) via transcription activator-like effector nuclease (TALEN) enhanced angiogenesis [78]. hAMSCs influenced the mitogen-activated protein kinase signaling pathway to protect cells against oxidative stress–mediated dysfunction [79]. hAMSCs and their conditioned medium (CM) inhibited T cells, reduced the marker expression of Th1 and Th17 cell populations, promoted regulatory T cells, and reduced the cytotoxicity of natural killer cells [80, 81]. Furthermore, CM from hAMSCs had anti-inflammatory [82], anti-neoplastic [83], and immunomodulatory properties [84] and caused oxidative stress inhibition [85].

**Effects and mechanisms of hAMSCs on POF (Fig. 3)**

The secretion of FIGF-1, HGF, GF2, and VEGF by human AMSCs improves the ovarian function of POF. The follicle numbers were recovered to the normal level during week 4 of hAMSC transplantation in the medium-dose CTX group (70 mg/kg). hAMSCs increased ki67+AMH+ cell numbers in patients with diminished ovarian reserve (DOR) and POF (Table 1) [68]. The number of follicles and oocytes and the level of serum E2 significantly increased, but the serum FSH levels significantly decreased in mice with POF + hAMSCs. Levels of Stra8 and integrin beta-1 were upregulated compared with those in model mice [86]. H2O2 is an endogenous reactive oxygen species, and strong oxidants can cause DNA damage, inflammation, and cell and tissue injury [87–89]. Liu et al. established mice with POF in which bilateral ovaries were burned with 10% hydrogen peroxide. Results indicated that the ovarian function, levels of FSH and estrogen, and fertility rates were recovered in mice with POF-hAMSC transplantation, and normal newborn mice were produced [67]. In mice with natural ovarian aging, hAMSCs exerted a therapeutic effect on mouse ovarian function by increasing follicle numbers. Furthermore, hAMSCs significantly enhanced the proliferation of GCs, and the co-culture of hGCs with growth factors (EGF and HGF from hAMSCs) stimulated the proliferation rate of GCs and inhibited the apoptotic rate more effectively [90]. The efficacy of low-intensity pulsed ultrasound–pretreated hAMSCs were superior to that of normal hAMSCs [89]. Some studies have shown that the hAMSC-mediated activation of GSK3β/β-catenin signaling was dependent upon the PI3K/Akt signaling pathway [91].
Human UC–derived MSCs

Characteristics of human UC–derived MSCs

MSCs can be isolated from various UC compartments or from the complete UC. In particular, the Wharton’s jelly–derived MSCs (WJ-MSCs) are acquired by removing the UC vessels (arteries and veins). Human UC–derived MSCs (huMSCs) have different biological characteristics, such as painless collection method and infinite self-renewal ability. huMSCs can differentiate into three different germ layers and migrate into the damaged tissue or inflamed regions, contributing to tissue repair. WJ-MSCs have higher proliferation capacity, plasticity, immunomodulatory activity, and self-renewal ability than MSCs from other origins [92]. These huMSCs are suitable candidates for allogeneic transplantation due to their high safety and abundance, shorter expansion times, and low immunogenicity. huMSCs tested positive for surface markers, including CD90, CD73, CD29, CD105, and CD44. They attenuated the inflammatory and oxidative stress, as well as reduced the expression of senescence-related proteins and micro-RNAs (miRs) [93]. huMSCs exhibited a similar inhibitory effect on T-cell proliferation as on hBMMSCs at a ratio of 1:10, and the percentage of migrating cells was significantly higher in huMSCs compared with BMMSCs [94]. Moreover, no correlation was found between transplanted huMSCs and the risk of tumorigenesis [95].

Effects and mechanisms of huMSCs on POF (Table 2)

In 2013, Wang et al. [12] found that umbilical MSCs (uMSCs) could treat POF in mice. The methods for transplanting huMSCs were as follows: intravenous injection (IV) and in situ ovarian microinjection (MI). Both methods of transplantation improved ovarian function, but IV was better able to restore ovarian function compared with MI [96]. Human UC vein MSCs migrated to the cyclophosphamide-injured ovaries, and 57.1%, 32.2%, and 15% were located in the medulla, cortex, and epithelium, respectively. Table 2 shows the main effects of huMSCs on POF and the species and references for each study.

### Table 1 The therapeutic effects of hAMSCs on patients' GCs with premature ovarian failure [68]

| Treatment |
|-----------|
| DOR (n = 29) | POF (n = 36) |
| No. of AMH cell | Control | hAMSCs | P value | Control | hAMSCs | P value |
| 22% | 83% | < 0.01 | 4.5% | 45% | < 0.01 |
| No. of FSHR cell | 41% | 84% | < 0.01 | 17% | 51% | < 0.01 |
| No. Of FOXL2 cell | 34% | 88% | < 0.01 | 19% | 70% | < 0.01 |
| No. of CYP19A1 cell | 45% | 92% | < 0.01 | 34% | 81% | < 0.01 |

### Table 2 Effects and mechanisms of huMSCs on POF

| Infertility model | Treatment | Main effect of huMSCs on POF | Species | References |
|------------------|-----------|-------------------------------|--------|------------|
| CTX-induced POF  | Intravenous injection | Stem cell homing (+), number of healthy follicles at different stages (+), granulosa cell apoptosis (−) | Mice | [12] |
| Superovulation-induced POF | Intravenous injection (IV) and in situ ovarian micro injection (MI) | Restore ovarian function (+, IV > MI), homing in the medulla, cortex, and epithelium of injured ovaries | Mice | [96, 97] |
| Aging female rats | IV | HGF, VEGF, and IGF-1 (+) | Rats | [98] |
| ZP3-induced POF | IV | E2, P, and IL-4 (+); FSH, IFN-γ, and IL-2(−); Th1/Th2 (−); improve endometrial conditions (+); number of healthy follicles (+); number of atretic follicles (−) | Mice | [99] |
| CTX-induced POF | IV | Folliculogenesis (+), NGF and pregnancy rate (+), NGF and TrkA (+), FSHR and caspase-3 (−) | Rats | [100] |
| Paclitaxel-induced POF | IV | FSH (−); E2 (+); antral follicle (+); CK 8/18, TGF-β, and PCNA (+); CASP-3(−) | Rats | [101] |
| Busulfan and CTX-induced POF | HuMSC-MVs (IV) | Homing (+); ovarian weight (+); ovarian angiogenesis (+); recover the disturbed estrous cycle (+); total AKT, p-AKT, VEGF, IGF, and angiogenin (+) | Mice | [102] |
| Cisplatin-induced POF | HuMSC-EXOs | Granulosa cell apoptosis (−), DNA repair proteins (+) | GCs | [103] |
| Busulfan and CTX-induced POF | Co-culture of UC-MSCs and GCs (i.p.) | HO-1 expressed in UC-MSCs can restore the ovarian function | Mice | [104] |
| CTX-induced POF | Collagen/UC-MSC transplantation | Ovarian volume (+), number of antral follicles (+), GC proliferation (+), CD31 (+), phosphorylation of FOXO3a and FOXO1 (+) | Mice | [105, 106] |
cortex, and epithelium, respectively [97]. huMSCs promoted the ovarian expression of HGF, VEGF, and IGF-1 and improved ovarian reserve function [98]. The serum levels of P, E2, and IL-4 increased, but the IFN-γ, FSH, and IL-17 levels decreased following huMSC transplantation. Also, the total number of healthy follicles increased and the number of atretic follicles decreased in mice with huMSC-POF [99]. Zheng et al. [100] used cyclophosphamide to create a POF rat model, and cultured huMSCs were transplanted by tail vein injection. They found that huMSCs reduced POF caused by chemotherapy and increased nerve growth factor (NGF) and tropomyosin receptor kinase A (TrkA) levels and decreased follicle-stimulating hormone receptor (FSHR) and caspase-3 levels via the NGF/TrkA signaling pathway. Further, huMSCs improved the ovarian function after paclitaxel injection through a direct triggering effect on the ovarian epithelium and/or indirectly enriching the ovarian niche by regulating the tissue expression of TGF-β, CK 8/18, and PCNA. These molecules are essential in regulating folliculogenesis and inhibiting CASP-3-induced apoptosis [101]. With the advancement of science and technology, scientists have performed in-depth research on the huMSC treatment of POF. huMSC membranous vesicles (MVs) were detectable within the ovaries and migrated to the ovarian follicles 24 h after transplantation. HuMSC-MV transplantation might recover ovarian function by increased angiogenesis through the PI3K/Akt signaling pathway [102]. Exosomes derived from huMSCs (huMSC-EXOs) were also used to prevent and treat chemotherapy-induced GC apoptosis in vitro [103]. In 2020, Yin et al. [104] demonstrated that heme oxygenase-1 (HO-1) expressed in huMSCs was important in restoring the ovarian function, which was mediated via the activation of JNK/Bcl-2 signaling pathway–regulated autophagy and the upregulation of the circulation of CD8+CD28− T cells. Collagen scaffold loaded huMSC transplantation in mice with POF, which improved ovarian volume and number of antral follicles and promoted ovarian angiogenesis with the increased expression of CD31; the treatment effect was very significant [105]. huMSCs on a collagen scaffold (collagen/UC-MSCs) can activate primordial follicles by phosphorylation of FOXO3a and FOXO1 in vitro [106].

hAFMSCs is noninvasive, safe, and without social controversy, consistent with human menstrual blood MSCs [108–110]. In vitro, they can be expanded in different media formulations and exhibit a heterogeneous morphology with obvious epithelioid and fibroblast-shaped cells [111]. hAFMSCs have a high renewal ability and can be extended for more than 250 doublings without any loss of chromosomal telomere length [112]. Furthermore, the potential of induced pluripotent stem cells (iPSCs) derived from AF was better and more effective than that of BM-MSCs [113]. AFMSCs expressed pluripotency markers, including Nanog, Oct-4, and sex-determining region Y-Box 2 (SOX-2) and SOX-4, and embryonic stem cell markers, including CD117, SSEA-4, TRA1–60, and TRA–1–81 [114, 115]. Some studies reported the presence of common features between primordial germ cells and AFMSCs [116]. AFMSCs are amenable for clinical application and tissue engineering due to their low immunogenicity, anti-inflammatory properties, high proliferative ability, and differentiation capacity in vitro. Also, AFMSCs lacked carcinogenesis after transplantation in nude mice.

**Effects and mechanisms of hAFMSCs on POF (Fig. 4)**

Some studies showed that hAFMSCs expressed multiple growth factors such as EGF, transforming growth factor beta (TGF-β), transforming growth factor alpha (TGF-α), and bone morphogenetic protein 4 (BMP-4) [117, 118]. In 2012, Liu et al. [119] proved that CD44+/CD105+ hAFMSCs transplanted into the ovaries of mice with POF survived for at least 3 weeks, and CD44+/CD105+ hAFMSCs underwent normal cycles of cell proliferation and self-renewal in ovarian tissues of mice with POF. HAFMSC-derived exosomes (hAFMSCs-EXOs) enhanced follicular regeneration, regular estrous cycles, and AMH level through the miRNA 21/PTEN/caspase 3 signaling pathway [120]. Compared with hBM-MSCs, hAFMSCs secreted higher levels of exosomes. Therefore, hAFMSCs appeared to be a preferable source of exosomes for clinical applications [121]. However, hAFMSCs-EXOs has rarely been reported in studies of POF treatment, so in the future, scholars can focus on the therapeutic effects and mechanism of hAFMSCs-EXOs in POF.

**Human menstrual blood–derived MSCs**

**Characteristics of human menstrual blood–derived MSCs**

Human menstrual blood–derived MSCs (hMB-MSCs) were discovered by Meng et al. and Cui et al., as a novel source of MSCs [19, 122]. hMB-MSCs expressed surface markers CD9, CD29, CD41a, CD44, CD59, CD73, CD90, and CD105; human telomerase reverse transcriptase (hTERT); embryonic stem cell marker OCT-4 [19]; and germ cell–specific genes, including DAZL, VASA, c-MOS (oocyte maturation factor mos), STRA8, BLIMP1
(B-lymphocyte–induced maturation protein 1), STELLA (developmental pluripotency-associated protein 3, stella-related protein), SCP3, and SCP1; GDF9, ZPA, and ZPC (zona pellucida gene family) [123]. In addition, hMB-MSCs secrete cytokine growth factors (GM-CSF and PDGF-BB), angiogenic factors (ANG-2, VEGF, HGF, and EGF), and metalloproteinases (e.g., MMP-3 and MMP-10) [19]. hMB-MSCs can differentiate into endothelial, neurocytic, cardiomyocytic, myocytic, cartilaginous, respiratory epithelial, pancreatic, adipocytic, hepatic, and osteogenic cells [124, 125]. Liu et al. demonstrated that hMB-MSCs could differentiate into ovarian tissue–like cells [126], and Lai et al. confirmed the differentiation of hMB-MSCs into germ cells [123]. hMB-MSCs were easy to access compared with hPMSCs and huMSCs. Also, they exhibited MSC-like properties. hMB-MSCs are therefore a novel source of stem cells that can be used for tissue repair [122]. hMB-MSCs also secrete the C-X-C chemokine receptor type 4 (CXCR4) and the respective receptor for stromal cell–derived factor-1 (SDF-1), which plays an important role in MSC migration [127]. Throughout these years, an increasing number of studies paid attention to hMB-MSCs because they possessed higher proliferation rates and painless procedures [124].

Effects and mechanisms of hMB-MSCs on POF (Fig. 5)

In 2014, Liu et al. [126] injected (DiO)-labeled hMB-MSCs with green fluorescence into ovaries of POF model mice and found that hMB-MSCs could survive in POF mouse ovaries for at least 14 days. The levels of AMH, FSHR, inhibin α/β, and Ki67 increased following hMB-MSC transplantation in mice with POF. Even more surprising was that the mRNA expression in mouse ovarian cells after hMB-MSC transplantation was similar to that observed in human ovarian cells, suggesting that hMB-MSCs differentiated into ovarian granulosa–like cells in ovaries of mice with POF following stimulation of the ovarian niche. hMB-MSC transplantation could reduce apoptosis of GCs and the fibrosis of the ovarian interstitium. Especially, transplanted hMB-MSCs directly migrated to the ovarian interstitium to repair ovarian function rather than directly differentiating into oocytes. Meanwhile, hMB-MSCs exerted protective effects on damaged ovaries partially by secreting FGF2 [128]. Yan et al. isolated MB-MSCs from three healthy female volunteers and cocultured them with hGCs treated with epirubicin. They found that MB-MSCs modulated epirubicin-induced DNA damage repair to GCs by regulating protein expression [129]. hMB-MSCs combined with Bushen Tiaoehong recipe improved the ovarian function of epirubicin-induced mice with POF, which
might be related to inhibiting the expression of GADD45b and promoting the expression of CyclinB1 and CDC2. This therapy combined with stem cells and other treatments also provided a new research direction in POF treatment [130]. Moreover, Dil-labeled hMB-MSCs were found to be localized in the GC layer of immature follicles. hMB-MSCs improved hormone secretion in rats with POF (e.g., AMH, FSHR, FST, E2, and P4). hMB-MSC transplantation not only changed ovarian ultrastructure but also improved ovarian function [131].

Human adipose tissue–derived MSCs (hADMSCs)

Characteristics of human adipose tissue–derived MSCs

Adipose tissue is suggested to be an abundant and accessible source of adult MSCs. Human adipose tissue–derived MSCs (hADMSCs) were obtained from the subcutaneous adipose tissue removed during liposuction surgeries or abdominoplasties. Moreover, the high content of hADMSCs in adipose tissue excludes the need for long-term culture in vitro and reduces the risk of chromosomal abnormalities [132]. Compared with hBMMSCs, hADMSCs had higher proliferative and self-renewal abilities and exhibited higher genetic stability in long-term culture [133]. A single unique marker was not identified in hADMSCs, but hADMSCs expressed CD34, CD14, and CD45. hADMSCs inhibited T-cell proliferation by secreting a variety of soluble mediators, including prostaglandin E2 (PGE2) and IFN-γ/indoleamine 2, 3-dioxygenase, and inhibiting the NF-κB pathway [134, 135]. Hypoxia-exposed exosomes derived from hADMSCs improved angiogenesis by activating the protein kinase A (PKA) signaling pathway and promoting the expression of VEGF [136].

Effects and mechanisms of hADMSCs on POF (Fig. 6)

Human adipose stem cell–derived exosomes (hADMSC-Exos) promoted the hGC proliferation rate and inhibited the hGC apoptotic rate in POI via the regulation of SMAD (SMAD2, SMAD3, and SMAD5) signaling pathway [137]. Combined treatment with hADMSCs and estrogen increased the Treg proliferation and Foxp3 and TGF-β1 mRNA expression in POI and decreased the IFN-γ mRNA expression [138]. Moreover, the combined therapy of ADMSCs, VEGF, and platelet-rich plasma improved rat ovarian function significantly more than expected in the cyclophosphamide-induced POF model. The expression of BMP4, IGF-1, and TGF-β increased in rats with POF [139]. Transplanted hADMSCs were located only in the interstitium of ovaries. hADMSCs secreted FGF2, IGF-1, HGF, and VEGF. hADMSC transplantation improved ovarian function in rats with chemotherapy-induced POI at least partly through a paracrine mechanism [140]. Obviously, the involvement of hADMSCs in the therapeutic mechanism of POF has been less explored. hADMSCs also effectively reduced fibrosis and inflammation [141]. However, whether it affects fibrosis during the treatment of POF still needs further research.

Effects of other MSCs on POF

The peritoneum mesothelial consists of the intraperitoneal or intestinal space, abdominal wall, and omentum. The peritoneum mesothelium lines body cavities and has the same origin as the ovarian surface epithelium. Besides, the repair and reconstruction of peritoneum mesothelial cells can be performed through the secretion of growth factors (bFGF and VEGF), cytokines, and extracellular matrix [142]. Characterized peritoneum MSCs (PeMSCs) were differentiated into ovarian cell–like cells using 10% human follicular fluid and 50% human cumulus-CM for 21 days, and the expression of oocyte (Zp3 and Gdf9), germ cell (Ddx4 and Dazl), GC (Amh), and theca cell (Lhr) markers was assessed [143]. Skin-derived MSCs (SMSCs) improved the ovarian follicle microenvironment of mice with POF, and the levels of pro-inflammatory cytokines TNF-α, TGF-β, IL-8, IL-6, IL-1β, and IFN-γ significantly decreased [144].

![Fig. 6](image-url) Effects and mechanisms of hADMSCs on POF
Problems and prospects

The past years have witnessed considerable advances in the knowledge base related to the use of MSCs for regenerative medicine. Recent breakthrough discoveries in engineering MSCs have made them an ideal source for future cell therapy in POF. It is critical to ensure the safety of MSC clinical application by understanding their impacts on tumor initiation and progression. Although many experimental and clinical assays have been developed, clinical applications of MSCs have limitations, including insufficient cell sources, immunogenicity, subculture, and ethical issues. For clinical trials, the functional potential and microbiological safety of cells must be considered, and it should be ensured that cultured cells remain untransformed. Setting up a professional system to test the quality of MSC production is extremely challenging. In addition, the large variability in cell quality is derived from different donors and tissues. Thus, more reliable and effective MSCs obtained using less invasive isolation techniques have become treatment options. Hence, cell-free therapy, which uses stem cells as a source of therapeutic molecules, can be developed to treat different disease models (Fig. 7). The main effective components of MSCs should be identified in the treatment of POF, which can avoid potential side effects caused by unnecessary treatments. Exosomes, which are important messengers between cells, regulate other cells. Numerous studies have been conducted on the biological effects of exosomes secreted by stem cells [145]. On the contrary, MSC-secreted exosomes are smaller and easier to produce and have no risk of tumor formation, facilitating their comprehensive study and clinical use in the future (Fig. 7) [146, 147]. Besides, stem cells can spread rapidly to the nearby organs or tissues, and the collagen scaffolds were believed to support the survival of transplanted cells at the initial phase of transplantation in vivo. For example, transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility. Therefore, MSCs that can be used combined with other therapies to prompt the treatment of POF should be explored.

Conclusions

The transplantation of MSCs has brought hope for patients with POF. Especially MSCs were obtained using less invasive isolation techniques because they were not only noninvasively obtained but also out of the ethical debate. In addition, cell-free therapy (therapeutic molecules from MSCs) has been extensively researched to overcome such challenges. It is expected that POF can be successfully treated using the main effective components of MSCs and combined therapy soon.

Abbreviations

AD: Adipose tissue; AMH: Anti-Müllerian hormone; BM: Bone marrow; BMP-4: Bone morphogenetic protein 4; BMP-15: Bone morphogenetic protein 15; bFGF: Basic fibroblast growth factor; DOR: Diminished ovarian reserve; E2: Estradiol; ER: Endoplasmic reticulum; EGF: Epidermal growth factor; FSH: Follicle-stimulating hormone; FSHR: Follicle-stimulating hormone receptor; GnRH: Gonadotropin-releasing hormone; GDF-9: Growth differentiation factor 9; GCs: Granulosa cells; GCP-2: Granulocyte chemotactic peptide 2; HO-1: Heme oxygenase-1; HRT: Hormone replacement therapy; hMSCs: Human mesenchymal stem cells; hPMSCs: Human placenta-derived mesenchymal stem cells; hAMSCs: Human amniotic mesenchymal stem cells;
hBMSCs: Human bone marrow mesenchymal stem cells; huMSCs: Human umbilical cord-derived mesenchymal stem cells; hAFMSCs: Human amniotic fluid mesenchymal stem cells; hPMSCs: Human adipose tissue-derived mesenchymal stem cells; hGMP: Hepatocyte growth factor; IGF-1: Insulin-like growth factor-1; hTERT: Human telomerase reverse transcriptase; IFN-γ: Interferon-γ; IRE1α: Stress inositol-requiring enzyme 1α; LH: Luteinizing hormone; MAP: Mitogen-activated protein kinase; NGF: Nerve growth factor; POF: Premature ovarian failure; POI: Premature ovarian insufficiency; PB: Peripheral blood; PGE2: Prostaglandin E2; PTEN: Phosphatase and tensin homolog deleted on chromosome ten; PDCD4: Recombinant human programmed cell death 4; PeMSCs: Pentonemone mesenchymal stem cells; SDF-1α: Stroma cell-derived factor-1α; SMSCs: Skin-derived mesenchymal stem cells; sSSEA: Tage-specific embryonic antigen; SOX-2: Sex-determining region y-Box 2; TGF-α: Transforming growth factor alpha; TGFB: Transforming growth factor beta; TNF-α: Tumor necrosis factor-α; TALE N: Transcription activator-like effector nuclease; TrkA: Tropomyosin receptor kinase A; UC: Umbilical cord; VEGF: Vascular endothelial growth factor

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Authors’ contributions

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References

1. Coulam CB. Premature gonadal failure. Fertil Steril. 1982;38(6):645–55.
2. Pastore LM, Christianson MS, Stelling J, et al. Reproductive ovarian testing and the alphabet soup of diagnoses: DOR, POI, POF, POR, and FOR. J Assist Reprod Genet. 2018;35(1):17–23.
3. Orlando E, Regini C, Vellucci FL, Petraglia F, Luisi S. Genes involved in the pathogenesis of premature ovarian insufficiency. Minerva Ginecol. 2015; 67(5):421–30.
4. Ebrahimi M, Asbagh FA. The role of autoimmunity in premature ovarian failure. Iran J Reprod Med. 2015;13(8):461.
5. Yan G, Schoenfeld D, Penney C, Hunteial K, Taylor AE, Faustman D. Identification of premature ovarian failure patients with underlying autoimmunity. J Womens Health Gend Based Med. 2000;9(3):275–87.
6. Kenney LB, Lauffer MR, Grant FD, Grier H, Diller L. High risk of infertility and long term gonadal damage in males treated with high dose cyclophosphamide for sarcoma during childhood. Cancer. 2001;91(3):613–21.
7. Sassarini J, Lumsden MA, Critchley HO. Sex hormone replacement in ovarian failure—new treatment concepts. Best Pract Res Clin Endocrinol Metab. 2015;29(1):105. https://doi.org/10.1016/j.beem.2014.09.010.
8. Lee HJ, Selseniemi K, Nikula Y, Nikula T, Klein R, Dombkowski DM, Tilly J. Bone marrow transplantation generates immature oocytes and rescues long-term fertility in a preclinical mouse model of chemotherapy-induced premature ovarian failure. J Clin Oncol. 2007;25(22):3198–204.
9. Mohammadi M, Jaafari M, Mirzaei H, Mirzaei H. Mesenchymal stem cell: a new horizon in cancer gene therapy. Cancer Gene Ther. 2016;23(9):285–6.
10. Yantao He, Dongmei Chen, Lingling Yang et al. The therapeutic potential of bone marrow mesenchymal stem cells in premature ovarian failure. He et al. Stem Cell Res Ther (2018); 9:263.
11. Phinney DG, Prokop DJ. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair—current views. Stem Cells. 2007;25(11):2896–902.
12. Wang S, Yu L, Sun M, Su W, Wang C, Wang D, Yao Y. The therapeutic potential of umbilical cord mesenchymal stem cells in mice premature ovarian failure. Biomed Res Int. Biomed Res Int. 2013;2013:69491.
13. Augello A, Kurth TB, De Bari C. Mesenchymal stem cells: a perspective from in vitro cultures to in vivo migration and niches. Eur Cell Mater. 2010; 20(11):e33.
14. Barry FP, Murphy JM. Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol. 2004;36:568–84.
15. Lee OK, Kuo TK, Chen WM, et al. Isolation of multipotent mesenchymal stem cells from umbilical cord blood. Blood. 2004;103:1669–75.
16. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13:4279–95.
17. In Y Anker PS, Scherpen SA, Kleijburg-van der Keur C, et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells. 2004;22:1338–45.
18. Korbling M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood. 2001;98:2900–8.
19. Meng X, Ichim TE, Zhong J, et al. Endometrial regenerative cells: a novel stem cell population. J Transl Med. 2007;5:57. https://doi.org/10.1186/1479-5876-5-57.
20. Manger K, Wildt L, Kalden JR, et al. Prevention of gonadal toxicity and preservation of gonadal function and fertility in young women with systemic lupus erythematosus treated by cyclophosphamide: the PREGO-Study. Autoimmun Rev. 2006;5:269–72.
21. Stearns V, Schneider B, Henry NL, et al. Breast cancer treatment and ovarian failure: risk factors and emerging genetic determinants. Nat Rev Cancer. 2006;6:886–93.
22. van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update. 1999;5:483–92.
23. Deniz G, Anto None C, Liebens F, et al. Treatment of premature menopause in breast cancer patients. Acta Chir Belg. 2007;107(2):263–6.
24. Rossella E Nappi, Chiara Cassani, Margherita Rossi et al. Dealing with premature menopause in women at high-risk for hereditary genital and breast cancer. Minerva Ginecol 2016;68(5):602–612.
25. Lu L, Chen G, Yang J, et al. Bone marrow mesenchymal stem cells suppress growth and promote the apoptosis of glioma U251 cells through downregulation of the PI3K/AKT signaling pathway. Biomed Pharmacother. 2019;112:108625.
26. Jiang S, Mo C, Guo S, et al. Human bone marrow mesenchymal stem cells-derived microRNA-205-containing exosomes impede the progression of prostate cancer through suppression of RHPN2. J Exp Clin Cancer Res. 2019;38(1):495.
27. Chen S, Yu J, Wang Q, et al. Human bone marrow mesenchymal stem cells promote gastric cancer growth via regulating c-Myc. Stem Cells Int. 2018; 2018:9501747.
28. Shiraiishi K, Kamei N, Takeuchi S, et al. Quality evaluation of human bone marrow mesenchymal stem cells for cartilage repair. Stem Cells Int. 2017; 2017:8704294.
44. Chen X, Wang Q, Li X, et al. Heat shock pretreatment of mesenchymal stem cells exhibited by their differentiation into cardiac and neuronal cells. Mol Cell Biochem. 2018;481(1-2):17–26.

30. Neshati V, Mallazadeh S, Fazly Bazzoz DS, et al. MicroRNA-499a-5p promotes differentiation of human bone marrow-derived mesenchymal stem cells to cardiomyocytes. Appl Biochem Biotechnol. 2018;186(1-2):45–55.

33. Fillmore N, Huqi A, Jagdip S, et al. Effect of fatty acids on human bone marrow mesenchymal stem cell energy metabolism and survival. PLoS One. 2015;10(3):e0120257.

56. Castro-Marrone MA, Montesinos JJ. Immunoregulation by mesenchymal stem cells: biological aspects and clinical applications. J Immunol Res. 2015;2015:39497.

32. Castro-Manrreza ME, Montesinos JJ. Immunoregulation by mesenchymal stem cells from adipose tissue. Tissue Eng. 2007;13:1173–1188.

50. Komaki M, Numata Y, Morikawa K, et al. Exosomes of human placenta-derived mesenchymal stem cells stimulate angiogenesis. Stem Cell Res Ther. 2017;8(1):219.

37. Besikcioglu HE, Sarı E, Erçil C, et al. Protection from cyclophosphamide-induced ovarian damage with bone marrow-derived mesenchymal stem cells during puberty. Gynecol Endocrinol. 2014;30(2):135–40.

36. Liu J, Zhang H, Zhang Y, et al. Homing and restorative effects of bone marrow-derived mesenchymal stem cells on cisplatin injured ovaries in rats. Mol Cells. 2014;37(1):65–72.

55. Komaki M, Numata Y, Morikawa K, et al. Exosomes of human placenta-derived mesenchymal stem cells stimulate angiogenesis. Stem Cell Res Ther. 2017;8(1):219.

34. Fu X, He Y, Xie C, Liu W. Bone marrow mesenchymal stem cell differentiation potential of human bone marrow mesenchymal stem cells for inhibiting the apoptosis of ovarian granulosa cells enhanced the follicular microenvironment to recover ovarian function in rats. J Reprod Dev. 2018;64(1):63–70.

58. Li H, Zhao W, Wang L, et al. Human placenta-derived mesenchymal stem cells partially reverse infertility in chemotherapy-induced ovarian failure. Reprod Sci. 2018;25(1):61–68.

40. Gabr H, Rateb MA, El Sissy MH, et al. The effect of bone marrow-derived mesenchymal stem cells on chemotherapy induced ovarian failure in albino rats. Microsc Res Tech. 2016;79(10):938–947.

39. Mohamed SA, Shalaby SM, Abdelaziz M, et al. Human mesenchymal stem cells inhibit apoptosis of granulosa cells induced by IRE1α cytokine milieu. Cytokine Growth Factor Rev. 2001;12(1):53–72.

29. Mohanty S, Jain KG, Nandy SB, et al. Iron oxide labeling does not affect viability, proliferation, migration and angiogenic properties of human amniotic membrane mesenchymal stem cells. Stem Cell Res Ther. 2018;9(1):81.

33. Dabrowska S, Andrzejewska A, Strzemecki D, et al. Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. J Neuroinflammation. 2019;16(1):216.

28. Fu X, He Y, Xie C, Liu W. Bone marrow mesenchymal stem cell transplantation improves ovarian function and structure in rats with chemotherapy-induced ovarian damage. Cytotherapy. 2008;10:353–63.

57. Huang J, Zhang H, Deng W, et al. Human choriocarcinoma-derived mesenchymal stem cells transplantation restores ovarian function in a chemotherapy-induced mouse model of premature ovarian failure. Stem Cell Res Ther. 2019;10(1):81.
71. Ladda M, Chaitat T, Pakpoom K, Sirikul M. The immunosuppressive capacity of human mesenchymal stromal cells derived from amnion and bone marrow. Biochem Biophys Rep. 2016;8:34–40.

72. Ghaseemzadeh M, Hosseini E, Ahmadi M, Kamalzad A, Amirzadeh N. Comparable osteogenic capacity of mesenchymal stem or stromal cells derived from human amnion membrane and bone marrow. Cytotherapy. 2018;20:729–39.

73. Dabrowski FA, Burdzinska A, Kulesza A, Sladowska A, Zolocinska A, Gala K, et al. Comparison of the paracrine activity of mesenchymal stem cells derived from human umbilical cord, amniotic membrane and adipose tissue. J Obstet Gynaecol Res. 2017;43:1758–68.

74. Manochantri S, U-pratya Y, Khoslamai P, Roghishan S, Chayosumrit M, Tantrawatpan C, et al. Immunosuppressive properties of mesenchymal stromal cells derived from amnion, placenta, Wharton’s jelly and umbilical cord. Intern Med J. 2013;43:430–9.

75. Topoluk N, Hawkins R, Tokish J, Mercuri J. Amniotic mesenchymal stromal cells exhibit preferential osteogenic and chondrogenic differentiation and enhanced matrix production compared with adipose mesenchymal stromal cells. Am J Sports Med. 2017;45:2637–46.

76. Li Y, Liu Z, Jin Y, Xing W, Sang Y, Jiang J, et al. Differentiation of human amniotic mesenchymal stem cells into human anterior cruciate ligament fibroblast cells by vitro coculture. Biomed Res Int. 2017;2017:7360354.

77. Fairbairn NG, Randolph MA, Redmond RW. The clinical applications of human amnion in plastic surgery. J Plast Reconstr Aesthet Surg. 2014;67:652–75.

78. Jeong SI, Park Y, Ryu HA, et al. Dual chemotactic factors-secreting human amniotic mesenchymal stem cells via TALEN-mediated gene editing enhanced angiogenesis. Int J Cardiol. 2018;260:156–62.

79. Wang Y, Ma J, Du Y, Mao J, Chen N. Human amnion-derived mesenchymal stem cells protect human bone marrow mesenchymal stem cells against oxidative stress-mediated dysfunction via Erk1/2 MAPK signaling. Mol Cells. 2016;39:186–94.

80. Li J, et al. Human amnion-derived stem cells have immunosuppressive properties on NK cells and monocytes. Cell Transplant. 2015;24:2065–76.

81. Planta S, et al. Amniotic membrane mesenchymal cells-derived factors skew T cell polarization toward Treg and downregulate Th1 and Th17 cells subsets. Stem Cell Rev. 2015;11:394–407.

82. Ono M, et al. Effects of human amnion-derived mesenchymal stromal cell transplantation in rats with radiation proctitis. Cytotechnology. 2015;17:1545–59.

83. Rolfo A, Giuffrida D, Giuffrida MC, Todros T, Calogero AE. New perspectives on umbilical cord and umbilical membrane mesenchymal stem cells for transplantation therapy in rats with radiation proctitis. Cytotherapy. 2015;17:1545–59.

84. Yuan K, et al. Nitric oxide-mediated immunosuppressive effect of human amniotic membrane-derived mesenchymal stem cells on the stability and migration of microglia. Brain Res. 2014;1560:13–9.

85. Jiao H, Shi K, Zhang W, et al. Therapeutic potential of human amniotic mesenchymal stem cells derived from human amnion in plastic surgery. J Plast Reconstr Aesthet Surg. 2014;67:56(1):28–33.

86. Rodrigues CE, Capacha JMC, de Braganca AC, et al. Human umbilical cord-derived mesenchymal stromal cells protect against premature renal senescence resulting from oxidative stress in rats with acute kidney injury. Stem Cell Res Ther. 2017;8:19.

87. Bartolucci J, Verdugo FJ, Gonzalez PL, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: a phase 1/2 randomized controlled trial (RIMECARD trial) [randomized clinical trial of intravenous infusion umbilical cord mesenchymal stem cells on cardiopatthy]. Circ Res. 2017;121(10):1192–204.

88. Zhao Q, Zhang L, Wei Y, et al. Systematic comparison of hUC-MSCs at various passages reveals the variations of signatures and therapeutic effect on acute graft-versus-host disease. Stem Cell Res Ther. 2019;10(1):354.

89. Zhang I, Kong J, Fang L, et al. The protective effects of human umbilical cord mesenchymal stem cells on damaged ovarian function: a comparative study. Bioosci Trends. 2016;10(4):265–76.

90. Jalele L, Rezaie MJ, JaliLI, et al. Distribution of the CM-Dil-labeled human umbilical cord vein mesenchymal stem cells migrated to the cyclophosphamide–injured ovaries in C57BL/6 mice. Iran Biomed J. 2019;23(3):200–8.

91. Li J, Mao Q, He J, et al. Human umbilical cord mesenchymal stem cells improve the reserve function of perimenopausal ovary via a paracrine mechanism. Stem Cell Res Ther. 2017;8(1):55.

92. Lu X, Cui J, Cui L, et al. The effects of human umbilical cord-derived mesenchymal stem cell transplantation on endometrial receptivity are associated with Th1/Th2 balance change and Ulk1 cell expression of uterine in autoimmune premature ovarian failure mice. Stem Cell Res Ther. 2019;10:2124.

93. Zhao Q, Fu X, Jiang J, et al. Umbilical cord mesenchymal stem cell transplantation prevents chemotherapy-induced ovarian failure via the NGF/TkRa pathway in rats. Biomed Res Int. 2019;2019:6539294.

94. Elsafyony AK, Almasry SM, El-Tahouny SA, et al. Human umbilical cord blood-mesenchymal stem cells transplantation renovates the ovarian surface epithelium in a rat model of premature ovarian failure: possible direct and indirect effects. Tissue Cell. 2016;48(4):376–84.

95. Yang Z, Dui X, Wang C, et al. Therapeutic effects of human umbilical cord mesenchymal stem cell-derived microvesicles on premature ovarian insufficiency in mice. Stem Cell Res Ther. 2019;10(1):250.

96. Sun L, Li D, Song K, et al. Exosomes derived from human umbilical cord mesenchymal stem cells protect against cisplatin-induced ovarian granulosa cell stress and apoptosis in vitro. Sci Rep. 2017;7(1):2552.

97. Yin N, Wu C, Qiu J, et al. Protective properties of heme oxygenase-1 expressed in umbilical cord mesenchymal stem cells help restore the ovarian function of premature ovarian failure mice through activating the JNK/Bcl-2 signal pathway-regulated autophagy and upregulating the circulating of CD8+CD28−T cells. Stem Cell Res Ther. 2020;11:49.

98. Yang Y, Lei L, Wang S, et al. Transplantation of umbilical cord-derived mesenchymal stem cells on a collagen scaffold improves ovarian function in a premature ovarian failure model of mice. In Vitro Cell Dev Biol Anim. 2019;55(4):302–11.

99. Ding L, Yan G, Wang B, et al. Transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility. Sci China Life Sci. 2018;61(12):1554–65.

100. Prusa AR, Marton E, Rosner M, Bernaschek G, Hengstschlager M. Oct-4-expressing human amniotic fluid cells by reprogramming with two factors in feeder-free conditions. J Reprod Dev. 2013;59(1):72–7.

101. Cananzi M, De Coppi P. CD117+ amniotic fluid stem cells: state of the art and future perspectives. Human Reprod. 2003;18(7):1154–59.

102. Rai P, Parrish M, Tay IJ, Li N, Ackerman S, He F, et al. Streptococcus pneumoniae secretes hydrogen peroxide leading to DNA damage and apoptosis in lung cells. Proc Natl Acad Sci U S A. 2015;112:63421–30.

103. van der Vliet A, Janssen-Heininger YM. Hydrogen peroxide as a damage signal in tissue injury and inflammation: murderer, mediator, or messenger? J Cell Biochem. 2014;115:427–55.

104. Laburskoy VM, Gladyshev VN. Role of reactive oxygen species-mediated signaling in aging. Antioxid Redox Signal. 2013;19:1362–72. https://doi.org/10.1089/ars.2012.4891.

105. Ding C, Zou Q, Wang F, et al. Human amniotic mesenchymal stem cells improve ovarian function in natural aging through secreting hepatocyte growth factor and epidermal growth factor. Stem Cell Res Ther. 2018;9:555.

106. Liu JY, Ren K-K, Zhang W-J, et al. Human amniotic mesenchymal stem cells and their paracrine factors promote wound healing by inhibiting heat stress-induced skin cell apoptosis and enhancing their proliferation through activating PI3K/AKT signaling pathway. Stem Cell Res Ther. 2019;10(1):247.

107. Ranjarban H, Abediankarani S, Mohammadi M, et al. Wharton’s jelly derived-mesenchymal stem cells: isolation and characterization. Acta Med Iran. 2018;56(1):28–33.
114. Perin L, Sedrakian S, Da Sacco S, De Filippo R. Characterization of human amniotic fluid stem cells and their pluripotential capability. Methods Cell Biol. 2008;86:85–99.

115. Phromthai T, Ogilvin Y, Julavijitphong S, Titapant V, Chuenwattana P, Vantansiri C, Pattaranapanyasat K. A novel method to derive amniotic fluid stem cells for therapeutic purposes. BMC Cell Biol. 2010;11:79.

116. Antonucci D, Di Pietro R, Alfonsi M, et al. Human second trimester amniotic fluid cells are able to create embryoid body-like structures in vitro and to show typical expression profiles of embryonic and primordial germ cells. Cell Transplant. 2014;23(12):1501–15.

117. Liu T, Xu F, Du X, Lai D, Zhao Y, Huang Q, et al. Establishment and characterization of multi-drug resistant, prostate carcinoma-initiating stem-like cells from human prostate cancer cell lines. Mol Cell Biochem. 2010;340:265–73.

118. Liu T, Zou G, Gao Y, Zhao X, Wang H, Huang Q, et al. High efficiency of reprogramming CD34+ cells derived from human amniotic fluid into induced pluripotent stem cells with Oct4. Stem Cells Dev. 2012;21:2322–32.

119. Liu T, Huang Y, Guo L, et al. CD44+/CD105+ human amniotic fluid mesenchymal stem cells survive and proliferate in the ovary long-term in a mouse model of chemotheraphy-induced premature ovarian failure. Int J Med Sci. 2012;9(7):592–6.

120. Thabet E, Yusuf A, Abdelmonef DA, et al. Extracellular vesicles miRNA-21: a potential therapeutic tool in premature ovarian dysfunction. Mol Hum Reprod. 2020;26:103a06.

121. Trayco SA, Ahmed A, Tiggles JC, et al. A comparison of clinically relevant sources of mesenchymal stem cell-derived exosomes: bone marrow and amniotic fluid. J Pediatr Surg. 2019;54(18):86–90.

122. Cui CH, Uyama T, Miyado K, et al. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol Biol Cell. 2007;18:1586–94.

123. Lai D, Guo Y, Zhang Q, et al. Differentiation of human menstrual blood-derived endometrial mesenchymal stem cells into osteocyte-like cells. Acta Biochim Biophys Sin. 2016;48(11):988–1005.

124. Khoury M, Alcayaga-Miranda F, Illanes SE, et al. The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy. Front Bioeng Biotechnol. 2014;2:1548.

125. Alcayaga-Miranda F, Cuenca J, Luz-Crawford P, et al. Characterization of menstrual stem cells: angiogenic effect, migration and hematopoietic stem cell support in comparison with bone marrow mesenchymal stem cells. Stem Cell Res Ther. 2015;6:32.

126. Liu T, Huang Y, Zhang J, et al. Transplantation of human menstrual blood stem cells to treat premature ovarian failure in mouse model. Stem Cells Dev. 2014;23:1548–57.

127. Chen L, Jingjing Q, Xiang C. The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. Stem Cell Res Ther. 2019;10:1.

128. Wang Z, Wang Y, Yang T, et al. Study of the reparative effects of menstrual stem cells combined with estrogen on regulatory T cells in patients with premature ovarian insufficiency. Cell Transplant. 2014;23(12):1501–15.

129. Shi D, Liao L, Zhang B, et al. Human adipose tissue-derived mesenchymal stem cells facilitate the immunosuppressive effect of cyclosporin A on T lymphocytes through Jagged-1-mediated inhibition of NF-κB signaling. Exp Hematol. 2011;39:214–24.

130. Xue CL, Shen YM, Li X, et al. Exosomes derived from hypoxia-treated human adipose mesenchymal stem cells enhance angiogenesis through the PKA signaling pathway. Stem Cells Dev. 2018;27(7):456–65.

131. Huang B, Liu J, Ding C, et al. Exosomes derived from human adipose mesenchymal stem cells improve ovary function of premature ovarian insufficiency by targeting SMAD. Stem Cell Res Ther. 2018;9:216.

132. Song K, Cai H, Zhang D, et al. Effects of human adipose-derived mesenchymal stem cells combined with estrogen on regulatory T cells in patients with premature ovarian insufficiency. Int Immunopharmacol. 2018;55:257–62.

133. Lai D, Wang F, Dong Z, et al. Skin-derived mesenchymal stem cells help restore function to ovaries in a premature ovarian failure mouse model. PLoS One. 2014;9(5):e87499.

134. Zhang B, et al. HuMSC-exosome mediated-Wnt4 signaling is required for cutaneous wound healing. Stem Cells. 2015;33:2158–68. https://doi.org/10.1002/stem.1771.

135. Lou G, Chen Z, Zheng M, Liu Y. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. Exp Mol Med. 2017;49(6):e346.

136. Zhang M, Jin K, Gao L, Zhang Z, Li F, Zhou F, Zhanh L. Methods and technologies for exosome isolation and characterization. Small Methods. 2018;2:1800021.

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