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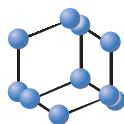
The Therapeutic Effect of Stem Cells on Chemotherapy-Induced Premature Ovarian Failure

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Abstract: Premature ovarian failure (POF) refers to ovarian dysfunction in women under 40 years old. It is characterized by low estrogen, high gonadotropin, amenorrhea, and infertility, which seriously affect physical and mental health of women. The pathogenic factors of POF include iatrogenic factors, autoimmune factors, genetic factors, oxidative stress, infection, thyroid dysfunction, and adrenal diseases. Chemotherapy is a common cause of POF and is gaining increasing attention. With the development of modern medicine and advances in understanding cancer, women's cancer survival rates have been significantly increased. Currently, the main treatment options for POF are hormone supplement and *in vitro* activation (IVA), but there is still no specific treatment for POF. Stem cells, known as undifferentiated cells of multicellular organisms, exhibit characteristics of self-renewal, directional differentiation into different cells, and low immunogenicity. Thus, they have potential in regenerative medicine and provide a promising direction for POF treatment. In this review, we summarize the latest research progress of various stem cells in chemotherapy-induced POF models to provide a theoretical basis for further research and treatment.

1. INTRODUCTION

Premature ovarian failure (POF), also known as primary ovarian insufficiency(POI), is characterized by the cessation of follicular production, amenorrhea, low estrogen, and high serum gonadotropin before the age of 40 [1]. It is a serious disease that endangers women's physical and mental health. The incidence of POF increases with age; the highest incidence rate is observed in 40-year-old women. The incidence of POF is around 1/10000 in 20-year-old women and ~1% in 40-year-old women [2]. POF pathogenesis includes iatrogenic factors (such as chemotherapy), autoimmune factors, genetic factors, thyroid and adrenal diseases, infection, oxidative stress, and idiopathic factors [3]. For different forms of POF, the early stage of ovarian function loss is usually asymptomatic. Currently, patients are often diagnosed

with POF at a relatively late stage [4]. Most of the follicles have been exhausted, and as the patients age, the quality of the remaining follicles also declines. Therefore, treating POF patients with fertility supplements is extremely difficult. At present, the first-line treatment of POF is hormone replacement therapy (HRT). For patients with POF, long-term HRT treatment can control POF symptoms and prevent the adverse consequences of POF. However, HRT treatment cannot restore ovarian function effectively, and long-term HRT treatment will also have many adverse consequences, such as cardiovascular disease and osteoporosis [5]. A 2016 study showed that long-term HRT treatment is one of the triggers of breast cancer [6]. *In vitro* activation (IVA) is another approach to treating POF. After IVA treatment, the number of mature oocytes in POF patients can increase, and the patients can successfully have their own children [7]. However, this treatment is ineffective when the quality of age-related oocytes has decreased. With the development of regenerative medicine, stem cell therapy is considered a new and effective method for

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POF treatment, and different types of stem cells have been used to treat POF.

Cancer has always been a worldwide health problem that is a major burden for patients and doctors. In the United States, more than 1.8 million new cancer cases are estimated to occur in 2020 [8]. As a result of advances in medicine, including cancer screening, diagnosis, and treatment, cancer mortality has decreased by about 29% from 1991 to 2017 [8]. However, about 5.8% of women will be affected by cancer before the age of 50 [8]. The four most common cancers in women are breast cancer (30%), lung cancer (12%), colon cancer (8%), and uterine corpus cancer (7%) [8]. With reduced mortality and improved survival rates (the five-year survival rate of breast cancer patients is 90%), complications after cancer treatment will be another serious problem that people will face. Among them, impaired fertility is one long-term side effect of cancer treatment.

Chemotherapy is a standard treatment for cancer and is a common cause of POF. About one-third of women diagnosed with cancer under the age of 40 develop POF after chemotherapy [9]. It can damage different organs, depending on the patient's sex and age. The ovary is often damaged by chemotherapy. Studies have shown that anticancer drugs can cause different degrees of ovarian damage, resulting in a decline in fertility [10]. In ovaries, chemotherapy-induced DNA damage, such as DNA double-stranded breaks, can induce apoptosis of granulosa cells (GCs) and oocytes [11]. The toxic effect of chemotherapy on dormant primordial follicles has not yet been reported, but chemotherapy can activate dormant primordial follicles, leading to the failure of the dormant follicle pool [11]. There are two main mechanisms underlying the effect of chemotherapy drugs on follicles: phosphatidylinositol 3-kinase (PI3K)-dependent signal pathway mediated activation of primordial follicles and tumor suppressor protein TP53 (p53)-dependent apoptosis [12]. The PI3K/phosphatase and tensin homolog deleted on chromosome ten (PTEN)/protein kinase B (Akt) signaling pathway has been shown to regulate the activation of ovarian resting follicles [13, 14]. The balance of the PI3K pathway is important for activating resting primordial follicles. PTEN plays a key negative regulatory role in the PI3K signaling pathway [14]. Chemotherapeutic drugs activate the PI3K/Akt signaling pathway, which results in the continuous activation of the primordial follicles in dormancy [15]. TAp63 is a key factor in the p53 pathway [16, 17] and is a homolog of p53 that exists in the nuclei of oocytes. Chemotherapeutic drugs induce DNA damage in oocytes, inducing checkpoint kinase 2 (CHK2) and subsequently activating TAp63. As a result, several downstream factors, including Phorbol-12-Myristate-13-Acetate-Induced Protein 1 (NOXA), p53-upregulated modulator of apoptosis (PUMA), and TAp73 (another homolog of p53), are activated, resulting in the DNA damage-induced programmed cell death of oocytes [12]. Vascular damage and ovarian cortex fibrosis are also involved in chemotherapy-induced ovarian damage [18]. According to their types and functional classifications, commonly used chemotherapy drugs include alkylation molecules, platinum molecules, anthracyclines, vinblastine, antimetabolic products, the taxane family of related drugs, and others. They can damage ovaries to varying degrees [12]. Among them, alkylation molecules cause the most significant damage to ovarian tissues since their active metabolites crosslink with oocyte DNA, inhibiting their synthesis and function. The most serious damage is DNA double-strand breaks, which can be induced by cyclophosphamide (CTx) and lead to apoptosis. Platinum-based compounds can also bind to DNA to form crosslinks. Antimetabolites, such as methotrexate, inhibit the synthesis of DNA and RNA, whereas vinblastine inhibits cell mitosis. Anthracycline antibiotics inhibit DNA synthesis and function. Adriamycin can also cause interstitial fibrosis and ovarian vascular abnormalities in a dose-dependent manner [19]. In mice, CTx can induce estrous cycle disorders, decrease estrogen, increase follicle-stimulating hormone (FSH), and cause follicular abnormalities. Therefore, CTx is often used to establish mouse models of chemotherapy-induced POF.

2. STEM CELL TREATMENT IN CHEMOTHERAPY-INDUCED POF

Stem cells are the undifferentiated cells of multicellular organisms. There are four types of stem cells, i.e., unipotent stem cells, multipotent stem cells, pluripotent stem cells, and totipotent stem cells. Pluripotency is mainly influenced by the expression of transcription factors, such as octamer-binding transcription factor 4 (OCT4), sex determining region Y-box 2 (SOX2h), lin-28 homolog A (Lin28), and Nanog Homeobox (NANOG) [1]. Stem cells are found in the embryonic, fetal, and adult life stages. Stem cells have the characteristics of general cells, such as self-division abilities. They also have characteristics that general cells do not have, such as self-renewal abilities. They can also differentiate into other cell lineages, if the differentiated cells are still stem cells, they will also have self-renewal abilities, such as pluripotent stem cells differentiate into unipotent stem cells. This feature enables stem cells to treat a variety of cellular diseases, such as leukemia. However, to ensure that stem cells differentiate into the target cell lineage and promote their survival and division in patients, it is necessary to overcome the rejection of stem cells by the patients' immune system. At the same time, it is also essential to consider the technical difficulties and ethical limits associated with obtaining various types of stem cells from different tissues. Surprisingly, adipose mesenchymal stem cells (ADMSCs) are not easier to obtain than embryonic stem cells (ESCs), and there are fewer ethical concerns regarding their use. In the treatment of infertility based on stem cells, ESCs, induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), extraembryonic tissue stem cells, and ovarian stem cells (OSCs) have been used [20]. In chemotherapy-induced POF mice, various stem cell therapies can be used to stimulate ovulation and improve symptoms. Several studies have described

different methods to isolate and culture stem cells for POF therapy [21]. Here, we review the recent progress in the use of stem cells to treat chemotherapy-induced POF.

3. ESCs

ESCs are pluripotent cells with self-renewal capacity that are isolated from mammalian blastocysts [22-24]. As ESCs have an independent replication ability and can differentiate into many cell types, their application in regenerative medicine has sparked great interest [22-24]. In Liu's study [25], extracellular vesicles (EVs), derived from ESCs (ESCs-EVs), were found to restore the hormones estradiol (E2), anti-mullerian (AMH), and FSH to normal levels, reduce atresia, and increase the number of normal follicles. EVs are secreted by many types of cells, participate in the communication between cells, and regulate receptor cells' function by transferring small molecule proteins, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and cytokines [26]. They share similar functions with their parent cells in promoting tissue regeneration. At the same time, they can avoid the potential risks associated with cell transplantation and provide a safer alternative for clinical treatment [27]. This study found that the PI3K/Akt pathway was downregulated by CTx and that ESCs-EVs restored ovarian function by activating the PI3K/Akt pathway, thereby inhibiting the apoptosis of GCs [25].

4. INDUCED PLURIPOTENT STEM CELLS

iPSCs are produced by reprogramming adult cells with specific transcription factors [28]. During the process of iPSC reprogramming, OCT4, SOX2h, Lin28, and NANOG play an important role [29]. In 2013, Liu *et al.* [30] reported that microRNA-17-3p (miR-17-3p) induced the differentiation of human iPSCs (hiPSCs) into hormone-sensitive ovarian epithelial (OSE)-like cells via the inhibition of vimentin expression. When OSE-like cells were transplanted into a POF mouse model, vimentin expression decreased whereas E2 levels and ovarian weight increased. Kang *et al.* demonstrated that, *in vitro*, mouse iPSCs differentiated into functional GC-like cells, synthesizing and secreting E2 [31]. Juan Zhang *et al.* [32] observed that functional GC-like cells generated from iPSCs and ESCs in rats express the specific GC receptors, but whether these cells are *bona fide* GCs needs to be confirmed. When co-cultured with GCs, iPSCs and ESCs showed similar changes in morphology, functions, and gene expression [32]. In 2015, Leng *et al.* [33] successfully reprogrammed iPSCs in POF patients. The iPSCs' morphology, function, and gene expression were similar to those of hESCs. In addition, in the presence of bone morphogenetic protein4 (BMP4) and Wnt3a, the iPSCs could differentiate into germ cells. Therefore, iPSCs may address two important problems in using ESCs: human immune rejection after stem cell transplantation and ethical problems associated with using human embryos that are difficult to overcome.

5. EXTRAEMBRYONIC STEM CELLS

Amniotic fluid stem cells (AFSCs) provide a new direction for stem cell therapy to treat POF because of their primitive state, low immunogenicity, and easy accessibility [34, 35]. AFSCs have similar morphology, immunophenotypes, and mesoderm differentiation potential to MSCs. However, AFSCs are easier to obtain from amniotic fluid and proliferate faster than MSCs. Furthermore, unlike ESCs and iPSCs, AFSCs do not develop into teratomas *in vivo* [36]. In 2014, Xiao *et al.* [37], using a CTx-induced POF mouse model system, showed that AFSCs could increase healthy follicles and restore fertility. AFSCs can prevent follicular atresia and increase the number of healthy follicles. The transplanted AFSCs were not involved in follicular development, and there was no evidence that AFSCs directly differentiated into GCs to replace the damaged cells in POF mouse ovaries. Some studies have shown that AFSCs can secrete a variety of cytokines, such as TGF-β and vascular endothelial growth factor (VEGF), which are necessary for follicular development [38-41]. In 2016, Xiao *et al.* [42] confirmed that exosomes from AFSCs have an anti-apoptosis effect on GCs damaged by CTx. Exosomes are particles separated from the endoderm after fusion with the plasmalemma. Exosomes released by stem cells are a newly discovered means of cell-cell interaction and provide a promising approach for stem cell therapy [43]. GCs are necessary for follicles' survival. AFSCs-derived exosomes can prevent follicular atresia induced by CTx in mice by delivering microRNAs highly enriched in miR-146a and miR-10a. These two miRNAs can regulate the anti-apoptotic effect of GCs injured by CTx *in vitro*, and miR-10a plays a leading role. MiR-10a can also be delivered into CTx-induced mice directly through liposomes and can inhibit the apoptosis of ovarian cells and preserve atretic follicles effectively [42]. Chemotherapy drugs, such as CTx, can stimulate the activation of the p53 pathway and its downstream targets, including Casp9 and Bim, thus leading to cell apoptosis [44]. Mir-10a regulates apoptosis by inhibiting apoptosis promoting factor Bim [42]. Zhang *et al.* [45] injected human amniotic epithelial cells (hAECs) into the unilateral ovaries of POF mice and observed healthy mature follicles in the ovaries of these treated mice.

6. MSCs

MSCs are multipotent stem cells derived from the mesoderm that are easy to obtain and have low immunogenicity [46]. MSCs can be obtained from a variety of tissues, including, but not limited to bone, umbilical cord, placenta, endometrium, amniotic fluid, and adipose tissue [47]. MSCs are widely used to treat various diseases. Different kinds of MSCs have been reported that can restore the ovarian function of mice with chemotherapy-induced POF.

6.1. Human Endometrial Mesenchymal Stem Cells

In 2004, stem cells derived from the endometrium were identified [48]. In 2012, further studies elucidated

the presence of endometrial mesenchymal stem cells (EMSCs) in the endometrium [49]. In 2015, Lai *et al*. [50] isolated human EMSCs (hEMSCs) from menstrual blood and transplanted them into busulfan- and CTx-induced POF mice. The results showed that the transplantation of hEMCSs increased the weight of mice, improved the estrus cycle, and restored fertility. In 2019, Reig A *et al*. [51] transplanted the entire uterine cell (UC) preparation containing EMSCs into the CTx-induced chemotherapy POF mouse model. After one week, the number of primordial follicles and oocytes in the ovaries of mice receiving UC increased significantly, and follow-up observations showed that the pregnancy rate and fertility rate also increased significantly.

Epirubicin is a first-line chemotherapy drug widely used in cancer treatments [52]. Epirubicin may inhibit the activity of CDC2/CyclinB1 complexes by increasing GADD45b protein expression in the GCs' cell cycle, thus inhibiting GC proliferation and inducing POF [53]. In 2019, Guo F *et al*. [53] found that menstrual blood-derived mesenchymal stem cells (MB-MSCs) could inhibit GADD45b expression in the cell cycle pathway, repair the damage caused by epirubicin, increase the levels of E2 and AMH, increase the number of follicles, and reduce the number of atresia follicles in POF mice. However, 28 days after transplantation, the estrous cycle of POF mice had not recovered significantly. Bushen Tiaochong Recipe (BSTCR) is a traditional Chinese medicine prescription with the expression of FSHR and insulin-like growth factor-1 (IGF-1) mRNA, which can improve GCs' response to gonadotropins, promote GCs' proliferation in ovaries, and enhance the secretion of steroid hormones [54]. In 2019, Guo *et al*. [55] found that MB-MSCs, combined with BSTCR, increased the expression of CDC2 and CyclinB1 by downregulating GADD45b expression, resulting in increased levels of serum E2 and AMH, decreased serum FSH, increased numbers of follicles at all levels, decreased atresia follicles, and recovery of the estrus cycle.

6.2. Chorionic Plate MSCs

Chorionic plate MSCs (CP-MSCs) are a type of MSCs isolated from the chorionic plate of human placentas. Similar to bone marrow mesenchymal stem cells (BMSCs), CP-MSCs can secrete a variety of growth factors [56]. In 2018, Lij *et al*. [57] found that serum E2 and FSH levels basically returned to normal, the number of follicles increased, and the estrous cycle almost fully recovered after six weeks of intravenous injections of CP-MSCs into CTx-induced POF mice. After transplantation, superovulation showed that the number of oocytes had increased significantly. In addition, CP-MSCs can secrete low VEGF levels and high IGF-1 levels, platelet-derived growth factor, and hepatocyte growth factor (HGF).

6.3. Human Amniotic MSCs

Human amniotic mesenchymal stem cells (hAMSCs) share similar characteristics with MSCs, and

they also have the same phenotypic characteristics as ESCs [58]. In 2019, Li *et al*. [59] found that the effects of treating CTx-induced POF rats with hAMSCs were mediated mainly through a paracrine mechanism. hAMSCs did not differentiate into oocytes or GCs but secreted a variety of growth factors, such as granulocyte-colony-stimulating factor (G-CSF), IGF-1, HGF, VEGF, and fibroblast growth factor 2 (FGF2). hAMSCs can improve the local microenvironment of ovaries in POF rats, increase the ratio of *B-cell lymphoma-2* (*Bcl-2*)/*Bcl-2*-associated X protein (Bax) and endogenous VEGF expression, inhibit GCs' apoptosis, and promote angiogenesis to reduce ovarian damage and restore ovarian function. In addition, another study in 2017 [60] observed that low-intensity pulsed ultrasound pretreatment enhanced hAMSCs' paracrine effect.

In 2019, Jalalie *et al*. [61] transplanted human umbilical vein mesenchymal stem cells (HuCV-MSCs), labeled with CM-Dil, into CTx-induced POF mice. They observed that HuCV-MSCs' distribution in different parts of the ovary was not uniform. Most of them migrated to the medulla and stroma of the ovaries, and a small number migrated to the cortex and germinal epithelium of the ovaries. This may result from the fact that the medulla is rich in blood vessels, which is conducive to the paracrine effect of MSCs and the formation of new blood vessels. This is consistent with other MSCs reports [59, 62-64].

In 2019, Huang *et al*. [65] extracted the liver tissue from healthy early pregnancy fetuses (10-12 weeks) by legal abortion and extracted the fetal MSCs (fMSCs) from the liver. They transplanted fMSCs into CTx-induced POF mice and found that they played an antioxidant role by downregulating reactive oxygen species, malondialdehyde (MDA), and lactate dehydrogenase (LDH); upregulating superoxide dismutase (SOD), glutathione reductase, catalase (CAT), and glutathione peroxidase (GPx) levels. fMSCs also restored the number of follicles and serum sex hormone levels. In addition, fMSCs may enhance GCs' biological activity by modulating melatonin membrane receptor 1 (MT1) and its downstream genes.

6.4. Human ADMSCs

Human ADMSCs (hADMSCs) can be derived from adult fat tissues. Compared with other MSCs, extracting hADMSCs is simple and minimally invasive, and they can be amplified stably under basic culture conditions [66, 67]. Previous studies have shown that hADMSCs have been used to treat POF [66]. SMA and mother against decapentaplegic (MAD)-related proteins (SMADs) play a key role in germ cell development. SMAD2 and SMAD3 regulate follicular development and ovulation to maintain female reproductive ability. SMAD3 knockout mice show ovulation defects [68]. SMAD5 plays a role in primordial germ cells' proliferation. SMAD5 knockout increased germ cell apoptosis and apoptosis-related gene levels, such as *Fas*, *FasL*, *caspase-8*, and *caspase-3* [69]. Huang *et al*. [70] found that exosomes derived from hADMSCs

could reverse the downregulated mRNA and protein expression levels of SMAD2, SMAD3, and SMAD5 in CTx-induced POF mice. At the same time, the protein expression levels of *Fas*, *FasL*, *caspase-3*, and *caspase-8* were significantly lower after treatment with hADMSC-derived exosomes. This suggests that the ovarian function of POF can be improved by regulating SMAD signaling pathways using hADMSCs, which is consistent with previous studies [45, 71].

6.5. Human Umbilical Cord MSCs

There are a large number of MSCs in cord tissue, which are termed human umbilical cord mesenchymal stem cells (UCMSCs) [72]. In 2013, Wang *et al*. used UCMSCs to treat POF [46]. In 2017, Li *et al*. [73] found that UCMSCs secrete IGF-1, VEGF, and HGF after transplantation into rats. In 2019, Yang *et al*. [74] combined collagen scaffolds with UCMSCs to provide a three-dimensional microenvironment, successfully improving the survival rate and high expression of VEGF, TGF -β1, FGF2, and HGF in UCMSCs, thus promoting GC proliferation. In 2017, Sun *et al*. [75] used hUCMSC-derived exosomes to improve cisplatin-induced GC stress and apoptosis *in vitro*. In 2019, Yang *et al*. [76] extracted microvesicles (MVs) from the supernatant of cultured hUCMSCs. MVs are a type of vesicle with a diameter of less than 1 μm that carry membrane and cytoplasmic components of the source cells. Through surface-expressed ligands and receptors, MVs transfer mRNA and protein to the target cells, thereby affecting their phenotype and function [77]. MSCs are the main cells that produce MVs, and their secretory activity is at least 10 times higher than that of other cells [78]. MVs released by MSCs can protect tissues *in vivo* and *in vitro* and promote tissue repair. Four weeks after hUSMSC-MVs transplantation, the number of blood vessels and CD34$^+$ cells in the ovaries of POF mice increased significantly. In addition, the expression levels of total Akt, p-Akt, and VEGF in POF mouse ovaries were increased significantly, suggesting that hUCMSC-MVs may activate the PI3K-Akt signaling pathway, promote VEGF expression, and induce the formation of new blood vessels [79].

6.6. BMSCs

BMSCs are a type of low immunogenicity adult stem cells that widely exist in the bone marrow microenvironment. BMSCs are the first MSCs used to evaluate the efficacy of chemotherapy-induced POF rat models on ovarian function [80]. BMSCs can improve POF through various mechanisms. In POF mice, BMSCs were induced by cytokines and migrated to the ovary but did not differentiate into oocytes [79]. The migration and homing of BMSCs are influenced mainly by chemokines and growth factor receptors, such as IL-8 and HGF receptors [81]. BMSCs migrated to the hilum, medulla, and cortex [62]. This is mainly due to the rich medullary vessels, which are conducive to the expression of VEGF, FGF-2, and IL-6 in BMSCs and promote the formation of arteries *in vitro* and *in vivo* through paracrine mechanisms [79]. BMSCs can also

inhibit GCs' apoptosis. BMSCs can upregulate *Bcl-2* and proto-oncogene (*c-myc*), downregulate the expression of *cyclin-dependent kinase inhibitor 1A* (*p21*) and Bax, and play an anti-apoptosis role [80, 82]. Ovarian atrophy and fibrosis are known to occur in POF models. After BMSC transplantation, the collagen content decreased significantly. This was related to HGF, bFGF, and adrenomedullin (ADM) [79]. In addition, BMSCs can also play an immunomodulatory role by not only inhibiting the function of immune cells leading to immune tolerance, but they can also secrete anti-inflammatory factors and inhibit inflammation [83]. In addition, in 2017, Fu *et al*. [84] found that BMSCs can overexpress miR-21, target to downregulate programmed cell death 4 (PDCD4) and PTEN, enhance PI3K/Akt signaling, inhibit the apoptosis of GCs, and preserve ovarian function. In 2019, Yang *et al*. [85] found that the extracellular mir-144-5p of BMSCs had the same effect on PTEN. Sun *et al*. [86] confirmed that miR-644-5p, carried by BMSC exosomes, could be transferred to GCs to regulate p53 expression, thus inhibiting GC apoptosis.

7. OSCs

The traditional view is that the number of oocytes in female mammals' follicular pool is fixed after birth and gradually declines until depletion after puberty [87]. However, Johnson *et al*. found that, when they observed follicular atresia in POF mice at different times, the incidence of atresia was higher than that of reduction [88]. As a result, they speculated that ovarian cells could produce new follicles. Subsequently, it was found that OSCs play a role in inducing ovarian regeneration and maintaining ovarian function [89]. Many studies have verified OSCs' existence in several mammals using various methods, such as stem cell separation and purification [90-92]. OSCs are dual potential stem cells, derived from the ovarian cortex, that can generate new stem cells through symmetrical division. They can also differentiate into ovarian germ cells and primordial GCs through asymmetric division [93, 94]. The discovery of OSCs provides a new direction for further understanding ovarian follicle renewal and endocrine function in the reproductive cycle. It also brings a new potential strategy for promoting POF treatment. The existence of OSCs is well-known in non-mammalian model organisms, such as drosophila, but they are rarely used in mammals [95]. Liu *et al*. suggest that OSCs can improve the treatment of infertility and may solve POF disease in the near future [96].

CONCLUSION

The loss of normal ovarian function in women before the age of 40 is known as POF, which can lead to infertility and other complications. With the increasing use of chemotherapy, POF has gained increasing attention. Due to POF's specificity and complexity, there is still no specific treatment for POF. In recent years, a variety of stem cells has been used and achieved promising results in chemotherapy-

induced POF models. Almost all studies have provided evidence that stem cells from different sources play a role in POF treatment, but clinical experiments are more limited. Furthermore, determining how to reduce the immune risk of stem cell transplantation and increase the success rate of stem cell treatment is still a problem that needs to be addressed.

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The authors declare no conflict of interest, financial or otherwise.

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