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Review

Tissue-Specific Stem Cells

Pathogenesis and stem cell therapy for premature ovarian failure

S Dan, L Haibo, L Hong*

Abstract

Introduction

One of the most common significant causes for infertility in women is premature ovarian failure. However, the pathogenesis of premature ovarian failure requires further investigation. Three major causes for premature ovarian failure, including X chromosome-linked genetic defects, are autoimmune disorders and long-term toxicity associated with chemotherapy exposure. Chemotherapy-induced premature ovarian failure is reversible for the infertility of women. Damaged ovarian function can be rescued after stem cell transplantation. Nevertheless, the mechanism behind this still remains unclear. Although these stem cells may potentially differentiate into oocytes or granulosa cells, studies have proved they could not develop into fully functional follicles *in vivo*. Both the proliferation and apoptosis of granulosa cells are critical in the development of follicles. Greater numbers of studies have revealed stem cells transplanted into the damaged ovary are more inclined to differentiate into granulosa cell-like cells to replenish the lost granulosa cells. Additionally, factors produced by stem cells could inhibit stromal cell apoptosis, thereby playing a part in rescuing damaged ovarian function. This review discusses several kinds of stem cells which have been studied for treating premature ovarian failure, to get comprehensive understanding for the stem cell therapy mechanisms.

Conclusion

Clinical applications of stem cell therapy have become popular for treating premature ovarian failure. Oocyte and granulosa cells regeneration along with the re-establishment of hormone or cytokine profiles supporting stem cell follicular development may be involved in the improvement of both the damaged ovary function and fertility recovery. Increased understanding of this mechanism will promote its wide clinical application.

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Introduction

Premature ovarian failure (POF) is an ovarian defect that is characterised by the cessation of ovarian function and premature ovarian follicle depletion before 40 years of age; it is also known as premature menopause. This condition may cause female infertility due to an ovulation, hypoestrogenism, sex steroid deficiencies and elevated gonadotropins in women less than 40 years of age[1]. According to pathogenesis, there are two types of POF: one has a limited number of remaining follicles, and the other has an abundant number of follicles with maturation defects. The POF pathophysiology is believed to differ from normal menopause. The declined ovarian function in the first type of POF is reversible, whereas in the latter one the changes are permanent[2,3].

The aetiology of POF is complex. Genetic pathogenesis is among the most commonly known causes[4]. The X chromosome-linked defects play major roles in these genetic pathogeneses, which include X monosomy (also called Turner's syndrome)[5,6], trisomy X[7], mosaicism and X chromosome deletions[8].

Immunological pathogenesis has also been studied in POF aetiology[9]. Autoimmune disorders associated with humoral and cellular immunity result in antibody creation or T-cell-mediated injury of ovarian cells such as granulosa cells (GCs), oocytes and the zona pellucida[10–13].

Chemotherapeutic agents have been widely used to treat cancer patients. Great numbers of studies confirmed that the most commonly seen side effect of chemotherapy is in the reproductive system, most frequently associated with infertility[14–16]. According to a study the treatment of busulfan/cyclophosphamide has mostly affected the ovaries, with lesser effects on the spleen, lungs and kidneys, and no effects on heart, liver, stomach or pancreas[17]. One report suggests that the younger females who suffered from chemotherapy-induced POF still retain enough ovarian function with good quality oocytes to support a successful pregnancy[18]. Although previous studies have proven that fertility could be recovered for the women suffering from chemotherapy-induced POF, further research is required.

Studies related to stem cells that are capable of generating oocytes have been undertaken in mice. This outcome brings some hope for new POF treatments. Stem cells derived from different sources may have some effect on the rescue of ovary function, such as recovering ovary sex hormone function, reducing apoptosis of GCs, and increasing the number of follicles. It has been argued that mechanisms involved in these stem cells can restore ovarian function for the following reasons:

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(1) The *in vivo* evidence of their ability to develop into fully functional follicles is still rare. (2) The transplanted stem cells have been proven to differentiate into GC-like cells much more easily than into oocytes. (3) The improved ovary after stem cell transplantation is a complex mix of many unclear factors requiring further investigation. (4) Stem cell therapy for the POF may increase ovarian granulosa cell tumour (GCT) occurrence arising from sex-cord stromal cells of the ovary, even though it is an uncommon cancer[19]. Taken together, the work remains controversial for clinical and experimental stem cell therapy and presently has no direct clinical application. The aim of this review was to discuss pathogenesis and stem cell therapy for POF.

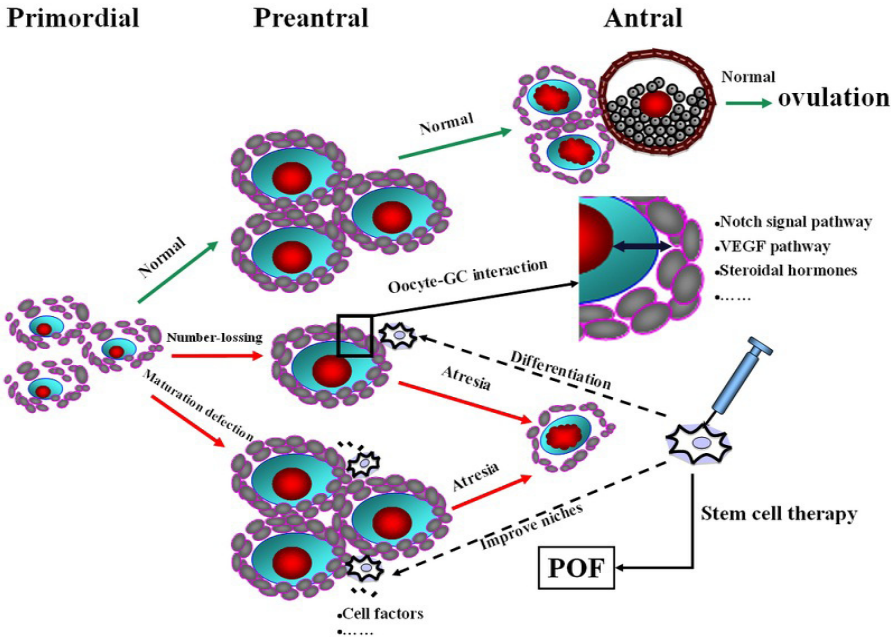

Figure 1: The hypotheses for POF induction by chemotherapy and the stem cell therapy.

Discussion

Mechanisms involved in premature ovarian failure-inducing chemotherapeutic agents

Chemotherapeutic agents are classified into five classes according to their mode of action: alkylating agents, antimetabolites, aneuploidy inducers, radiomimetics and topoisomerase II inhibitors. Antitumour effects of these drugs are often accompanied by their damage on other organs, especially the reproductive system[14]. There are several hypotheses for POF induction by chemotherapy (Figure 1). First, chemical agents can impair follicular stock by driving ovarian cell apoptosis, leading to a finite number of primordial follicles and ensuing POF[20]. Second, some chemical agents interfere with local hormonal regulation related to either follicular recruitment or rest. Third, some chemical agents may interrupt interactions between the oocytes and GCs, which are crucial for follicular growth and maturation[21]. For the above reasons, follicular storage decreases or the follicles do not fully mature, increasing the POF risk.

Folliculogenesis is balanced between granulosa cells proliferation and apoptosis

The development and maturation of ovarian follicles includes several stages: primordial, primary, secondary and antral follicles. These processes are classified mainly by GC proliferation. GCs are the primary cell type in the ovary, providing the physical support and microenvironment required for the developing oocyte. The GC provides biosynthesis of some important ovarian steroids. Primary follicles are characterised by an oocyte surrounded by a single layer of seven or more cuboidal GCs. With GC proliferation, the oocyte is surrounded by two to four complete GC layers, described as preantral follicles; antral follicles form when there are five or more complete GC layers with or without a visible antrum. A follicle has one of two paths: ovulation or atresia. Atretic follicles are defined as containing a degenerating oocyte or more than 10% pyknotic GCs, initiated by either oocytes or GC death[22]. Although atresia is the fate for most follicles, excessive follicle atresia represents a follicle developmental defect such as POF, which is caused by the excessive apoptosis of either an oocyte or somatic cells[23].

GCs are one of the most important follicle components; their proliferation, differentiation and apoptosis are all critical for folliculogenesis. In human foetal ovaries, primitive GCs are available for an unlimited number of germ cells entering epithelial cords to form primordial follicles. Meanwhile, in an adult human, a single germ cell with a single epithelial nest of primitive GCs results in excessive germ cell degeneration during the periovulatory periods. This balance between the proliferation and apoptosis of GCs is the key factor deciding the fate of follicles in adult human ovaries[24].

Oocyte–granulosa cells interaction is crucial for the fate of follicles

Study has revealed that the effect of GC apoptosis on oocytes is mediated by reactive oxygen spe-

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cies (ROS). Germ cells appear more susceptible to oxidative stress as compared with somatic cells[25]. Low levels of ROS have no effect on oocyte development, whereas extensive ROS production followed by GCs excess apoptosis has an adverse effect on oocytes. Additionally, even for GCs, they have varying susceptibility to apoptosis according to the different stages of the cell cycle[23,26].

Oocyte–GC or GC–GC cross talk is important for follicular development. Follicles with oocytes have shown a decreased percentage of apoptotic GCs as compared with follicles without oocytes, although the difference is not statistically significant; this finding reveals oocytes protect GCs from apoptosis to some degree[27,28].

Some signal pathways have been proven to participate in the oocyte–GC cross talk, including the Notch signal pathway, a classical pathway involved in cell proliferation, differentiation and apoptosis[29]. The interaction between GC-expressed NOTCH1-2/3 and oocyte-expressed JAG1 plus DLL3 (known as the Notch ligands) inhibits oocyte apoptosis[30] and promotes GCs proliferation[31]. Another proven signal pathway involved in GC–oocyte and GC–GC cross talk is the vascular endothelial growth factor pathway (VEGF). Note that FLT1, as a VEGF receptor, is overexpressed on oocytes. VEGF produced by GCs can protect oocytes from apoptosis through FLT1 and thus protect itself from apoptosis through neuropilin-1 (NRP1) (another VEGF receptor expressed on GCs), thereby helping follicles early against atresia[32,33].

The role of steroidal hormones on follicular development

Both follicle growth and survival are regulated by a variety of steroidal hormones through either paracrine or autocrine mechanisms[34]. Relevant hormones such as gonadotropins, estradiol, luteotropic hormone (LH) and follicle-stimulating hormone (FSH) are produced by either the ovary or hypothalamus. There is a distinct endocrine profile seen with POF, which is partially considered to contribute to the endogenous apoptosis pathways within follicle activation, thereby leading to abnormal follicular atresia. Oestrogen and progesterone are mainly secreted by GCs in the ovary, which is important for stimulating proliferation as well as protecting them against apoptosis by autocrine mechanisms[35,36]. Chemotherapeutic agents would damage GCs production. The ovaries produce little to no oestrogen in ovarian failure (premature or menopause), resulting in loss of the negative feedback system to the hypothalamus and pituitary glands. Thus, the pituitary glands produce elevated levels of FSH. High levels of FSH reduce the number of GC FSH receptors (FSHR). Studies have revealed that oestrogen (as a protocol of hormone replacement therapy (HRT)) may increase both the number and sensitivity of FSHRs on GCs and promote follicular recruitment[37].

The LH surge is an important event for follicle maturation, which occurs following the stimulation of gonadotropin-releasing hormone in the preovulatory stage. Studies have shown that the LH surge appearance would improve GC differentiation and avoid apoptosis in rodents[38]. The progesterone receptor has been proven to be a potential mediator which is induced by the LH surge, therefore promoting GC proliferation and follicular survival.

HRT, in aiming to correct the disordered hormone profile, has been used as one of the most commonly effective treatments for treating POF[37]. However, HRT carries a notably increased risk of vascular disease, osteoporosis and even ovarian cancer and breast cancer for these patients[39,40].

Stem cell therapy for premature ovarian failure

As shown in some clinical reports, stem cell transplantation could help the recovery of ovarian function in some women who suffered premature menopause by chemotherapeutic agents. We will discuss in detail its promise as an ideal potential treatment for POF.

The view of oogenesis being restricted to embryonic life in most mammalian species has been challenged[41]. However, some studies continue to refute this[42]. It is still acceptable to note that the primordial follicle population remains limited during female reproductive life. Once the storage is depleted, females are considered to have entered reproductive senescence or menopause. People have been trying to use stem cell therapy for POF-induced infertility based on the possibility of long-term replenishment for damaged oocytes. These transplanted stem cells could reside in the ovarian tissue and rescue ovarian function, as seen in the preclinical mouse model of chemotherapy-induced POF[43]; however, these mechanisms require further investigation. Other studies showed that stem cells could inhibit stromal cell apoptosis through the secretion of stanniocalcin-1 and some other paracrine factors[44–46]. Thus, the recovery of damaged ovarian function in the POF after stem cell transplantation is complex, with transplanted stem cells salvaging the sufficient number of existing oocytes and also helping to repair the damaged ovarian niches. There are several stem cell types that have been investigated in POF treatment. Their recovery of ovary function demonstrates some significant differences from other techniques, some of which are listed in Table 1.

Follicles generated from embryonic and induced pluripotent stem cells

Pluripotent stem cells (PSCs) have the potential to be induced into oocytes: within the past decade, studies have showed that mouse

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Table 1 The stem cells used in POF therapy

Stem cells types	References	Stem cells and germ cells markers	Chemotherapy	Morphologically of ovary after stem cells trans-planted	Hormone or cytokines profile changes	Tracking of stem cells	Survival time
Bone marrow transplantation	Lee et al.[43]	/	/	/	BMP15↑, FMR1↑, FSHR↑, INHA↑, AMH↑, NOBOX↑, FOXO3↑, EIF2B↑, FIGLA↑and GDF9↑	Reactivate host oogenesis; not generate oocytes	/
CD44 +/CD105 + human amniotic fluid mesenchy-mal stem cells	Liu et al.[73]	CD29, CD44, CD73, CD90, CD105 and CD166	Intraperitoneal injection of cyclophosphamide	/	/	/	Survive and proliferate over the long-term in the ovarian tissues.
Adipose-derived stem cells	Sun et al.[63]	/	Intraperitoneal injection of cyclophosphamide	Follicle number ↑, ovulation number↑ and apoptotic GCs↓	HGF ↑, VEGF↑, PGF↑ and TGF-β↑	Not participate in follicle regeneration	A large number of engrafted cells died within 1 month after transplantation.
Umbilical cord mesenchymal stem cells	Wang et al.[64]	CD29, CD44,CD90 and CD105	Intraperitoneal injection of cyclophosphamide	Apoptosis of GC↓, number of follicles↑and oocyte containing follicles↑	E2 ↑	Not develop into follicles	/
Human amniotic fluid cells	Lai et al.[72]	BLIMP1, STELLA, DAZL, VASA, STRA8, SCP3, SCP1 and GDF9	Intraperitoneal injection of cyclophosphamide and busulphan	Oocytes at all stages ↑	AMH↑and FSHR ↑	Differentiated into GCs; not germ cell	/

AMH, antimüllerian hormone; BMP15, bone morphogenetic protein15; FSHR, follicle-stimulating hormone receptor; HGF, hepatocyte growth factor; PGF, placental growth factor; POF, premature ovarian failure; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-β; E2, oestrogen; INHA, inhibin alpha; FIGLA, factor in the germline alpha GC, granulosa cell.The mark of '/'represent that there is no report by now.

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embryonic stem cells (ESCs) can form oocyte-like cells *in vitro*[47]. Mouse ESCs can be induced into follicle-like structures with a single oocyte-like cell, surrounded by one or more layers of tightly adherent somatic cells[48].

New studies have shown the process of oocyte generation from ESCs[49]. ESCs are first induced into primordial germ cell (PGC)-like cells that are in turn aggregated with somatic cells of female embryonic gonads. These aggregations are transplanted under the ovarian bursa, where it matures and prepares for fertilisation. This reconstitution of oogenesis from ESCs not only has immense applications for both human and animal reproduction, but also has meaningful applications in basic biology[50].

Although multiple studies have focused on the differentiation of ESCs into oocytes[51], this technique has a very low frequency for follicles capable of maturation, fertilisation, embryogenesis and development into live offspring *in vitro*. Other studies showed evidence rat ESCs that differentiated into ovarian cell types, such as somatic cells. These somatic cells of follicle-like structures have some characteristics of endogenous ovarian-derived GCs[52,53]. Studies have implied that applications of ESC in POF may be based more on development into GCs as the supplement for extensive chemotherapy-induced apoptosis, rather than direct differentiation into a fully functional follicle.

Similar to ESC, induced PSCs (iPSCs) are another option for POF stem cells therapy. The iPSCs can also be induced into oocytes *in vitro*[54]. One study reported that goat iPSCs could be generated into germ cell-like cells and differentiates into goat oocyte-like structures[55]. Hence, studies have demonstrated that culturing with GCs could help to differentiate them into GC-like cells[56]. The rat iPSCs and ESCs could be then differentiated into GC-like cells *in vitro,* providing evidence of possible cell therapy for POF.

Mesenchymal stem cells in stem cell therapy of premature ovarian failure

Mesenchymal stem cells (MSCs) have been studied for repairing damaged ovaries induced by chemotherapy[57]. Umbilical cord mesenchymal stem cells (UCMSCs) have many advantages over other MSCs. The low expression of human leukocyte antigen major histocompatibility complex I (MHC I) and the absence of MHC II molecules seen in UCMSCs allows them to properly evade immune reaction, even in allogeneic transplantations[58–60]. Hence, UCMSCs transplantation often results in little to no immune rejection[61]. Although studies for use in POF treatment remain rare, UCMSCs transplantation could rescue mouse ovary function through the paracrine pathway. For example, UCMSCs could reduce GC apoptosis through effects on its G-protein coupled receptor protein signalling and MAPK pathways, both of which are also important for follicle and oocyte growth.

Adipose-derived stem cells (ADSCs), as another type of MSC, can be differentiated into multiple cell types; however, they have poor immunogenic properties[62]. The ADSCs protective role in POF has been investigated in mice[63]. In labelling these transplanted MSCs, studies found they do not develop into ovarian follicles[64]. However, the follicle and ovulation numbers significantly increase after these stem cells are transplanted into mice. Many growth factors such as VEGF, transforming growth factor-β and placental growth factor can be secreted by ADSCs, which are important for both follicle and oocyte growth. Therefore, we preliminarily concluded that these MSCs function primarily by improving the damaged ovarian niches that are induced by chemotherapy.

Cells derived from human amniotic fluid in premature ovarian failure stem cell therapy

Cells derived from human amniotic fluid (hAFCs) exhibit stem cell characteristics, such as high differentiation potential and proliferative activity[65,66]. These kind of stem cells express not only stem cell markers[67–69], but also germ cell markers such as BLIMP1 and DAZ *in vitro*[70,71]. One study reported that implanted hAFCs participate in follicle formation in the chemically damaged murine ovary[72]. Although GFP tracking of transplanted hAFCs demonstrated infiltration into a chemically damaged murine ovarian niche, this portion of hAFCs in the ovary ultimately differentiated into GCs but not germ cells. No evidence has shown that hAFCs recover ovarian function in the POF by restoring folliculogenesis.

CD44 +/CD105 + hAFCs isolated from HuAFCs have shown their special properties in the stem cell transplantation treatment for POF[73]. These stem cells underwent normal cell division and proliferation over the long-term, possibly avoiding the lack of survival and self-renewal seen in other transplanted stem cells located in ovarian tissues.

Bone marrow-derived cells in premature ovarian failure stem cell therapy

Bone marrow transplantation (BMT) has been used to rescue ovarian function and fertility in some reproductive-age women after long-term chemotherapy use[43,74]. Some investigators suggested interactions of bone marrow (BM)-derived cells with ovarian surface epithelium stem cells would give rise to PGCs; some unexplained return of ovarian function after BMT has been attributed to the alternative oogenesis derived from BM stem cells[75,76]. Study has shown that these allogeneic oocytes developed from BMT could not alleviate ovarian infertility[77]. Meanwhile, doubts arose from the report by Johnson that

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germ cells formed in BM completely disappeared in ovariectomised mice. Moreover, this study showed that BM cells, or any other normally circulating cells travelling to the ovaries through the bloodstream, exhibited properties of committed blood leukocytes instead of mature and ovulated oocytes. Thus, mechanisms involved in BMT treatment of POF require further investigation.

Although these PSCs have different mechanisms in repairing damaged ovarian tissue associated with POF, they have a common treatment goal in re-establishing normal hormonal function, increasing follicle and ovulation number and reducing GC apoptosis. There are many prospects for stem cell therapy mechanisms associated with POF. Among these variations, we elucidated several kinds of stem cells and tried to define the exact way these transplanted stem cells helped to recover the damaged ovary function.

Possible challenges related to premature ovarian failure stem cell therapy

Greater amounts of research about stem cell therapy in POF treatment have been carried out. The survival time associated with these transplanted stem cells is becoming more important. Some stem cells have been proven to have the potential for improving the damaged ovarian niches *in vitro*. However, the poor survival time *in vivo* remains a challenge for greater clinical application.

The other challenge relates to tumour occurrence. Inhibiting the GC apoptosis and improving its proliferation have proven to be a common pathway in processing stem cell therapy for POF. Both of these stem cell types, whether they differentiated into GCs or offered a niche supporting GC proliferation, give rise to the GCTs. We should not ignore this evidence although the associated evidence remains minimal.

Conclusion

POF has been considered as one of the most important causes for the infertility of women. The return of ovary function has been seen in many cases after treatments with HRT and stem cell therapy. Clinical applications of stem cell therapy have become popular for treating POF. Oocyte and GC regeneration along with the re-establishment of hormone or cytokine profiles supporting stem cell follicular development may be all involved in the improvement of both the damaged ovary function and fertility recovery. Thus, many complex mechanisms are involved in stem cell POF therapy. Increased understanding of this mechanism will promote its wide clinical application.

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Abbreviations list

ADSCs, adipose-derived stem cells; BM, bone marrow; BMT, bone marrow transplantation; ESCs, embryonic stem cells; FSH, follicle-stimulating hormone; GCs, granulosa cells; GCT, granulosa cell tumour; hAFCs, human amniotic fluid; HRT, hormone replacement therapy; iPSCs, induced pluripotent stem cells; LH, luteotropic hormone; MHC, major histocompatibility complex; MSCs, mesenchymal stem cells; PGCs, putative germ cells; POF, premature ovarian failure; PSCs, pluripotent stem cells; UCMSCs, umbilical cord mesenchymal stem cells; VEGF, vascular endothelial growth factor pathway.

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