REVIEW
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Mesenchymal stem cells for restoration of ovarian function

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With the progress of regenerative medicine, mesenchymal stem cells (MSCs) have received attention as a way to restore ovarian function. It has been reported that MSCs derived from bone marrow, adipose, umbilical cord blood, menstrual blood, and amniotic fluid improved ovarian function. In light of previous studies and advances in this field, there are increased expectations regarding the utilization of MSCs to restore ovarian function. This review summarizes recent research into potential applications of MSCs in women with infertility or primary ovarian insufficiency, including cases where these conditions are induced by anticancer therapy.

Keywords: Mesenchymal stem cell; Ovarian function

Characteristics of mesenchymal stem cells

Mesenchymal stem cells (MSCs), which were termed more than 25 years ago [1], represent a class of cells from human [2] and mammalian bone marrow and periosteum [3] that could be isolated and expanded in culture while maintaining their *in vitro* capacity to be induced to form a variety of mesodermal phenotypes and tissues. The acronym MSC can be understood as referring to mesenchymal stromal cells, multipotent stromal cells, mesenchymal progenitor cells, bone marrow stromal cells, bone marrow-derived MSCs, mesenchymal precursor cells, skeletal stem cells, and multipotent mesenchymal stromal cells [4]. To promote terminological clarity, the International Society for Cellular Therapy (ISCT) has officially defined MSCs to be multipotent mesenchymal stromal cells, suggesting that this should refer to cells from stromal tissues with plastic-adherent characteristics, while reserving the term "mesenchymal stem cells" to denote the subpopulation that actually has the two cardinal properties of stem cells (self-renewal and the capacity to differentiate down multiple lineages) [5]. The ISCT proposed three criteria to define MSCs. First, MSCs must be plastic-adherent in standard culture conditions. Second, more than 95% of MSCs must express cluster of differentiation (CD)105, CD73, and CD90, while lacking expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and human leukocyte antigen (HLA) class II. Third, these cells must be able to differentiate into osteoblasts, adipocytes, and chondroblasts under standard *in vitro* differentiating conditions [5].

MSCs can be derived from several tissues in the adult or infant human body, including adipose tissue, peripheral blood, umbilical cord blood, banked umbilical cord blood, umbilical cord, umbilical cord membrane, umbilical cord vein, Wharton's jelly of the umbilical cord, placenta, decidua basalis, ligamentum flavum, amniotic fluid, amniotic membrane, dental pulp, chorionic villi of the human placenta, fetal membranes, menstrual blood, breast milk, and urine [6]. MSCs display a powerful ability to regulate immune responses, including by suppressing T cell proliferation, influencing dendritic cell maturation and function, suppressing B cell proliferation and terminal differentiation, and modulating other immune cells such as natural killer cells and macrophages [7]. Another utility of MSCs in cell therapies is homing and transendothelial migration. In the circulation, MSCs

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are transported to the site of damage through the vascular system, by chemokine (C–C motif), adhesion molecules (P-selectin and the VCAM-1), and matrix metalloproteinases (MMPs; MMP-2 and membrane type 1 MMP) [8]. After MSCs home to damaged tissue sites for repair, they interact closely with local stimuli, such as inflammatory cytokines, ligands of Toll-like receptors, and hypoxia, which can stimulate MSCs to produce large amounts of growth factors that perform multiple functions for tissue regeneration [8]. Based on these actions of MSCs, Caplan proposed reconceptualizing the acronym MSC as referring to "medical signaling cells [9]."

General ovarian function and premature ovarian failure

Follicles are the functional units of the ovary, and consist of an oocyte and its supporting cells, such as granulosa cells, theca cells, and stromal cells. The cells in the follicle release an oocyte monthly, resulting in fertility, and produce hormones such as estradiol and progesterone to maintain women's overall health and to sustain pregnancy [10].

Premature ovarian failure (POF; also known as primary ovarian insufficiency), which in other words represents premature menopause, is a mysterious and complicated disease. The prevalence of POF is one in 250 women under the age of 35 years and one in 100 women under the age of 40 years. The most important mechanisms in POF are follicle dysfunction and follicle depletion [11]. Although the cause of POF has not yet been fully elucidated, genetic, endocrine, paracrine, mitochondrial dysfunction–related, and metabolic factors can affect the quality of the follicular pool and oocytes [12]. Recently, POF after chemotherapy has emerged as a major long-term adverse effect of anticancer treatment, which increases the risk of infertility and degenerative health problems. Such responses to chemotherapy may be a particular problem in young women because loss of ovarian reserve is closely related to the risk of female infertility. The exact mechanism through which anticancer drugs exert ovarian toxicity has not been fully established [13], and it seems to depend on the type of drug and the type of cell tested [14]. Stroma and granulosa cells are especially strongly affected by most anticancer drugs via apoptosis. Oocytes are known to be affected by indirect toxicity through the stroma and granulosa cells that surround them. An alkylating agent, cyclophosphamide (CTX) induces double-strand breaks of DNA in actively proliferating cells, such as granulosa cells and stromal cells, and oocytes also experience damage caused by CTX and other anticancer drugs [13]. However, another interesting explanation has been proposed for the exhaustion of primordial follicles that are not proliferating and are therefore less sensitive to DNA damage. Primordial follicles in the resting state or activation were found to be controlled by the intracellular phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR signaling pathway [15]. Phosphatase and tensin homolog (PTEN) is a reversible inhibitor of PI3K, and is known to be a tumor suppressor in humans [16]. Anticancer drug treatment such as CTX or cisplatin was found to induce depletion of primordial follicles via overrecruitment [17], and oocyte-specific PTEN deletion induced premature activation of the primordial follicle pool in a mouse model [18]. Therefore, the preservation of fertility and ovarian function should be considered as a major issue for reproductive women receiving chemotherapy. Several options exist for fertility preservation, such as cryopreservation of embryos, mature oocytes, or ovarian tissue. However, most protocols are for fertility preservation before anticancer therapy. Therefore, it is necessary to investigate possible ways to restore ovarian function.

MSC therapy and recovery of ovarian function

MSC therapy has been considered as a new option to treat female infertility or to restore ovarian function. Numerous studies have verified the protective effect of ovarian function resulting from administration of MSCs obtained from various cell sources in animal models of POF (Table 1) [19-48]. These studies of MSC transplantation have shown therapeutic potential through restoration of ovarian function and structure [19,49]. MSCs have been found to secrete growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF) into culture medium [30], to reduce germ cell and stromal cell apoptosis, and to enhance folliculogenesis through improvements in the microenvironment [48]. As in other forms of cell therapy, two different administration methods have been considered for the use of MSCs to recover ovarian function. Intravenous administration through the tail vein has been introduced in mouse and rat models, and techniques for local administration into the ovaries have also been extensively developed [50]. In POF resulting from chemotherapy with an anticancer drug, transplantation of MSCs was found to induce ovarian function recovery, including estradiol production and improvements in ovarian structure [30,33]. MSCs showed a protective effect on apoptosis in stromal cell or granulosa cells in response to anticancer drugs, such as CTX or cisplatin (Table 1). Certain cytokines, including VEGF, HGF, and IGF-1 produced by MSCs may inhibit apoptosis in granulosa cells and upregulate B-cell lymphoma-2 *in vivo* [51]. Another expected mechanism of MSCs is their antifibrotic effects. Ovarian fibrogenesis is related to certain cytokines, including MMPs, tissue inhibitors of MMPs, transforming growth factor β-1, VEGF, and endothelin-1. MSCs may inhibit the proliferation of fibroblasts and decrease the deposition of extracellular matrix [51]. Angiogenesis is important mechanism in ovarian recovery. VEGF, fibroblast growth

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Table 1. Studies on ovarian function supported by MSC administration

Study	Cell source	Subject	Patient/animal	Administration	Journal
Gabr (2016) [20]	Autologous bone marrow MSC	Premature ovarian failure	Patient	Ovarian tissue/artery	J Tissue Sci Eng
Edessy (2016) [21]	Autologous bone marrow MSC	Idiopathic premature ovarian failure	Patient	Ovarian autologous MSC injection	Acta Med Int
Ding (2018) [22]	Human amniotic MSC	Natural aging	12–14-month-old mice	Into the ovary	Stem Cell Res Ther
Grady (2018) [23]	Mares' bone marrow MSC (age, 20–29 year)	Natural aging	Mare	Intra-ovarian	J Assist Reprod Genet
Kalhori (2018) [24]	Mouse bone marrow	Polycystic ovarian syndrome	Mice	Tail vein	Cytotherapy
Feng (2018) [25]	Human menstrual blood-derived	CTX	Mice	Tail vein	Stem Cell Rev
Bao (2018) [26]	Mouse bone marrow	CTX, busulfan	Mice	Tail intravenously	Gynecol Endocrinol
Ling (2017) [27]	Human amnion-derived MSC	CTX	Rat	Tail vein	Stem Cell Res Ther
Mohamed (2018) [28]	Human bone marrow	CTX, busulfan	Mice	Into the ovary	Reprod Sci
Yin (2018) [29]	Human placenta-derived	pZP3 to produce autoimmune injury	Mice	Into the ovary	Reprod Sci
Elfayomy (2016) [30]	Human umbilical cord blood	Paclitaxel	Rat	Direct injection into the bilateral ovary	Tissue Cell
Gabr (2016) [31]	Rat bone marrow	CTX	Rat	Intravenously	Microsc Res Tech
Pan (2017) [32]	Human umbilical cord/ human amniotic	CTX	Rat	Into the ovary	Arch Gynecol Obstet
Song (2016) [33]	Human umbilical cord	CTX	Rat	Tail intravenous/ bilateral ovary	Biomed Res Int
Su (2016) [34]	Rat adipose-derived	Tripterygium glycosides	Rat	Into the ovary	Hum Reprod
Lai (2015) [35]	Human endometrial	CTX, busulfan	Mice	Tail vein	J Transl Med
Fouad (2016) [36]	Human amniotic membrane/ adipose tissue	CTX	Rat	Intravenously	J Adv Res
Kilic (2014) [37]	Rat bone marrow	CTX	Rat	Intraperitoneal injection	Gynecol Endocrinol
Liu (2014) [38]	Human menstrual blood stem cell	CTX	Mice	Engrafted in the ovary	Stem Cells Dev
Liu (2014) [39]	Rat bone marrow	Cisplatin	Rat	Tail vein	Mol Cells
Xiao (2014) [40]	Amniotic fluid stem cell	CTX, busulfan	Mice	Into the ovary	PLoS One
Takehara (2013) [41]	Human adipose-derived	CTX	Rat	Into the ovary	Lab Invest
Wang (2013) [42]	Human umbilical cord	CTX	Mice	Intravenously	Biomed Res Int
Wang (2013) [43]	Human amniotic epithelial cell	CTX	Mice	Into the ovary	Stem Cell Res Ther
Zhang (2017) [44]	Human bone marrow	Human ovarian tissue transplantation	Immune-deficiency mice	Ovarian transplantation	Reprod Biol Endocrinol
Abd-Allah (2013) [45]	Male rabbit bone marrow	CTX	Rabbit	Intravenously in the earveins	Cytotherapy
Guo (2013) [46]	Rat bone marrow	Perimenopause	Rat	Tail vein	BMC Cell Biol
Liu (2012)[47]	Human amniotic fluid	CTX	Mice	Into the ovary	Int J Med Sci
Fu (2008) [48]	Rat bone marrow	CTX	Rat	Into the bilateral ovary	Cytotherapy

MSC, mesenchymal stem cell; CTX, cyclophosphamide.

factor-2, and in particular angiogenin from MSCs induced neovascularization and facilitated blood perfusion of damaged ovarian tissues [44,51]. Ovarian function in POF mice recovered after human placenta-derived MSC transplantation through the regulation of regulatory T cells and associated cytokines [29]. After human amniotic MSCs were transplanted into naturally aged mice at 12–14 months, transplanted MSCs played a central role in inhibiting ovarian aging by secreting epidermal growth factor and HGF [22]. However, the mechanism through which MSC transplantation promotes ovarian function needs to be further investigated.

New candidate MSCs for restoring ovarian function

Multiple doses of MSCs in the range of 1–5 $\times 10^6$ cells per kilogram of body weight are required for clinical application [52], and for animal experiments, quantities of 1×10^6 to 5×10^8 cells per mouse [24] or rat [30] have been used. However, obtaining MSCs from adult tissue requires appropriate donors, and in most cases invasive procedures must be performed. Furthermore, long-term culture potentially increases the risk of inducing chromosomal aberrations and heterogeneous cell populations, making it difficult to standardize protocols [52]. Human embryonic stem cells (hESCs) are derived from the inner cell mass of blastocysts, which is pluripotent and can differentiate into all three germ layers. Several studies have reported that MSCs can be derived from hESCs, and that they express MSC surface markers and differentiate into three germ layers (such as chondrocytes, osteoblasts, and adipocytes) [53]. Furthermore, it was reported that these cells exerted immunomodulatory effects in an *in vitro* experiment [54]. hESC-derived MSCs were found to be equivalent to bone marrow- or adipose-derived MSCs, making them an alternative source of MSCs for restoration of ovarian function [52]. However, ethical issues involving the use of human embryos remain, and concerns are still being discussed regarding the unwanted, unexpected, or uncontrolled differentiation of hESCs in transplantation. Nevertheless, clinical trials investigating the potential of therapy based on hESCs and hESC-derived MSCs for various diseases have been launched [55]. Induced pluripotent stem cells (iPSCs), could be another source of MSCs. iPSCs can be obtained with minimally invasive procedures, and avoid the ethical concerns about embryo use and hESCs. Furthermore, using autologous or HLA-matched iPSC lines may make it possible to minimize immunological problems [56,57].

Anothor candidate for MSCs is exosomes, which are membrane-bound biological nanoparticles secreted from cells. They circulate systemically, and carry in mRNA, long noncoding RNA, microRNA, proteins, and lipids. Stimulatory or inhibitory functional outcomes in response to exosomes have been found for processes including cell proliferation, apoptosis, cytokine production, immune modulation, and metastasis in cancer physiology [58]. Exosomes from MSC-mediated cell therapy were inroduced in numerous disease models, and have been found to promote functional recovery [59]. Exosomes derived from human adipose or umbilical cord blood MSCs improved ovarian function in a mouse model of premature ovarian insufficiency [60,61]. However, some problems with standardization in exosome isolation, characterization, and adiministration techniques still need to be resolved [59,62].

Safety issues of MSCs

The safety issues of MSCs should be addressed, because after MSC administration, mild adverse effects have been observed. The most severe adverse effect is that unfortunately, long-term cultured MSCs promote tumor growth and metastasis. A large number of cells must be produced for clinical-grade production of MSCs, requiring *in vitro* expansion, but MSCs at higher passages could lead to cell transformation. Depending upon the severity of disease, the optimal dose and specific administration time must be determined. It is necessary to thoroughly understand the underlying mechanisms that regulate and modulate MSCs, and appropriate administration methods should be developed.

Conclusion

MSCs have become the most efficient cell type in clinical applications of cell therapy. Multiple degenerative diseases and several immune-related diseases have been reported to respond to MSC transplantation. MSCs from several sources, including bone marrow, adipose tissue, umbilical cord, umbilical cord blood, placenta, amniotic fluid, endometrium, Wharton's jelly, and menstrual blood, have been the subjects of successful experiments. According to many reports, MSCs could promote the recovery of ovarian function through inhibition of granulosa cell apoptosis and follicular atresia by upregulation of anti-Müllerian hormone and follicle-stimulating hormone receptor expression in granulosa cells. The ongoing research into the regenerative use of MSCs to recover ovarian function can be a source of hope to POF patients and infertile or subfertile women.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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