Journal of Biosciences and Medicines, 2024, 12, 263-280
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Current Status of Stem Cells in the Treatment of Premature Ovarian Failure

Guojie Ji[1,2], Huanhuan Hu[1], Rui Liu[1], Guanjie Li[1], Jiangshan Zhao[1], Huigen Feng[1,2*]

[1]Key Laboratory of Fertility Preservation, Sanquan College of Xinxiang Medical University, Xinxiang, China
[2]School of Life Sciences and Technologies, Xinxiang Medical University, Xinxiang, China
Email: jiguojie87@163.com, *huigenfeng1963@163.com

How to cite this paper: Ji, G.J., Hu, H.H., Liu, R., Li, G.J., Zhao, J.S. and Feng, H.G. (2024) Current Status of Stem Cells in the Treatment of Premature Ovarian Failure. *Journal of Biosciences and Medicines*, **12**, 263-280.
https://doi.org/10.4236/jbm.2024.127025

Received: June 17, 2024
Accepted: July 21, 2024
Published: July 24, 2024

Abstract

Premature ovarian failure (POF) is a prevalent cause of female infertility. POF features include estrogen hypofunction, amenorrhea, infertility, and high gonadotropin levels. The etiology of POF is genetic diseases, autoimmune diseases, enzyme defects and environmental factors. The development of Regenerative medicine has made stem cell and exosome (EXOs) therapy effective for POF. This review discusses POF stem cell research and development.

Keywords

Etiology, Infertility, Premature Ovarian Failure, Regenerative Medicine, Stem Cells

1. Introduction

Premature ovarian failure (POF), also known as primary ovarian insufficiency, is among the important causes of female infertility [1]. POF prevalence in women is 0.01% at 20, 0.1% at 30, and 1% at the age of 40; however, it has been rising recently [2]. Clinical study has demonstrated that POF is characterized by amenorrhea, low estrogen, elevated gonadotropin, premenopausal syndrome, and infertility [3].

POF is a heterogeneous disease with diverse pathogenesis, including chromosomal, genetic, autoimmune, metabolic, infectious and iatrogenic factors [4]. Currently, conventional treatment methods mainly include hormone replacement, immune regulation, and stem cell therapy [1]. However, existing treatments for POF are less effective; POF has negative consequences like increased risk of cardiovascular diseases and breast and ovarian cancer, osteoporosis and sexual dysfunction [5]. POF is caused by numerous complex factors, including

radiotherapy, chemotherapy, targeted therapies (bevacizumab and tyrosine kinase inhibitors), and antiangiogenic drugs [4].

MSCs can be formed from bone marrow, adipose tissue, amniotic fluid, umbilical cord tissue, placental tissue, and menstrual blood and have minimal immunogenicity and multidirectional division [6]. Many researchers consider that MSCs can restore ovarian function and treat infertility [7]. EXOs have been increasingly studied in recent years. EXOs derived from different cells (bone marrow mesenchymal stem cells (BMSCs), endothelial cells of human aorta (HAEC), amniotic fluid-derived stem cells (AFSCs) and human adipose mesenchymal stem cells (HAMSCs)) are vital in treating POF [8]-[11]. Further data suggest that MSCs and EXOs may treat POF, although more research is needed to understand the mechanisms.

2. Etiology of POF

2.1. Role of Genetics

POF may have numerous gene mutations. Only a few POF cases are reported for each mutation [12]. X chromosome and autosomal disorder have been observed to play an important role in POF cases [13]. Structural abnormalities and translocations between X chromosomes and autosomal, including Turner syndrome, trisomy X, fragile X syndrome, X-linked gene mutations and premutations, and autosomal-related gene abnormalities [14]. The causes of POF are summarized in Table 1.

Table 1. Etiology summary of POF.

Etiology	Example	References
X chromosome	Turner syndrome	[15]
	Bone Morphogenetic Protein15 (BMP15)	[18]
	Fragile X Syndrome	[20] [22]
Autosomal	Mutations in the LH and FSH receptors	[24]
	Galactosemia, Inhibin mutations	[25]
	Mutations of *FOXL2*, *NOBOX*, *INHA*, *SF1*, *GDF9*	[26] [27]
Autoimmunity	Vitiligo, Myasthenia gravis, Addison's disease, Systemic lupus erythematosus, Celiac disease, Autoimmune polyglandular syndrome	[4] [32]
	$CD4^+$T cells, $CD4^+/CD8^+$ cells	[35]
Chemoradiotherapy	Cyclophosphamide, Docetaxel, Pirarubicin	[17]
Environmental	Smoking, Viral infections	[40] [41]
Vaccination	HPV-vaccination	[42]
Enzyme deficiency	17,20-Delactase	[46]
	17a-hydroxylase	[47]

2.1.1. X Chromosome Abnormality

Genetically, ovarian failure is associated with X-chromosome abnormalities. Ovarian dysplasia, characterized by primary amenorrhea, short stature, and specific phenotypic traits, can also be caused by minor chromosomal abnormalities like deletions, homologs, X-autosomal translocation, and Turner syndrome [15]. Oocyte failure occurs in women with Turner syndrome due to partial X chromosomal deletion [16]. Ovarian function is affected by zinc finger X-chromosomal protein (ZFX) and ubiquitin-specific peptidase 9 X-linked (USP9X) on the short arm of the X chromosome [17]. Moreover, studies have also reported that missense mutation of BMP15, located on Xp11·2, leads to POF; this gene is only expressed in the ovary and involved in follicular development [18].

Fragile X chromosomes raise follicle-stimulating hormone (FSH) lebels in women [19]. About 20% of women with Fragile X precursor mutations show symptoms of Fragile X, associated primary ovarian insulinicity (FXPOI) [20]. Fragile X syndrome is a triple repeat disorder caused by mutations in the Fragile X type mental retardation 1 (FMR1) [21]. Genes linked to premature births have about 60 to 199 copies and are not considered deleterious [22]. Preliminary studies suggest that unimpaired heterozygotes may have premature menopause and higher twin birth rates, symptoms of ovarian failure [23].

2.1.2. Autosomal Disease

Other genetic causes of POF are monogenic disorders, including galactosemia and inhibin mutations [24]. POF occurs in 70% - 80% of people with galactosemia, a rare autosomal recessive condition. Because galactose is poisonous to follicles, the initial number of oogonia declines and atresia follicles rise during the fetal period [25]. Studies have shown that mutations in *FOXL2*, *NOBOX*, *GDF9*, *SF1*, and *INH-α* lead to POF during folliculogenesis [26] [27]. *FOXL2* is a single-exon gene expressed in undifferentiated granulosa cells that encodes a forkhead transcription factor and is crucial in ovarian maintenance and development [28]. *NOBOX* works in early folliculogenesis, and without *NOBOX* in mice, the transition from primordial to growing follicles is blocked [29]. SF1 is expressed in various cells in adults and fetuses and affects reproductive development [30]. Gene polymorphism of *INH-α*, which plays an important role in folliculogenesis, is related to POF and can reduce FSH secretion during folliculogenesis [31].

2.2. Autoimmune Diseases

15% - 20% of POF patients developed autoimmune diseases, like vitiligo, Addison's disease, systemic lupus erythematosus, myasthenia gravis, celiac disease, and autoimmune polyglandular syndrome [4] [32]. After the first antibody against oocytes was detected about 35 years ago, many other antibodies against the adrenal cortex, testis and other organs were detected [33]. Numerous pieces of evidence point to the autoimmune disease's origin, mostly comprising the following [34] [35]: 1) Lymphocytic oophoritis; 2) Displays ovarian autoantibodies; 3) Associated autoimmune disease. $CD4^{+}$T cells are increased in patients

with autoimmune diseases, and the $CD4^+/CD8^+$ ratio may be increased or decreased.

2.3. Chemotherapy

Radiotherapy and chemotherapy are the leading causes of POF. Radiotherapy and chemotherapy can prolong survival in young cancer patients, but DNA damage reduces oocyte shape and function. Because primordial follicle cells have no regenerative capacity, the destruction of these cells leads to POF and infertility [36]. In 2016, Guerreiro *et al.* found that anticancer drugs (doxorubicin and paclitaxel) could reduce the primordial preantral follicles and developing follicles in goats [37]. To prevent chemotherapy induced POF, temporary ovarian suppression with luteinizing hormone release hormones agonists (LHRHa) can be used [38].

2.4. Environmental

Smoking and viral infection have been linked to infertility and POF. Smokers had menopause earlier than non-smokers, and ovarian failure before 46 is more common in smokers [39]. Cigarettes contain more than 4,000 chemicals that are thought harmful to reproductive health. Smoking causes a drop in Estradiol (E2) levels, increases the thickness of the oocyte zona pellucida, and causes follicle loss and ovarian damage [40]. Aromatic hydrocarbon receptors in oocytes and granulosa cells bind polycyclic hydrocarbons in cigarettes and activate the pro-apoptotic gene *BAX* [41]. Infections with cytomegalovirus, mumps virus, and varicella-zoster virus can also cause POF [42].

2.5. Vaccination

Some individuals developed secondary amenorrhea when their menstrual cycle altered from normal to irregular and infrequent after HPV vaccines. This resulted in decreased serum estradiol levels, elevated FSH and Luteinizing hormone (LH), and immunological reaction leading to POF [43]. However, in 90% of cases, the etiology is unknown, and studies suggest that POF may be a side effect of vaccines [44].

2.6. Enzyme Deficiency

Proteins and enzymes deficit in the steroidogenic pathway can diminish serum androstenedione follicle fluid, testosterone, and E2 levels, causing POF [45]. Deficiencies of enzymes other than 21-hydroxylase are extremely uncommon, specifically 17, 20-de lactase, and unlike other enzyme deficiencies that affect adrenal synthesis, glucocorticoids, and androgens, 17, 20-de lactase, activity influences androgens and subsequent estrogen formation [46]. However, there are some reports of specific defects in the activity of one enzyme, 17a-hydroxylase, a rare enzyme that has been associated with puberty, primary amenorrhea, hypogonadotropin, hypertension and hypokalemia, which can also lead to ovarian failure

due to follicle maturation and defects in ovarian steroid synthesis [47].

3. Treatment of POF

POF has multiple causes and treatments. No medicine treats POF entirely. POF treatment includes hormone replacement therapy, psychosocial support, immunotherapy, donor oocytes and stem cell therapy [48]. Currently, stem cell therapy is anticipated to represent the optimal treatment modality for addressing POF.

3.1. Hormonotherapy

Hormone replacement therapy could increase growth hormone secretion, so this treatment can prevent bone loss, menopausal symptoms and improve cardiovascular health in POF patients [49]. Hormone therapy can cause heart disease, stroke, venous thrombosis, endometrial, breast, and ovarian cancer [50]. Sex hormone defenses with endothelial dysfunction may increase the risk of cardiovascular disease and mortality in young women, which may be related to POF. Hormone therapy improves endothelium function in six months [51].

3.2. Melatonin Supplement

As a potential drug for POF treatment, melatonin lessens cisplatin-induced follicle loss by averting phosphorylation of members of the PTEN/AKT/FOXO3a pathway, increases ovarian size, restores the number of primordial follicles, and protects ovaries during chemotherapy in female cancer patients and maintain fertility [52]. Although it is involved in folliculogenesis, its mechanism of regulating ovarian function has not been elucidated. Melatonin is now found in many tissues, including reproductive tissues like the ovary and placenta. Recent research has demonstrated that reproductive organs like the ovary and placenta produce melatonin [53]. Melatonin, derived from the blood, accumulates in mature follicles to support ovulation and stimulates nonspecific humoral and cell-mediated immunity, modulating the immune system in vitro and in vivo [36]. Melatonin's antioxidant effect on follicles improves survival in female cancer patients and POF and prevents chemotherapy-induced reproductive loss [54].

3.3. Immunoregulation

Immunomodulatory therapies like corticosteroids and monoclonal antibodies (etanercept) are effective in POF due to autoimmune ovarian damage [55]. Cellular antibodies produced by steroids in POF can bind to the corpus luteum, granulosa, and pleural cells [56]. Moreover, recovery of ovarian function has also been observed in patients with myasthenia gravis treated with thymectomy.

3.4. Stem Cells Therapy

3.4.1. Application of Stem Cells in POF Therapy

Stem cells can self-renew and come from numerous sources. Stem cells used in

POF therapy include umbilical cord mesenchymal stem cells (UC-MSCs), embryonic stem cells (ESCs), spermatogonial stem cells (SSCs), ovarian mesenchymal stem cells (O-MSCs) and induced pluripotent stem cells (iPSCs) [57]. Based on contemporary research, the primary emphasis of stem cell therapy for POF lies in clinical trials and has not been integrated into clinical practice, with UC-MSCs emerging as the predominant modality for POF treatment. Biological therapy and biological effects are illustrated in **Table 2**.

Table 2. Biological therapy and biological effects.

Treatment method	Biological effect	References
Bone marrow mesenchymal stem cells (BMMSCs)	Inhibits apoptosis of granulosa cells and increases the number of follicles	[63]
Amniotic stem cells (ASCs)	Reduce follicular atresia and stimulate the proliferation of Granule cells (GCs)	[67] [68]
Amniotic fluid mesenchymal stem cells (AFMSCs)	Reduce follicular atresia and inhibit ovarian cell apoptosis	[74]
Adipose mesenchymal stem cells (AMSCs)	Inhibits apoptosis of granulosa cells and increases the number of follicles	[2]
Placental mesenchymal stem cells(PMSCs)	Promote follicle development, inhibit granulosa cell apoptosis, reduce follicular atresia	[80]
Human menstrual blood stem cells (hMenSCs)	Granular cell apoptosis and ovarian interstitial fibrosis	[81]
Ovarian germ line stem cells (GSCs)	Regulate growth and development ability	[85]
UC-MSCs	Reduction in the number of atretic follicles, restoration of ovulation, suppression of inflammation and excessive fibrosis	[88]-[90]
Induced pluripotent stem cells (hiPS)	Vimentin expression, reduced follicular atresia	[91]
Exocomes (EXOs)	Enhance follicle regeneration and inhibit granulosa cell apoptosis	[10] [11]

1) Bone marrow mesenchymal stem cells

In a chemotherapy-induced POF rat model, BMMSCs were the first stem cells tested for therapeutic potential. BMMSCs can differentiate into various cell types, including endometrial [58], endothelial cells [59], and granule cells [60]. It has been reported that BMMSCs transplantation can restore ovarian function and increase fertility in female mice [61] and rats [62] with ovarian damage caused by chemotherapy. BMMSCs protect mice from chemotherapy-induced germ cell death and DNA damage [63]. BMMSCs can differentiate into GCs to

support oocytes and affect oocyte development [60]. Studies have shown that miR-21 regulates apoptosis in GCs and follicular development. BMMSCs overexpressing miR-21 for chemotherapy-induced POF can increase ovarian weight, follicle number and E2 level, decrease FSH level and the number of GCs apoptosis, which is related to the inhibition of GCs apoptosis by targeting the phosphatase and tensionin homologs deleted on chromosome 10 and recombinant human programmed cell death (PDCD4). Heat shock preconditioning improves BMMSC anti-apoptosis and POF treatment efficacy [64]. Other studies have reported that BMMSCs can migrate to the uterus and induce recovery and regeneration of the damaged endometrium in human and animal models [65].

2) Amniotic mesenchymal stem cells

The amniotic membrane is the embryo-covering membrane from which human amniotic mesenchymal stem cells (hAMSCs) can be extracted. Multiple differentiation capacities and anti-inflammatory properties comparable to those of MSCs from other sources have been demonstrated for hAMSCs. Xiao *et al.* showed that transplantation of hAMSCs in POI mice resulted in sustained healthy follicle growth, reduced follicular atresia rate, and restored fertility [66]. Liu *et al.* used 10% hydrogen peroxide to burn the bilateral ovaries of mice to establish a POF mouse model, and the results showed that the ovarian function, FSH, estrogen levels, and mice fertility with hAMSCs transplantation were restored, and the mice could produce normal offspring. With these discoveries, the researchers noted that, at the protein level, FSH-R, VEGF, IGF-1, TNF-α, and IL-1β were increased, and increased expression levels of genes like FOXL2, OCT4, GDF-9, and LIF after ovarian tissue transplantation. hAMSCs exerted a therapeutic effect on ovarian function in mice with naturally aging ovaries by increasing the number of follicles [67]. Co-culture of hGCs with EGF and HGF secreted by hAMSCs can stimulate the proliferation rate of GCs and can effectively inhibit the apoptosis of GCs [68]. hAMSCs pretreated with low-intensity pulsed ultrasound are more effective than normal hAMSCs [69]. These preliminary discoveries support the role of hAMSCs in POF infertility; however, their efficacy and safety in clinical applications remain to be proven.

3) Amniotic fluid mesenchymal stem cells

When injected into POF mice ovaries, amniotic fluid mesenchymal stem cells (AFMSCs) survive for at least three weeks and proliferate and self-renew. AFMSCs show mesodermal trilineage differentiation potential and immunophenotype like MSCs [70]. AFMSCs can express growth factors like EGF, TGF-α and β, and BMP-4 *in vivo* [71]. miR-146a can potentially reduce cellular damage in various injury models, while miR-10a has been implicated in regulating apoptosis in human cumulus cell complexes (COCs) [72]. In POF patients, miR-146a or miR-10a-knockde-out AFMSCs suppress ovarian cell death and follicular atresia [73]. Although AFMSCs cannot differentiate into GCs and germ cells *in vivo*, AFMSCs can restore POF ovarian function by preventing follicular atresia in mice. Interactions between AFMSCs and GCs may be crucial in these roles.

4) Adipose-derived mesenchymal stem cells

As a new source of MSCs, adipose-derived mesenchymal stem cells (ADMSCs) have been successfully used in tissue regeneration. ADMSC transplantation in chemotherapy-induced POF mice lowered GC apoptosis, enhanced ovarian angiogenesis, and improved ovarian function, follicle number, and ovulation [2]. Mashayekhi *et al.* isolated ADMSCs from the abdominal adipose tissue of nine women. Four patients restored their menstrual cycle, and four had lower FSH levels after intravaginal injection, indicating that this POF treatment is safe, practicable, and unique [74]. The addition of collagen scaffolds increased the survival of ADMSCs in the ovaries of female POF rats compared to ADMSC treatment alone [75]. Studies have shown that hADMSCs transplantation can improve ovarian function in chemotherapy-induced POI models through a paracrine mechanism and, combined with estrogen, can also increase Treg proliferation, Foxp3 and TGF-β1 mRNA expression in POI, and decreased IFN-γ mRNA expression in POI patients [76]. ADMSCs are among the essential therapeutic cells for ovarian function recovery, despite scant investigations on their mechanism in POF therapy [77].

5) Placental mesenchymal stem cells

Placental mesenchymal stem cells (PMSCs) are pluripotent non-hematopoietic progenitor cells with high differentiation and proliferation potential. Compared to MSCs from other sources, their phenotype and characteristics have greater advantages [78]. Yin *et al.* found increased production of cytokines like TGF-β, which controlled inflammation and restored ovarian function. Researchers also noted that promoting follicular atresia and inhibiting ovulation by inhibiting IFN-γ secretion; after two weeks of hPMSCs treatment, the estrous cycle of POF mice was significantly restored, and serum FSH, LH, E2, and Antimullerian hormone (AMH) levels were reversed. PMSCs could promote follicle growth and inhibit GCs apoptosis, improving ovarian reserve capacity [79]. Transplantation of PMSCs is among the effective methods to restore ovarian function in chemotherapy-induced POF mice.

6) Menstrual blood-derived endometrial stem cells

Menstrual blood-derived endometrial stem cells (MenSCs) are derived from women's menstrual blood and have the basic features of MSCs [80]. They have attracted widespread attention since their discovery in 2007, and there is no report on autoimmune rejection of MenSCs.

In POF mice, MenSCs can be encouraged to develop into ovarian tissue-like cells, notably ovarian granulosa-like cells, which increases ovarian indicators, weight, normal follicle number, serum inhibin, E2, AMH levels, reduced GCs apoptosis, and ovarian interstitial fibrosis [81]. In Ashman syndrome, MenSCs transplantation can improve endometrial structure in women [82] and induce anti-inflammatory factors and angiogenesis in rats, thereby enhancing fertility [83]. MenSCs transplantation has become an effective and novel method for treating POF.

7) Ovarian germline stem cells

Ovarian germline stem cells (GSCs), well-known in non-mammalian model organisms, can grow and develop. However, the existence of ovarian GSCs has been revealed in new studies in mice, rats and humans [84]. Ovarian mesenchymal stem cells (PO-MSCs) have also been reported, and gene expression analysis showed that PO-MSCs, unlike fibroblasts, also express CD44, CD90, and stromal cell precursor surface antigen (STRO-1) [85]. This will be a new approach to address POF barriers soon.

8) Umbilical cord mesenchymal stem cells

UC-MSCs are pluripotent stem cells that can develop into many cell lines. UC-MSCs injected into the ovaries of chemotherapy-induced POF rats [86] and mice [87] can significantly reduce serum FSH levels, increase P4, E2 and AMH levels and the total number of normal follicles, reduce the number of atretic follicles, restore the estrous cycle and ovulation period. After pregnancy, offspring can be produced normally, indicating that ovarian function and reproductive potential have been restored. UC-MSCs suppress inflammation and excessive fibrosis, promote cell proliferation, release VEGF, develop into oocyte-like structures and endometrial cells, and exhibit germ cell-specific mRNA and protein markers [88]. Further studies found that UC-MSCs reduced the apoptosis of mouse GCs by activating the JNK/Bcl-2 signaling pathway to regulate autophagy, upregulate $CD8^{+}CD28^{-}$T cells, and affect GPCR, MAPK and insulin pathways, thereby improving ovarian function [89]. Ding *et al.* transplanted UC-MSCs into mouse ovaries through collagen scaffolds and proved that collagen/hUC-MSCs transplantation could activate primordial follicles during folliculogenesis, promote ovarian angiogenesis, GCs proliferation, and increase AMH and E2 levels. It can also enhance ovarian volume and antral follicles to maintain ovarian function [90].

9) Human induced pluripotent stem cells

Human induced pluripotent stem cells (hiPS) can differentiate into hormone-sensitive ovarian epithelial (OSE)-like cells E2 and ovarian weight increased, while vimentin and fibronectin decreased in POF mice. Transplantation of granulosa salivary cells (OGLCs) into POF mice promoted ovarian tissue growth and ovarian granulosa cell marker expression, increased E2 level, and decreased the number of atretic follicles [91]. Oocytes were produced after transplanting iPS-induced ectoderm-like cells and primordial germ cells (PGCs)-like cells into mouse ovarian sacs [92].

10) Stem cells from other sources

Peritoneal mesothelial cells can complete the repair and reconstruction of ovarian function by secreting growth factors (like bFGF and VEGF), cytokines and extracellular matrix [93]. Peritoneal mesenchymal stem cells (PeMSCs) can be differentiated into ovarian cell-like cells with 10% human follicular fluid and 50% human cumulus-CM and express oocytes (Zp3 and Gdf9), germ cells (Ddx4amdDazl), GCs (Amh) and mucosal cells (Lhr) markers [94]. Skin-derived

stem cells (SMSCs) can express germ cell markers and form oocyte-like cells *in vitro* and improve the ovarian follicle microenvironment in POF mice by reducing the levels of pro-inflammatory cytokines (TNF-α, TGF-β, and IFN-γ), restoring the infertile mice fertility [95].

3.4.2. Application of Exosomes in POF

Exosomes (EXOs) are essential carriers of intercellular communication, and they contain many cellular substances, like proteins, lipids, and noncoding RNAs (like miRNAs). miRNAs can govern cell-to-cell signal transmission in various disorders and affect molecular processes [96]. miRNAs carried by EXOs derived from BMMSCs can promote ovarian recovery in POF animals [8]. Compared to hBMMSCs, hAFMSCs secreted higher levels of EXOs, and hAFMSCs-EXOs enhanced follicle regeneration inhibited apoptosis of GCs recovered estrus cycle and AMH levels through miRNA21/PTEN/caspase3 signaling pathway. Thus, hAFMSCs appear to be a good source of exosomes for clinical applications [10]. By modulating SMAD (SMAD2, SMAD3, and SMAD5) signal transduction, hAMSCs-EXOs increase the proliferation and decrease the apoptosis of hGCs in POI [11].

4. Conclusion

POF is a crucial condition, particularly for young women who have not yet completed childbearing, and infertility resulting from POF can leave many couples feeling sad and discouraged. Due to the complexity of this disease, there is no effective treatment. We must find better alternatives to treat this disease. POF patients may benefit from stem cell therapy, which is low immunogenic, accessible, and ethical. Stem cells from different sources and their produced EXOs can raise the number of follicles and sex hormones, reduce GC apoptosis, and recover female reproductive function. Therefore, stem cell therapy is a new and effective alternative strategy for treating POF, which is beneficial for regenerative medicine and clinical applications. Although there are existing reports that stem cells can restore ovarian function in POF patients, the relevant mechanism is unclear. Clarifying POF's physiological function and mechanism is expected to provide further ideas for POF ovarian repair.

Funding

This work was supported by the Henan Science and Technology Research Project (232102310303, 232102310065, 232102310317, 222102310436), Henan Province Colleges and Universities Young Backbone teacher Training Program (2023GGJS201), Backbone Teachers Program of Sanquan College of Xinxiang Medical University (SQ2023GGJS06), Academic Technology Leader Program of Sanquan College of Xinxiang Medical College (SQ2023XSJSDTR01).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Sheikhansari, G., Aghebati-Maleki, L., Nouri, M., Jadidi-Niaragh, F. and Yousefi, M. (2018) Current Approaches for the Treatment of Premature Ovarian Failure with Stem Cell Therapy. *Biomedicine & Pharmacotherapy*, **102**, 254-262. https://doi.org/10.1016/j.biopha.2018.03.056

[2] Zhang, C. (2020) The Roles of Different Stem Cells in Premature Ovarian Failure. *Current Stem Cell Research & Therapy*, **15**, 473-481. https://doi.org/10.2174/1574888x14666190314123006

[3] Kuang, H., Han, D., Xie, J., Yan, Y., Li, J. and Ge, P. (2013) Profiling of Differentially Expressed Micrornas in Premature Ovarian Failure in an Animal Model. *Gynecological Endocrinology*, **30**, 57-61. https://doi.org/10.3109/09513590.2013.850659

[4] Takahashi, A., Yousif, A., Hong, L. and Chefetz, I. (2021) Premature Ovarian Insufficiency: Pathogenesis and Therapeutic Potential of Mesenchymal Stem Cell. *Journal of Molecular Medicine*, **99**, 637-650. https://doi.org/10.1007/s00109-021-02055-5

[5] Omu, F.E., Elbiaa, A., Ghafour, A., Gadalla, I. and Omu, A.E. (2016) Beneficial Effects of Tibolone on Sexual Dys-Function in Women with Premature Ovarian Failure (POF). *Health*, **8**, 857-867. https://doi.org/10.4236/health.2016.89090

[6] Ullah, I., Subbarao, R.B. and Rho, G.J. (2015) Human Mesenchymal Stem Cells—Current Trends and Future Prospective. *Bioscience Reports*, **35**, e00191. https://doi.org/10.1042/bsr20150025

[7] Li, Y., Zhang, H., Cai, C., Mao, J., Li, N., Huang, D., *et al.* (2023) Microfluidic Encapsulation of Exosomes Derived from Lipopolysaccharide-Treated Mesenchymal Stem Cells in Hyaluronic Acid Methacryloyl to Restore Ovarian Function in Mice. *Advanced Healthcare Materials*, **13**, e2303068. https://doi.org/10.1002/adhm.202303068

[8] Yang, M., Lin, L., Sha, C., Li, T., Zhao, D., Wei, H., *et al.* (2020) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-144-5p Improves Rat Ovarian Function After Chemotherapy-Induced Ovarian Failure by Targeting PTEN. *Laboratory Investigation*, **100**, 342-352. https://doi.org/10.1038/s41374-019-0321-y

[9] Zhang, Q., Sun, J., Huang, Y., Bu, S., Guo, Y., Gu, T., *et al.* (2019) Human Amniotic Epithelial Cell-Derived Exosomes Restore Ovarian Function by Transferring MicroRNAs against Apoptosis. *Molecular Therapy—Nucleic Acids*, **16**, 407-418. https://doi.org/10.1016/j.omtn.2019.03.008

[10] Thabet, E., Yusuf, A., Abdelmonsif, D.A., Nabil, I., Mourad, G. and Mehanna, R.A. (2020) Extracellular Vesicles Mirna-21: A Potential Therapeutic Tool in Premature Ovarian Dysfunction. *Molecular Human Reproduction*, **26**, 906-919. https://doi.org/10.1093/molehr/gaaa068

[11] Huang, B., Lu, J., Ding, C., Zou, Q., Wang, W. and Li, H. (2018) Exosomes Derived from Human Adipose Mesenchymal Stem Cells Improve Ovary Function of Premature Ovarian Insufficiency by Targeting SMAD. *Stem Cell Research & Therapy*, **9**, Article No. 216. https://doi.org/10.1186/s13287-018-0953-7

[12] Di-Battista, A., Moysés-Oliveira, M. and Melaragno, M.I. (2020) Genetics of Premature Ovarian Insufficiency and the Association with X-Autosome Translocations. *Reproduction*, **160**, R55-R64. https://doi.org/10.1530/rep-20-0338

[13] Baronchelli, S., Conconi, D., Panzeri, E., Bentivegna, A., Redaelli, S., Lissoni, S., *et al.* (2011) Cytogenetics of Premature Ovarian Failure: An Investigation on 269 Affected Women. *BioMed Research International*, **2011**, Article ID: 370195.

https://doi.org/10.1155/2011/370195

[14] Franić, D. (2016) Genetic Etiology of Primary Premature Ovarian Insufficiency. *Acta Clinica Croatica*, **55**, 629-635. https://doi.org/10.20471/acc.2016.55.04.14

[15] Zinn, A. (2001) The X Chromosome and the Ovary. *Journal of the Society for Gynecologic Investigation*, **8**, S34-S36. https://doi.org/10.1016/s1071-5576(00)00104-0

[16] Lu, C., Chen, Y., Syu, S., Lu, H., Ho, H. and Chen, H. (2019) Generation of Induced Pluripotent Stem Cell Line-Ntuhi001-A from a Premature Ovarian Failure Patient with Turner's Syndrome Mosaicism. *Stem Cell Research*, **37**, Article ID: 101422. https://doi.org/10.1016/j.scr.2019.101422

[17] Yuemaier, M., Tuerhong, M., Keremu, A., Kadeer, N., Aimaiti, A., Wushouer, X., *et al.* (2018) Research on Establishment of Abnormal Phlegmatic Syndrome with Premature Ovarian Failure Rat Model and Effects of Balgham Munziq Treatment. *Evidence-Based Complementary and Alternative Medicine*, **2018**, Article ID: 3858209. https://doi.org/10.1155/2018/3858209

[18] Czakó, M., Till, Á., Zima, J., Zsigmond, A., Szabó, A., Maász, A., *et al.* (2021) Xp11.2 Duplication in Females: Unique Features of a Rare Copy Number Variation. *Frontiers in Genetics*, **12**, Article 635458. https://doi.org/10.3389/fgene.2021.635458

[19] Sherman, S.L. (2000) Premature Ovarian Failure among Fragile X Premutation Carriers: Parent-Of-Origin Effect? *The American Journal of Human Genetics*, **67**, 11-13. https://doi.org/10.1086/302985

[20] Holland, C.M. (2001) 47, XXX in an Adolescent with Premature Ovarian Failure and Autoimmune Disease. *Journal of Pediatric and Adolescent Gynecology*, **14**, 77-80. https://doi.org/10.1016/s1083-3188(01)00075-4

[21] Deng, P. and Klyachko, V.A. (2021) Channelopathies in Fragile X Syndrome. *Nature Reviews Neuroscience*, **22**, 275-289. https://doi.org/10.1038/s41583-021-00445-9

[22] Rehnitz, J., Alcoba, D.D., Brum, I.S., Dietrich, J.E., Youness, B., Hinderhofer, K., *et al.* (2018) FMR1 Expression in Human Granulosa Cells Increases with Exon 1 CGG Repeat Length Depending on Ovarian Reserve. *Reproductive Biology and Endocrinology*, **16**, Article No. 65. https://doi.org/10.1186/s12958-018-0383-5

[23] Cao, Y., Peng, Y., Kong, H.E., Allen, E.G. and Jin, P. (2020) Metabolic Alterations in FMR1 Premutation Carriers. *Frontiers in Molecular Biosciences*, **7**, Article 571092. https://doi.org/10.3389/fmolb.2020.571092

[24] Welt, C.K., Smith, P.C. and Taylor, A.E. (2004) Evidence of Early Ovarian Aging in Fragile X Premutation Carriers. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 4569-4574. https://doi.org/10.1210/jc.2004-0347

[25] Ruth, K.S., Day, F.R., Hussain, J., Martínez-Marchal, A., Aiken, C.E., Azad, A., *et al.* (2021) Genetic Insights into Biological Mechanisms Governing Human Ovarian Ageing. *Nature*, **596**, 393-397. https://doi.org/10.1038/s41586-021-03779-7

[26] Thakur, M., Feldman, G. and Puscheck, E.E. (2017) Primary Ovarian Insufficiency in Classic Galactosemia: Current Understanding and Future Research Opportunities. *Journal of Assisted Reproduction and Genetics*, **35**, 3-16. https://doi.org/10.1007/s10815-017-1039-7

[27] Bouazzi, L., Sproll, P., Eid, W. and Biason-Lauber, A. (2019) The Transcriptional Regulator CBX2 and Ovarian Function: A Whole Genome and Whole Transcriptome Approach. *Scientific Reports*, **9**, Article No. 17033. https://doi.org/10.1038/s41598-019-53370-4

[28] Chai, P., Li, F., Fan, J., Jia, R., Zhang, H. and Fan, X. (2017) Functional Analysis of a Novel FOXL2 Indel Mutation in Chinese Families with Blepharophimosis-Ptosis-Epicanthus Inversus Syndrome Type I. *International Journal of Biological Sciences*, **13**, 1019-1028. https://doi.org/10.7150/ijbs.19532

[29] Patton, B.K., Madadi, S., Briley, S.M., Ahmed, A.A. and Pangas, S.A. (2023) Sumoylation Regulates Functional Properties of the Oocyte Transcription Factors SOHLH1 and NOBOX. *The FASEB Journal*, **37**, e22747. https://doi.org/10.1096/fj.202201481r

[30] Lakhal, B., Ben-Hadj-Khalifa, S., Bouali, N., Philipert, P., Audran, F., Braham, R., *et al.* (2012) Mutational Screening of SF1 and WNT4 in Tunisian Women with Premature Ovarian Failure. *Gene*, **509**, 298-301. https://doi.org/10.1016/j.gene.2012.08.007

[31] Kim, H., Chun, S., Gu, B.S., Ku, S., Kim, S.H. and Kim, J.G. (2011) Relationship between Inhibin-*α* Gene Polymorphisms and Premature Ovarian Failure in Korean Women. *Menopause*, **18**, 1232-1236. https://doi.org/10.1097/gme.0b013e31821d6f7e

[32] Gao, H., Gao, L. and Wang, W. (2022) Advances in the Cellular Immunological Pathogenesis and Related Treatment of Primary Ovarian Insufficiency. *American Journal of Reproductive Immunology*, **88**, e13622. https://doi.org/10.1111/aji.13622

[33] Luborsky, J. (2002) Ovarian Autoimmune Disease and Ovarian Autoantibodies. *Journal of Women's Health & Gender-Based Medicine*, **11**, 585-599. https://doi.org/10.1089/152460902760360540

[34] Chernyshov, V.P., Radysh, T.V., Gura, I.V., Tatarchuk, T.P. and Khominskaya, Z.B. (2001) Immune Disorders in Women with Premature Ovarian Failure in Initial Period. *American Journal of Reproductive Immunology*, **46**, 220-225. https://doi.org/10.1034/j.1600-0897.2001.d01-5.x

[35] Forges, T. (2004) Autoimmunity and Antigenic Targets in Ovarian Pathology. *Human Reproduction Update*, **10**, 163-175. https://doi.org/10.1093/humupd/dmh014

[36] Jankowska, K. (2017) Premature Ovarian Failure. *Menopausal Review*, **2**, 51-56. https://doi.org/10.5114/pm.2017.68592

[37] Guerreiro, D.D., Lima, L.F.d., Rodrigues, G.Q., Carvalho, A.d.A., Castro, S.V., Campello, C.C., *et al.* (2016) *In Situ* Cultured Preantral Follicles Is a Useful Model to Evaluate the Effect of Anticancer Drugs on Caprine Folliculogenesis. *Microscopy Research and Technique*, **79**, 773-781. https://doi.org/10.1002/jemt.22697

[38] Lambertini, M., Ceppi, M., Poggio, F., Peccatori, F.A., Azim, H.A., Ugolini, D., *et al.* (2015) Ovarian Suppression Using Luteinizing Hormone-Releasing Hormone Agonists during Chemotherapy to Preserve Ovarian Function and Fertility of Breast Cancer Patients: A Meta-Analysis of Randomized Studies. *Annals of Oncology*, **26**, 2408-2419. https://doi.org/10.1093/annonc/mdv374

[39] Di Prospero, F., Luzi, S. and Iacopini, Z. (2004) Cigarette Smoking Damages Women's Reproductive Life. *Reproductive BioMedicine Online*, **8**, 246-247. https://doi.org/10.1016/s1472-6483(10)60525-1

[40] Camlin, N.J., McLaughlin, E.A. and Holt, J.E. (2014) Through the Smoke: Use of in Vivo and in Vitro Cigarette Smoking Models to Elucidate Its Effect on Female Fertility. *Toxicology and Applied Pharmacology*, **281**, 266-275. https://doi.org/10.1016/j.taap.2014.10.010

[41] Matikainen, T., Perez, G.I., Jurisicova, A., Pru, J.K., Schlezinger, J.J., Ryu, H., *et al.* (2001) Aromatic Hydrocarbon Receptor-Driven Bax Gene Expression Is Required for Premature Ovarian Failure Caused by Biohazardous Environmental Chemicals.

Nature Genetics, **28**, 355-360. https://doi.org/10.1038/ng575

[42] Huang, X.C., Jiang, Y.N., Bao, H.J., *et al.* (2024) Role and Mechanism of Epigenetic Regulation in the Aging of Germ Cells: Prospects for Targeted Interventions. *Aging and Disease*. https://doi.org/10.14336/AD.2024.0126

[43] Colafrancesco, S., Perricone, C., Tomljenovic, L. and Shoenfeld, Y. (2013) Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants. *American Journal of Reproductive Immunology*, **70**, 309-316. https://doi.org/10.1111/aji.12151

[44] Little, D.T. and Ward, H.R.G. (2012) Premature Ovarian Failure 3 Years after Menarche in a 16-Year-Old Girl Following Human Papillomavirus Vaccination. *BMJ Case Reports*, **2012**, bcr2012006879. https://doi.org/10.1136/bcr-2012-006879

[45] Kushnir, M.M., Naessen, T., Kirilovas, D., Chaika, A., Nosenko, J., Mogilevkina, I., *et al.* (2009) Steroid Profiles in Ovarian Follicular Fluid from Regularly Menstruating Women and Women after Ovarian Stimulation. *Clinical Chemistry*, **55**, 519-526. https://doi.org/10.1373/clinchem.2008.110262

[46] Kim, Y., Kang, M., Choi, J., Lee, B.H., Kim, G., Ohn, J.H., *et al.* (2014) A Review of the Literature on Common CYP17A1 Mutations in Adults with 17-Hydroxylase/17, 20-Lyase Deficiency, a Case Series of Such Mutations among Koreans and Functional Characteristics of a Novel Mutation. Metabolism, **63**, 42-49. https://doi.org/10.1016/j.metabol.2013.08.015

[47] Rabinovici, J., Blankstein, J., Goldman, B., Rudak, E., Dor, Y., Pariente, C., *et al.* (1989) *In Vitro* Fertilization and Primary Embryonic Cleavage Are Possible in 17α-Hydroxylase Deficiency Despite Extremely Low Intrafollicular 17β-Estradiol. *The Journal of Clinical Endocrinology & Metabolism*, **68**, 693-697. https://doi.org/10.1210/jcem-68-3-693

[48] Hewlett, M. and Mahalingaiah, S. (2015) Update on Primary Ovarian Insufficiency. *Current Opinion in Endocrinology, Diabetes & Obesity*, **22**, 483-489. https://doi.org/10.1097/med.0000000000000206

[49] Chen, H., Xiao, L., Li, J., Cui, L. and Huang, W. (2019) Adjuvant Gonadotropin-Releasing Hormone Analogues for the Prevention of Chemotherapy-Induced Premature Ovarian Failure in Premenopausal Women. *Cochrane Database of Systematic Reviews*, No. 3, CD008018. https://doi.org/10.1002/14651858.cd008018.pub3

[50] Rossouw, J.E., Prentice, R.L., Manson, J.E., Wu, L., Barad, D., Barnabei, V.M., *et al.* (2007) Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years since Menopause. *JAMA*, **297**, 1465-1477. https://doi.org/10.1001/jama.297.13.1465

[51] Kalantaridou, S.N., Naka, K.K., Papanikolaou, E., Kazakos, N., Kravariti, M., Calis, K.A., *et al.* (2004) Impaired Endothelial Function in Young Women with Premature Ovarian Failure: Normalization with Hormone Therapy. The Journal of Clinical Endocrinology & Metabolism, **89**, 3907-3913. https://doi.org/10.1210/jc.2004-0015

[52] Jang, H., Lee, O., Lee, Y., Yoon, H., Chang, E.M., Park, M., *et al.* (2016) Melatonin Prevents Cisplatin-Induced Primordial Follicle Loss via Suppression of PTEN/AKT/FOXO3a Pathway Activation in the Mouse Ovary. *Journal of Pineal Research*, **60**, 336-347. https://doi.org/10.1111/jpi.12316

[53] Lee, S.J., Schover, L.R., Partridge, A.H., Patrizio, P., Wallace, W.H., Hagerty, K., *et al.* (2006) American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients. *Journal of Clinical Oncology*, **24**, 2917-2931. https://doi.org/10.1200/jco.2006.06.5888

[54] Huang, J., Shan, W., Li, N., Zhou, B., Guo, E., Xia, M., *et al.* (2021) Melatonin Provides Protection against Cisplatin-Induced Ovarian Damage and Loss of Fertility in Mice. *Reproductive BioMedicine Online*, **42**, 505-519. https://doi.org/10.1016/j.rbmo.2020.10.001

[55] Zhang, Q., Huang, Y., Sun, J., Gu, T., Shao, X. and Lai, D. (2019) Immunomodulatory Effect of Human Amniotic Epithelial Cells on Restoration of Ovarian Function in Mice with Autoimmune Ovarian Disease. *Acta Biochimica et Biophysica Sinica*, **51**, 845-855. https://doi.org/10.1093/abbs/gmz065

[56] Simon, A. and Laufer, N. (2012) Repeated Implantation Failure: Clinical Approach. *Fertility and Sterility*, **97**, 1039-1043. https://doi.org/10.1016/j.fertnstert.2012.03.010

[57] Kim, H.K. and Kim, T.J. (2024) Current Status and Future Prospects of Stem Cell Therapy for Infertile Patients with Premature Ovarian Insufficiency. *Biomolecules*, **14**, Article 242. https://doi.org/10.3390/biom14020242

[58] Gao, L., Huang, Z., Lin, H., Tian, Y., Li, P. and Lin, S. (2019) Bone Marrow Mesenchymal Stem Cells (BMSCs) Restore Functional Endometrium in the Rat Model for Severe Asherman Syndrome. *Reproductive Sciences*, **26**, 436-444. https://doi.org/10.1177/1933719118799201

[59] Sun, X., Luo, L. and Li, J. (2020) Lncrna MALAT1 Facilitates BM-MSCs Differentiation into Endothelial Cells via Targeting miR-206/VEGFA Axis. *Cell Cycle*, **19**, 3018-3028. https://doi.org/10.1080/15384101.2020.1829799

[60] Besikcioglu, H.E., Sarıbas, G.S., Ozogul, C., Tiryaki, M., Kilic, S., Pınarlı, F.A., *et al.* (2019) Determination of the Effects of Bone Marrow Derived Mesenchymal Stem Cells and Ovarian Stromal Stem Cells on Follicular Maturation in Cyclophosphamide Induced Ovarian Failure in Rats. *Taiwanese Journal of Obstetrics and Gynecology*, **58**, 53-59. https://doi.org/10.1016/j.tjog.2018.11.010

[61] Badawy, A., Sobh, M., Ahdy, M. and Abdelhafez, M. (2017) Bone Marrow Mesenchymal Stem Cell Repair of Cyclophosphamide-Induced Ovarian Insufficiency in a Mouse Model. *International Journal of Women's Health*, **9**, 441-447. https://doi.org/10.2147/ijwh.s134074

[62] Fu, X., He, Y., Wang, X., Peng, D., Chen, X., Li, X., *et al.* (2017) Overexpression of Mir-21 in Stem Cells Improves Ovarian Structure and Function in Rats with Chemotherapy-Induced Ovarian Damage by Targeting PDCD4 and PTEN to Inhibit Granulosa Cell Apoptosis. *Stem Cell Research & Therapy*, **8**, Article No. 187. https://doi.org/10.1186/s13287-017-0641-z

[63] Kilic, S., Pinarli, F., Ozogul, C., Tasdemir, N., Naz Sarac, G. and Delibasi, T. (2013) Protection from Cyclophosphamide-Induced Ovarian Damage with Bone Marrow-Derived Mesenchymal Stem Cells during Puberty. *Gynecological Endocrinology*, **30**, 135-140. https://doi.org/10.3109/09513590.2013.860127

[64] Chen, X., Wang, Q., Li, X., Wang, Q., Xie, J. and Fu, X. (2018) Heat Shock Pretreatment of Mesenchymal Stem Cells for Inhibiting the Apoptosis of Ovarian Granulosa Cells Enhanced the Repair Effect on Chemotherapy-Induced Premature Ovarian Failure. *Stem Cell Research & Therapy*, **9**, Article No. 240. https://doi.org/10.1186/s13287-018-0964-4

[65] Meesuk, L., Tantrawatpan, C., Kheolamai, P. and Manochantr, S. (2016) The Immunosuppressive Capacity of Human Mesenchymal Stromal Cells Derived from Amnion and Bone Marrow. *Biochemistry and Biophysics Reports*, **8**, 34-40. https://doi.org/10.1016/j.bbrep.2016.07.019

[66] Xiao, G., Liu, I., Cheng, C., Chang, C., Lee, Y., Cheng, W.T., *et al.* (2014) Amniotic Fluid Stem Cells Prevent Follicle Atresia and Rescue Fertility of Mice with Prema-

ture Ovarian Failure Induced by Chemotherapy. *PLOS ONE*, **9**, e106538. https://doi.org/10.1371/journal.pone.0106538

[67] Liu, R., Zhang, X., Fan, Z., Wang, Y., Yao, G., Wan, X., *et al.* (2019) Human Amniotic Mesenchymal Stem Cells Improve the Follicular Microenvironment to Recover Ovarian Function in Premature Ovarian Failure Mice. *Stem Cell Research & Therapy*, **10**, Article No. 299. https://doi.org/10.1186/s13287-019-1315-9

[68] Ding, C., Zou, Q., Wang, F., Wu, H., Chen, R., Lv, J., *et al.* (2018) Human Amniotic Mesenchymal Stem Cells Improve Ovarian Function in Natural Aging through Secreting Hepatocyte Growth Factor and Epidermal Growth Factor. *Stem Cell Research & Therapy*, **9**, Article No. 55. https://doi.org/10.1186/s13287-018-0781-9

[69] Labunskyy, V.M. and Gladyshev, V.N. (2013) Role of Reactive Oxygen Species-Mediated Signaling in Aging. *Antioxidants & Redox Signaling*, **19**, 1362-1372. https://doi.org/10.1089/ars.2012.4891

[70] Naeem, A., Gupta, N., Naeem, U., Elrayess, M.A. and Albanese, C. (2022) Amniotic Stem Cells as a Source of Regenerative Medicine to Treat Female Infertility. *Human Cell*, **36**, 15-25. https://doi.org/10.1007/s13577-022-00795-1

[71] Liu, T., Huang, Y., Guo, L., Cheng, W. and Zou, G. (2012) $CD44^+/CD105^+$ Human Amniotic Fluid Mesenchymal Stem Cells Survive and Proliferate in the Ovary Long-Term in a Mouse Model of Chemotherapy-Induced Premature Ovarian Failure. *International Journal of Medical Sciences*, **9**, 592-602. https://doi.org/10.7150/ijms.4841

[72] Assou, S., Al-edani, T., Haouzi, D., Philippe, N., Lecellier, C.H., Piquemal, D., *et al.* (2013) Micrornas: New Candidates for the Regulation of the Human Cumulus-Oocyte Complex. *Human Reproduction*, **28**, 3038-3049. https://doi.org/10.1093/humrep/det321

[73] Jiang, W., Kong, L., Ni, Q., Lu, Y., Ding, W., Liu, G., *et al.* (2014) Mir-146a Ameliorates Liver Ischemia/Reperfusion Injury by Suppressing IRAK1 and TRAF6. *PLOS ONE*, **9**, e101530. https://doi.org/10.1371/journal.pone.0101530

[74] Mashayekhi, M., Mirzadeh, E., Chekini, Z., Ahmadi, F., Eftekhari-Yazdi, P., Vesali, S., *et al.* (2021) Evaluation of Safety, Feasibility and Efficacy of Intra-Ovarian Transplantation of Autologous Adipose Derived Mesenchymal Stromal Cells in Idiopathic Premature Ovarian Failure Patients: Non-Randomized Clinical Trial, Phase I, First in Human. *Journal of Ovarian Research*, **14**, Article No. 5. https://doi.org/10.1186/s13048-020-00743-3

[75] Su, J., Ding, L., Cheng, J., Yang, J., Li, X., Yan, G., *et al.* (2016) Transplantation of Adipose-Derived Stem Cells Combined with Collagen Scaffolds Restores Ovarian Function in a Rat Model of Premature Ovarian Insufficiency. *Human Reproduction*, **31**, 1075-1086. https://doi.org/10.1093/humrep/dew041

[76] Song, K., Cai, H., Zhang, D., Huang, R., Sun, D. and He, Y. (2018) Effects of Human Adipose-Derived Mesenchymal Stem Cells Combined with Estrogen on Regulatory T Cells in Patients with Premature Ovarian Insufficiency. *International Immunopharmacology*, **55**, 257-262. https://doi.org/10.1016/j.intimp.2017.12.026

[77] Kilic, S., Yuksel, B., Pinarli, F., Albayrak, A., Boztok, B. and Delibasi, T. (2014) Effect of Stem Cell Application on Asherman Syndrome, an Experimental Rat Model. *Journal of Assisted Reproduction and Genetics*, **31**, 975-982. https://doi.org/10.1007/s10815-014-0268-2

[78] Luan, X., Li, G., Wang, G., Wang, F. and Lin, Y. (2013) Human Placenta-Derived Mesenchymal Stem Cells Suppress T Cell Proliferation and Support the Culture Expansion of Cord Blood $CD34^+$ Cells: A Comparison with Human Bone Mar-

row-Derived Mesenchymal Stem Cells. *Tissue and Cell*, **45**, 32-38. https://doi.org/10.1016/j.tice.2012.09.002

[79] Yin, N., Zhao, W., Luo, Q., Yuan, W., Luan, X. and Zhang, H. (2018) Restoring Ovarian Function with Human Placenta-Derived Mesenchymal Stem Cells in Autoimmune-Induced Premature Ovarian Failure Mice Mediated by TREG Cells and Associated Cytokines. *Reproductive Sciences*, **25**, 1073-1082. https://doi.org/10.1177/1933719117732156

[80] Hong, I. (2024) Endometrial Stem Cells: Orchestrating Dynamic Regeneration of Endometrium and Their Implications in Diverse Endometrial Disorders. *International Journal of Biological Sciences*, **20**, 864-879. https://doi.org/10.7150/ijbs.89795

[81] Wang, Z., Wang, Y., Yang, T., Li, J. and Yang, X. (2017) Study of the Reparative Effects of Menstrual-Derived Stem Cells on Premature Ovarian Failure in Mice. *Stem Cell Research & Therapy*, **8**, Article No. 11. https://doi.org/10.1186/s13287-016-0458-1

[82] Tan, J., Li, P., Wang, Q., Li, Y., Li, X., Zhao, D., *et al.* (2016) Autologous Menstrual Blood-Derived Stromal Cells Transplantation for Severe Asherman's Syndrome. *Human Reproduction*, **31**, 2723-2729. https://doi.org/10.1093/humrep/dew235

[83] Domnina, A., Novikova, P., Obidina, J., Fridlyanskaya, I., Alekseenko, L., Kozhukharova, I., *et al.* (2018) Human Mesenchymal Stem Cells in Spheroids Improve Fertility in Model Animals with Damaged Endometrium. *Stem Cell Research & Therapy*, **9**, Article No. 50. https://doi.org/10.1186/s13287-018-0801-9

[84] Wang, C., Sun, Q., Li, S., Liu, G., Ren, J., Li, Y., *et al.* (2023) Isolation of Female Germline Stem Cells from Neonatal Piglet Ovarian Tissue and Differentiation into Oocyte-Like Cells. *Theriogenology*, **197**, 186-197. https://doi.org/10.1016/j.theriogenology.2022.12.004

[85] Stimpfel, M., Cerkovnik, P., Novakovic, S., Maver, A. and Virant-Klun, I. (2014) Putative Mesenchymal Stem Cells Isolated from Adult Human Ovaries. *Journal of Assisted Reproduction and Genetics*, **31**, 959-974. https://doi.org/10.1007/s10815-014-0254-8

[86] Wang, Z., Wei, Q., Wang, H., Han, L., Dai, H., Qian, X., *et al.* (2020) Mesenchymal Stem Cell Therapy Using Human Umbilical Cord in a Rat Model of Autoimmune-Induced Premature Ovarian Failure. *Stem Cells International*, **2020**, Article ID: 3249495. https://doi.org/10.1155/2020/3249495

[87] Umer, A., Khan, N., Greene, D.L., Habiba, U.E., Shamim, S. and Khayam, A.U. (2022) The Therapeutic Potential of Human Umbilical Cord Derived Mesenchymal Stem Cells for the Treatment of Premature Ovarian Failure. *Stem Cell Reviews and Reports*, **19**, 651-666. https://doi.org/10.1007/s12015-022-10493-y

[88] Zhang, L., Li, Y., Dong, Y., Guan, C., Tian, S., Lv, X., *et al.* (2022) Transplantation of Umbilical Cord-Derived Mesenchymal Stem Cells Promotes the Recovery of Thin Endometrium in Rats. *Scientific Reports*, **12**, Article No. 412. https://doi.org/10.1038/s41598-021-04454-7

[89] Yin, N., Wu, C., Qiu, J., Zhang, Y., Bo, L., Xu, Y., *et al.* (2020) 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 Research & Therapy*, **11**, Article No. 49. https://doi.org/10.1186/s13287-019-1537-x

[90] Yang, Y., Lei, L., Wang, S., Sheng, X., Yan, G., Xu, L., *et al.* (2019) Transplantation of Umbilical Cord-Derived Mesenchymal Stem Cells on a Collagen Scaffold Im-

proves Ovarian Function in a Premature Ovarian Failure Model of Mice. *In Vitro Cellular & Developmental Biology—Animal*, **55**, 302-311. https://doi.org/10.1007/s11626-019-00337-4

[91] Liu, T., Li, Q., Wang, S., Chen, C. and Zheng, J. (2016) Transplantation of Ovarian Granulosa-Like Cells Derived from Human Induced Pluripotent Stem Cells for the Treatment of Murine Premature Ovarian Failure. *Molecular Medicine Reports*, **13**, 5053-5058. https://doi.org/10.3892/mmr.2016.5191

[92] Hayashi, K. and Saitou, M. (2013) Generation of Eggs from Mouse Embryonic Stem Cells and Induced Pluripotent Stem Cells. *Nature Protocols*, **8**, 1513-1524. https://doi.org/10.1038/nprot.2013.090

[93] Duan, C., Han, J., Zhang, C., Wu, K. and Lin, Y. (2019) UA Promotes Epithelial-mesenchymal Transition in Peritoneal Mesothelial Cells. *Molecular Medicine Reports*, **20**, 2396-2402. https://doi.org/10.3892/mmr.2019.10476

[94] Mirzaeian, L., Eftekhari-Yazdi, P., Esfandiari, F., Eivazkhani, F., Rezazadeh Valojerdi, M., Moini, A., *et al.* (2019) Induction of Mouse Peritoneum Mesenchymal Stem Cells into Germ Cell-Like Cells Using Follicular Fluid and Cumulus Cells-Conditioned Media. *Stem Cells and Development*, **28**, 554-564. https://doi.org/10.1089/scd.2018.0149

[95] Lai, D., Wang, F., Dong, Z. and Zhang, Q. (2014) Skin-Derived Mesenchymal Stem Cells Help Restore Function to Ovaries in a Premature Ovarian Failure Mouse Model. *PLOS ONE*, **9**, e98749. https://doi.org/10.1371/journal.pone.0098749

[96] Aghabozorgi, A.S., Ahangari, N., Eftekhaari, T.E., Torbati, P.N., Bahiraee, A., Ebrahimi, R., *et al.* (2019) Circulating Exosomal Mirnas in Cardiovascular Disease Pathogenesis: New Emerging Hopes. *Journal of Cellular Physiology*, **234**, 21796-21809. https://doi.org/10.1002/jcp.28942