Regenerative Therapy 26 (2024) 1087–1098

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Mesenchymal stem cells: Guardians of women's health

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ARTICLE INFO

Article history:
Received 5 September 2024
Received in revised form
13 October 2024
Accepted 23 October 2024

Keywords:
Mesenchymal stem cells
Obstetrics and gynecology
Clinical therapy
Ovaries
Endometrium

ABSTRACT

Mesenchymal stem cells (MSCs) have attracted more and more attention because of their multidirectional differentiation potential, immune regulatory abilities and self-renewal capacity. In recent years, their use has become prominent in the domains of regenerative medicine and tissue engineering. MSCs have shown promise in therapeutic studies for a variety of diseases and have become a new source of innovative solutions for the treatment of some obstetric and gynecological diseases. This review systematically presents the latest research on the use of MSCs in the treatment of obstetrics- and gynecology-related diseases. Specifically, this review encompasses the latest findings related to the role of MSCs in premature ovarian failure, polycystic ovary syndrome, ovarian cancer, fallopian tube-related diseases, uterine adhesions, endometriosis, cesarean scar defects, postmenopausal osteoporosis, and pelvic floor dysfunction. The shortcomings and challenges of the future use of MSCs in disease treatment are also discussed, with the intent to motivate improvements in MSC applications in clinical therapy. It is believed that with further research, MSCs will play a more important role in the treatment of obstetrics- and gynecology-related diseases.

Contents

Abbreviations: α-SMA, α-smooth muscle actin; ADMSCs, adipose-derived mesenchymal stem cells; BMPs, bone morphogenetic proteins; BMDCs, bone marrow-derived cells; CASP-3, cysteine-aspartate protease 3; COL1A1, collagen type I alpha 1 chain; COL5A2, collagen type V alpha 2 chain; Cs, cisplatin; CSD, cesarean scar defect; CTGF, connective tissue growth factor; CTX, cyclophosphamide; FSH, follicle-stimulating hormone; GCST, granulocyte colony-stimulating factor; Gel-ADH, hydrazide-grafted gelatin; GPR35, G protein-coupled receptor 35; HA-CHO, oxidized hyaluronic acid; hBM-MSCs, human bone marrow mesenchymal stem cells; hEMSCs, human endometrial mesenchymal stem cells; hUCMSCs, human umbilical cord mesenchymal stem cells; IFN-γ, interferon-γ; IL-1β, interleukin-1β; IUA, Intrauterine adhesion; LPP, leak point pressure; LAMC2, laminin γ2; miR-146a, microRNA-146a; MB-MSCs, menstrual blood mesenchymal stem cells; MSCs, mesenchymal stem cells; PCNA, proliferating cell nuclear antigen; PCOS, polycystic ovary syndrome; PDGF, platelet-derived growth factor; PFD, pelvic floor dysfunction; PGA, polyglycolic acid; PI3K, phosphatidylinositol 3-kinase; POF, premature ovarian failure; PMO, postmenopausal osteoporosis; PTEN, phosphatase and tensin homolog; PTH, parathyroid hormone; PTHR-1, parathyroid hormone receptor-1; SUI, stress urinary incontinence; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1; VEGF, vascular endothelial growth factor.

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2024.10.011

1. Introduction

In 1991, scientists isolated MSCs, referred to as "fibroblast-like cells", from umbilical cord-derived Wharton's jelly and cultured them [1]. MSCs are stem cells with multidirectional differentiation potential that can differentiate into a wide range of cell types [2]. It was first demonstrated in 1999 that MSCs have the ability to differentiate into adipocytes, bone cells or chondrocytes in vitro. These findings have motivated scientists to study MSCs with the expectation that MSCs will play a significant role in the field of regenerative medicine [3]. MSCs can be transplanted into different people without fear of rejection because of their potent immunosuppressive function, thus preventing adverse reactions by the immune system [4]. MSCs can comprehensively repair damaged cells in the human body at the cellular level; these cells have not only regenerative and reparative effects on tissue cells but also powerful immunomodulatory functions [5]. These functions present a novel approach to cell regeneration therapy for challenging obstetrics and gynecologic diseases, such as ovarian, endometrial and pelvic dysfunction. It is believed that with in-depth research on MSCs, these cells will play a greater role in disease treatment and women's health in the future.

2. Application of MSCs to ovarian diseases

2.1. Premature ovarian failure

Premature ovarian failure (POF) is defined as the onset of amenorrhea before the age of 40 years, accompanied by endocrine abnormalities and menopausal symptoms, such as elevated levels of follicle-stimulating hormone (FSH) (FSH >40 U/L) and decreased levels of estrogen [6]. The onset of POF is associated with chemical drug damage, abnormal autoimmune function, genetics and other factors [7–9]. This disease has become a major cause of infertility among women [10,11]. Conventional clinical interventions for women with POF include estrogen–progestin replacement therapy, ovulation induction therapy, and immune intervention therapy [12,13]. However, these agents can alleviate only POF and cannot effectively restore the fertility of patients. On the other hand, MSCs have not only regenerative and repairing effects on tissue cells but also potent immunomodulatory effects [14]. MSC transplantation may be the best and most effective way to treat POF. The results of numerous studies conducted in this field have suggested that MSCs are an effective treatment for POF [15]. In animal experiments, several researchers transplanted platelet-derived MSCs into mice with cyclophosphamide (CTX)-induced POF. The results showed that chorionic plate-derived MSCs can restore serum hormone levels and promote the development of follicles and oocytes in mice and that the ovarian function of the mice was significantly improved [16] (Table 1). Similarly, human umbilical cord mesenchymal stem cells (hUCMSCs) were transplanted into rats with CTX-induced POF, and abnormalities in the hormone levels of Premature ovarian insufficiency rats were significantly improved, granulosa cell apoptosis was inhibited, and follicle growth and development were promoted [17] (Table 1). Although the conditions in mouse and rat studies are not consistent with those in actual humans, the results of these studies suggest that MSC transplantation has great potential in POF treatment. In clinical studies, researchers have injected human bone marrow mesenchymal stem cells (hBM-MSCs) into patients' ovaries, and the results showed that MSC treatment not only improved hormone secretion levels in patients with POF but also restored menstruation in some patients, allowing them to deliver healthy babies [18] (Table 1). Furthermore, one study indicated that all patients who underwent MSC transplantation had improved ovarian function, as evidenced by increased follicular development and improved ovum collection. The investigators also concluded that patients with POF who have a shorter duration of amenorrhea (less than one year) are more likely to benefit from MSC therapy [19] (Table 1). This finding indicates that intraovarian transplantation of hBM-MSCs may be a safe stem cell-based treatment that can restore fertility in patients with POF [20].

Chemotherapeutic agents are commonly used to treat malignant tumors. However, chemotherapy can lead to significant ovarian damage and decreased fertility, which are serious adverse effects [36]. Recently, hUCMSC-derived conditioned medium was shown to alleviate cisplatin (Cs)-induced follicular depletion and protect against fertility. hUCMSC-derived conditioned medium reduced Cs-induced apoptosis of oocytes and granulosa cells. MSCs may play a protective role against follicular and granulosa cells by increasing the expression of phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) via granulocyte colony-stimulating factor (GCST) [37] (Fig. 1a). These findings suggest that hUCMSC-CM has enormous potential for the treatment of chemotherapy-induced POF. Two patients with POF from the Caucasus who underwent laparoscopic intraovarian hBM-MSC transplantation for two months were also reported to have restored ovarian estrogen production and menstruation and improved preoperative menopausal symptoms [21] (Table 1). In summary, the application of MSC therapy can effectively improve ovarian function. This therapy provides new hope for patients with POF.

Table 1
Research progress on mesenchymal stem cells in obstetrics and gynecology diseases.

Source	Clinical research	Research status	References
Plate-derived MSCs	POF	The serum hormone levels of mice are restored, promoting the development of follicles and oocytes in mice. The ovarian function of mice is significantly improved.	[16]
hUCMSCs	POF	The abnormal hormone levels in rats are significantly improved, the apoptosis of granulosa cells is inhibited, and the growth and development of follicles are promoted.	[17]
hBM-MSCs	POF	MSC treatment not only improves hormone secretion levels in patients with POF but also restores menstruation to some of the patients and allows them to deliver healthy babies.	[18]
hUCMSCs	POF	Patients show increased follicular development and improved ovum collection. In addition, patients with POF with a shorter duration of amenorrhea (less than one year) are more likely to benefit from MSC therapy.	[19]
hBM-MSCs	POF	Two patients who underwent laparoscopic intraovarian hBM-MSC transplantation for two months were also reported to have restored ovarian estrogen production and menstruation and improved preoperative menopausal symptoms.	[21]
ADMSCs	PCOS	ADMSCs restore ovarian structure, increase the oocyte number and corpus luteum, and decrease the number of abnormal cystic follicles in a rat model of PCOS.	[22]
hBM-MSCs	PCOS	BMPs secreted by hBM-MSCs regulate cellular androgen secretion and alter enzymes required for steroidogenesis. BMP-2 can significantly inhibit the proliferation of cells, the expression of androgen synthesis genes and the expression of inflammatory genes. Overexpression of BMP-2 may enhance the efficacy of BM-MSC-based stem cell therapy.	[23]
hUCMSCs	Ovarian cancer	The hUCMSC-derived exosome miR-146a reduces the growth viability and tolerance of ovarian cancer cells to docetaxel and paclitaxel chemotherapy. This is achieved by the laminin γ2 (LAMC2)-mediated PI3K/Akt signaling pathway.	[24]
MSCs	Ovarian cancer	The promoter was implanted into the MSCs. This promoter is activated when the stem cells are exposed to external stress and then converts the cancer drug 5-fluorocytosine into an active state. This can pinpoint tumor tissue without harming healthy tissue.	[25]
hBM-MSCs	Fallopian tube diseases	MSCs mediate the expression of VEGF and PCNA in the fallopian tubes and promote tissue cell apoptosis to repair damaged tubes.	[26]
hUCMSCs	IUA	Implantation of collagen scaffolds with hUCMSCs in IUA rats can reduce the area of endometrial fibrosis, increase the number of endometrial glands, and promote the proliferation of endometrial cells.	[27]
hUCMSCs	IUA	The expression of fibrosis markers α-SMA and TGF-β is reduced in treated rats, and endometrial morphology and embryo implantation rate are significantly improved.	[28]
hUCMSCs	IUA	An injectable hydrogel based on HA-CHO and Gel-ADH was mixed with hUCMSCs to improve the retention rate of hUCMSCs in the endometrium.	[29]
hUCMSCs	IUA	Approximately 1500 MSCs were loaded into 560-μm homogeneous Matrigel microspheres. This provides a new minimally invasive alternative therapy for endometrial repair.	[30]
MSC-derived exosome	IUA	Cell experiments showed that exosome therapy can effectively improve the fibrosis level of damaged endometrial stromal cells, reduce the expression of fibrosis markers vimentin, COL1A1, and COL5A2, and increase the proliferation of endometrial adenocytes and angiogenesis of vascular endothelial cells.	[31]
MB-MSC- derived exosome	Endometriosis	Exosomes secreted by MB-MSCs significantly reduce the levels of abnormally expressed inflammatory factors and angiogenic markers in endometriosis. In addition, exosomes induce apoptosis in endometriosis cells.	[32]
MSCs	Endometriosis	Bone marrow remodeling by MSCs inhibits the development of endometriotic lesions, resulting in a 7-fold reduction in lesion volume	[33]
MSCs	PFD	Scientists have developed an injectable and self-healing hydrogel derived from beta-chitin. It promotes MSC homing in vivo, thereby improving the local microenvironment, increasing collagen deposition, and repairing periurethral tissue.	[34]
ADMSCs	PFD	MSC-loaded gelatin scaffolds are more effective because the supportive effect of gelatin scaffolds may promote and enhance nerve repair ability at an early stage	[35]

2.2. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is a disorder caused by abnormalities in endocrine and metabolic function in women with hyperandrogenemia, ovulation dysfunction, and insulin resistance [38]. PCOS is also considered an independent risk factor for developing gestational diabetes and hypertensive disorders during pregnancy [39]. Moreover, chronic low-grade inflammation has emerged as a key factor in the pathogenesis of PCOS [40]. MSCs have an immunomodulatory function and significantly reduce the expression of the proinflammatory factors tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN-γ) and the fibrosis-related gene connective tissue growth factor (CTGF) in ovarian and uterine tissues, affecting systemic inflammatory responses in mouse model [41] (Fig. 1a). These findings suggest that MSCs are promising for application in the treatment of PCOS.

In addition, in a rat model of PCOS, adipose-derived mesenchymal stem cells (ADMSCs) were found to restore ovarian structure, increase the oocyte number and corpus luteum, and decrease the number of abnormal cystic follicles [22] (Table 1). In a cellular model of PCOS, bone morphogenetic proteins (BMPs) secreted by BM-MSCs regulated cellular androgen secretion and altered

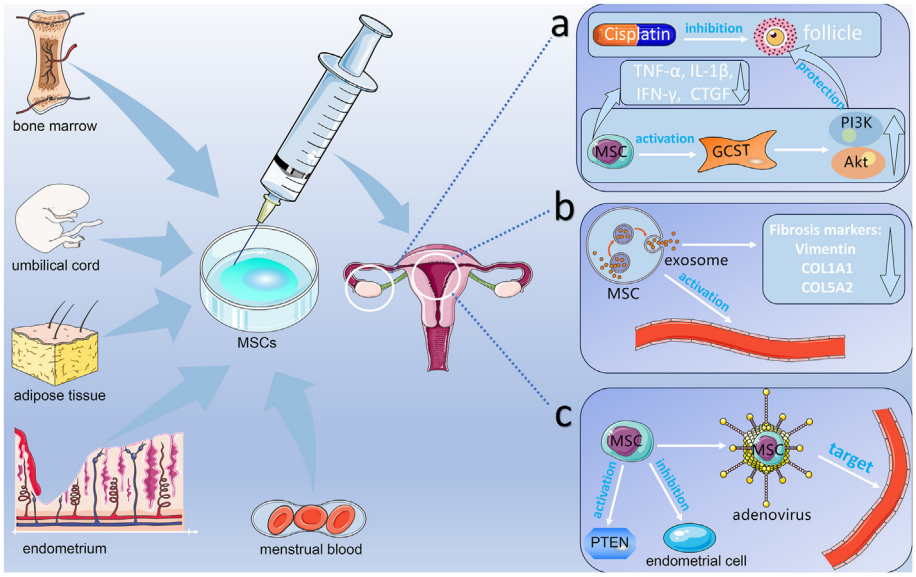

Fig. 1. Mechanisms of MSC functions in ovarian- and endometrial-related diseases.
a: hUCMSCs can reduce CS-induced oocyte and granulosa cell apoptosis and alleviate Cs-induced follicle depletion. b: MSC-derived exosome therapy effectively improves the degree of fibrosis in damaged endometrial stromal cells. c: An adenoviral vector is used to transport MSCs to target angiogenesis to inhibit the disease progression of endometriosis.

enzymes required for steroidogenesis. BMP-2 significantly inhibits the proliferation of cells, the expression of androgen synthesis genes, and the expression of inflammatory genes. These findings may underlie the therapeutic effects of MSCs on PCOS. Moreover, the overexpression of BMP-2 may enhance the efficacy of BM-MSC-based stem cell therapy [23] (Table 1). This makes MSC therapy a novel treatment for patients with PCOS.

MSCderived exosomes have been shown to have a therapeutic effect on PCOS [42]. MSCs and their secretions can also down-regulate androgen levels, increase insulin sensitivity, and decrease the levels of proinflammatory factors. Thus, MSC-derived exosomes have potential in the treatment of PCOS [43]. This approach is likewise a novel therapy for the treatment of PCOS. However, validation of the efficacy of MSC-derived exosomes in patients is needed.

2.3. Ovarian cancer

Among the female reproductive tract malignancies, ovarian cancer ranks third in incidence, and its mortality rate is the highest [44]. Thus, it is a malignancy that poses a serious threat to women's health. Ovarian malignant tumors include a variety of pathologic types, the most common of which is epithelial carcinoma [45]. The standard treatment modalities for newly diagnosed ovarian epithelial carcinoma include standardized surgery, platinum-based combination chemotherapy, and maintenance therapy when indicated [46]. However, the 5-year survival rate for patients with advanced disease remains below 30 %, and more than 70 % of patients with advanced disease experience disease relapse even after completing the standard initial therapy [47,48]. This makes clinical treatment very difficult. Recently, MSC-based therapies have received attention specifically for the treatment of ovarian cancer.

MSCs are able to sense signals released from sites of inflammation within the body and migrate to these sites [49]. The tumor microenvironment can induce MSC homing by secreting inflammatory factors [50]. By exploiting the tendency of MSCs to move toward tumor tissues, researchers can use MSCs as carriers for specific targeted drug therapy, leading to improved inhibition of tumor growth and reducing the adverse effects of drugs [51,52]. Existing studies have shown that MSCs can reduce the resistance of ovarian Previous studies have shown that MSCs can reduce ovarian cancer cell resistance to chemotherapeutic agents by inhibiting certain signaling pathways. For example, in one study, exosomal microRNA-146a (miR-146a) derived from hUCMSCs was reported to reduce the viability and tolerance of ovarian cancer cells to docetaxel and paclitaxel chemotherapy. One study showed that this effect is achieved through the laminin γ2 (LAMC2)-mediated PI3K/Akt signaling pathway [24] (Table 1). The application of hUCMSCs and their exosomes may have broad clinical application prospects in the treatment of ovarian cancer. Other researchers have genetically engineered MSCs by implanting a promoter into MSCs. The promoter is activated when cells feel external pressure, after which the anticancer drug 5-fluorocytosine is converted into an active state. The study showed that genetically engineered MSCs were able to precisely target tumor tissue without harming healthy tissue [25] (Table 1). This MSC-based method represents a new approach for ovarian cancer treatment. Other studies have shown that hUCMSC-derived conditioned medium can restore the function of damaged ovarian granulosa cells through anti-apoptotic and antioxidant effects. Moreover, hUCMSC-derived conditioned medium can restore the function of damaged ovarian granulosa cells through anti-apoptotic and antioxidant effects. hUCMSC-derived conditioned medium also can increase the mitochondrial metabolic activity that has been decreased by chemotherapy and transform the phenotype of injured ovarian granulosa cells back to a viable condition. This will benefit ovarian cancer patients in preserving and/or restoring fertility[53]. In summary, the application of MSCs for the treatment of ovarian cancer has good clinical prospects, but the underlying mechanisms are still not fully understood. It is hoped that further research on MSCs and their exosomes will lead to safer and more effective therapeutic strategies for ovarian cancer treatment.

3. Application of MSCs to fallopian tube diseases

The fallopian tubes are the channels that connect each ovary to the uterus. Specifically, they are the conduits through which the ovum is transported from the ovary to the uterus. Both of these

tubes are sites of fertilization, and the fallopian tubes are essential for conception; therefore, the treatment of associated diseases deserves our attention. There are many reports on the presence of stem cells in the female reproductive tract, but the status of these cells in the fallopian tube remains to be explored. The high levels of MSC-related proteins in the human fallopian tube proteome suggest that the human fallopian tube should contain many MSCs [54]. Other researchers have isolated mesenchymal-like cell populations from fallopian tube samples collected from hysterectomy patients. These populations of cells were found to express classic MSC markers [55], suggesting that resident stem cells may exist in the fallopian tubes. These stem cells, which reside in the fallopian tubes, play important roles in tissue healing and regeneration.

One study revealed that prominin 1 is expressed in the distal fallopian tube after the injection of BM-MSCs into mice with damaged fallopian tubes. This finding confirmed that stem cell activity is increased in the distal fallopian tube and beneficial for the repair of fallopian tube damage. Second, tissue and immune cell expression of vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen (PCNA) was significantly increased. In contrast, the expression of cysteine-aspartate protease 3 (CASP-3) in immune cells was significantly reduced (Fig. 2a). These findings suggest that MSCs mediate the expression of VEGF and PCNA in the fallopian tubes and that they inhibit cell apoptosis in the tissue to repair damaged tubes [26] (Table 1). This finding provides new hope for the repair of fallopian tube injury.

Tubal torsion can cause ischemia and reperfusion damage. Researchers have tested the effect of this damage on the recruitment of bone marrow-derived cells (BMDCs), including MSCs, into the fallopian tubes of female mice of reproductive age. Compared to that in uninjured fallopian tubes, BMDC recruitment in fallopian tubes with ischemia and reperfusion injury is increased by more than 2-fold. Moreover, recruited BMDCs are located in the interstitium of the fallopian tube. This finding indicates that BMDCs play a role in the healing process of the fallopian tube [56].

4. Application of MSCs to endometrial diseases

4.1. Intrauterine adhesion

Intrauterine adhesion (IUA), also known as Asherman's syndrome [57], refers to injury of the basal layer of the endometrium that occurs due to uterine surgery, infection or other factors. Fibrous tissue hyperplasia in the uterine cavity and partial or complete occlusion of the uterine cavity can cause infertility, recurrent abortion and other symptoms. This pathology of IUA is characterized by endometrial fibrosis and excessive extracellular matrix deposition [58]. At present, the main treatment methods are hysteroscopic adhesiolysis, hormone therapy and the placement of physical barriers into the uterine cavity. However, the clinical efficacy of these methods is unsatisfactory, and the recurrence rate of IUA remains high [59]. Therefore, there is an urgent clinical need to develop an effective treatment to reduce endometrial fibrosis and improve endometrial tolerance to avoid IUA and its recurrence, thereby improving clinical pregnancy outcomes [60].

MSCs are the basis of innovative ideas for IUA treatment, and numerous studies have made good progress [61,62]. In animal-based studies, the implantation of collagen scaffolds supplemented with hUCMSCs was shown to reduce the area of endometrial fibrosis, enhance the quantity of endometrial glands, and promote the proliferation of endometrial cells in IUA rats, thus improving the regenerative capacity of the endometrium [27] (Table 1 and Fig. 2d). Other studies have shown that human endometrial MSCs contribute to the morphological repair of injured mice endometrium and improve the thickness and integrity of the endometrium by promoting cell proliferation, angiogenesis, glandular formation, and epithelial and matrix regeneration [63]. Other scientists have used tail vein injections of UCMSCs to treat endometrial injury in rats. The expression of the fibrosis markers α-smooth muscle actin (α-SMA) and transforming growth factor-β (TGF-β) was reduced in the treated rats, and endometrial

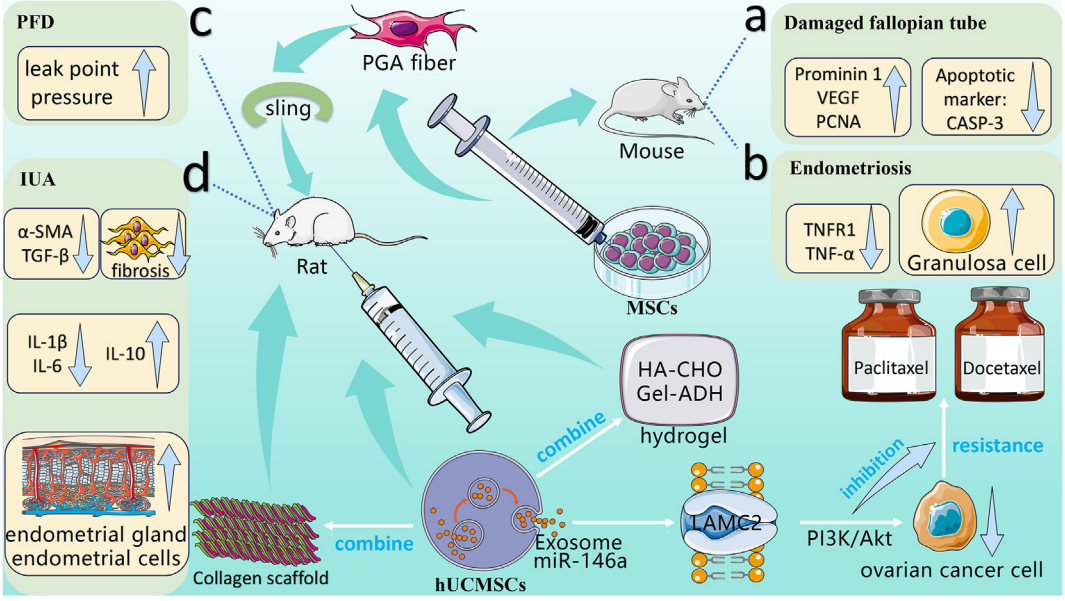

Fig. 2. Animal experiments related to the use of MSCs in obstetric and gynecologic diseases.
a: Expression of related factors after the injection of BM-MSCs into mice with fallopian tube damage. b: Expression of related factors after transplantation of BM-MSCs into mice with endometriosis. c: ADMSCs were seeded on PGA fibers and cultured for 4 weeks to establish a tissue engineering sling. Two months after the sling was implanted into the SUI rat model, the LPP increased significantly. d: Collagen scaffolds supplemented with hUCMSCs were implanted into IUA rats, or hUCMSCs were injected into IUA rats via the tail vein or via an injectable hydrogel based on HA-CHO, and Gel-ADH was mixed with hUCMSCs and injected into IUA rats. The corresponding changes could be detected in the rats.

morphology and the embryo implantation rate were significantly improved [28] (Table 1 and Fig. 2d). However, some studies have shown low retention of MSCs in target organs after intravenous injection [64]. Even so, hydrogel-based tissue engineering protocols have been shown to improve MSC retention in the endometrium. Therefore, some scientists have prepared injectable hydrogels based on oxidized hyaluronic acid and hydrazide-grafted gelatin, and when combined with hUCMSCs, the hydrogels displayed good biocompatibility. In a rat endometrial injury model, treatment with an injectable hydrogel loaded with hUCMSCs significantly increased endometrial thickness and the number of vessels and glands in the endometrium. Furthermore, the expression of IL-10, an anti-inflammatory cytokine, rose while that of pro-inflammatory cytokines (IL-1β and IL-6) dropped [29] (Table 1 and Fig. 2d). Nevertheless, some scientists still want to find a less invasive alternative. The researchers prepared 560-μm homogeneous Matrigel microspheres, each of which contained approximately 1500 MSCs within the sphere. These microspheres were then injected into the IUA rat endometrium. After 21 days, the endometrial thickness more than doubled, and the fertility rate increased from 25 % to 75 %, highlighting this new minimally invasive alternative therapy as a method for endometrial repair. This finding also provided a new direction for the transplantation of MSCs [30] (Table 1). This novel MSC therapy combining tissue engineering and regenerative medicine is a very promising treatment option for patients.

In one clinical study, 11 patients with IUA received 2 months of BM-MSC treatment, after which all of them showed improvements in the condition of their uterine cavity, with an increase in endometrial thickness from an average of 4.3 mm–6.7 mm [65]. Seven patients with severe IUA were also treated with autologous menstrual blood mesenchymal stem cells (MB-MSCs). None of the patients responded to conventional treatment before receiving MB-MSC treatment. After enrollment, the patients received MB-MSC transplantation followed by hormone therapy. After stem cell transplantation, the endometrial thickness of five patients increased significantly, reaching 7 mm; one patient conceived naturally, and two conceived through assisted reproductive technology [66]. In another study involving 26 patients with infertility due to IUA, all patients underwent at least one hysteroscopic adhesion release operation before enrollment, and the operation failed. The researchers used ultrasound guidance to perform hysteroscopic surgery on all patients and then placed UCMSCs combined with a degradable collagen scaffold complex into the patients' uterine cavity. The results showed that 10 of the 26 patients had a successful pregnancy, eight of them had delivered, and none of those who delivered had placental complications. All the infants, including two premature babies, were healthy [67].

In recent years, MSC-derived exosome therapy has also received considerable attention [68]. It is considered a cell-free therapy for the treatment of fibrotic diseases. One research team identified three key fibrosis markers in the endometria of patients with IUA, namely, vimentin, collagen type I alpha 1 chain (COL1A1), and collagen type V alpha 2 chain (COL5A2), and developed an exosome-based regimen that incorporated these markers (Fig. 1B). Cellular experiments have shown that exosome therapy can effectively reduce the level of fibrosis in damaged endometrial stromal cells, decrease the expression of the three fibrosis markers mentioned above, and increase the proliferation of endometrial glandular cells and angiogenesis of vascular endothelial cells [31] (Table 1). Other studies have shown that exosomes of placental MSCs have the ability to repair endometrial damage and improve the fertility of injured animals by regulating the TGF-β/Smad pathway through miR-125b-5p, miR-30c-5p and miR-23a-3p [69]. In summary, the utilization of MSCs and their exosomes in the management of IUA holds significant potential for clinical application.

4.2. Endometriosis

Endometriosis is a condition in which endometrial tissue growth occurs outside the uterine cavity [70], and it is one of the main causes of pelvic pain and infertility in women [71]. According to research statistics, 5–15 % of women of reproductive age suffer from endometriosis worldwide [72,73]. But the etiology and pathogenesis of endometriosis have not been clarified to date, which is the main reason for the lack of a cure for endometriosis [74]. In endometriosis, exosomes secreted by MB-MSCs have been shown to significantly reduce the levels of abnormally expressed inflammatory factors and angiogenic markers. In addition, exosomes induce apoptosis in endometriotic cells [32] (Table 1). This finding suggests that exosomes secreted by MB-MSCs may have a beneficial effect against endometriosis. MB-MSCs show potential for treating endometrial damage in refractory infertility. Studies have confirmed that MB-MSCs have similar proliferative and paracrine capabilities in infertile patients and volunteers, and effectively promote endometrial repair and fertility through intrauterine transplantation in mouse models, without significant complications [75]. These results provide a preclinical basis for the use of MB-MSCs as autologous transplantation therapy for endometrial repair.

Human endometrial mesenchymal stem cells (hEMSCs) have demonstrated tropism toward endometriotic lesions, suggesting that hEMSCs may be promising drug delivery systems for treating endometriosis [76]. Patients with endometriosis have increased angiogenesis at the lesion site [77,78]. Several researchers have designed targeted antiangiogenic drugs using adenovirus vectors loaded with MSCs to inhibit endometriosis disease progression [79]. It has also been demonstrated that hUCMSCs can upregulate the expression of the phosphatase and tensin homolog (PTEN) gene, inhibit endometrial cells from proliferating and promote their apoptosis [80] (Fig. 1c). MSC secretion of bioactive substances that alter the tissue microenvironment is considered one of the main mechanisms of their therapeutic effects [81]. BM-MSC transplantation promotes folliculogenesis by reducing tumor necrosis factor receptor 1 (TNFR1) expression and granulosa cell apoptosis in a mouse model of endometriosis [82]. One study revealed that after transplantation of MSCs into a mouse model of endometriosis, TNF-α expression in mouse bone marrow was reduced (Fig. 2b). Bone marrow remodeling by MSCs inhibits the development of endometriotic lesions, resulting in a 7-fold reduction in lesion volume. Determining the molecular basis of MSC-mediated bone marrow remodeling will improve the understanding of the effects of the immune system on endometriosis [33] (Table 1). This could lead to the identification of a novel therapeutic target for endometriosis treatment.

5. Application of MSCs to cesarean scar defect

A cesarean scar defect (CSD), also known as a uterine niche and uterine isthmus diverticulum, involves the thinning and depression of the myometrium at the site of the uterine incision after cesarean delivery. This complication is caused by inadequate healing of the myometrium at the wound site [83–85]. A higher maternal body mass index, gestational diabetes, and a history of previous cesarean section increase the risk of CSD [86,87]. Treatment for CSD includes mainly drug therapy and surgery. At present, the main drug treatment is oral contraceptives, and the main surgical treatment is minimally invasive [88]. However, there is still no consensus on which method to use. Recently, researchers have highlighted the use of MSCs for treating CSD as a promising therapeutic approach. Specifically, autologous BM-MSCs were injected into the uterine scars of rats that had been ligated for two months. Large clusters of blood vessels containing blood cells were found inside the scars,

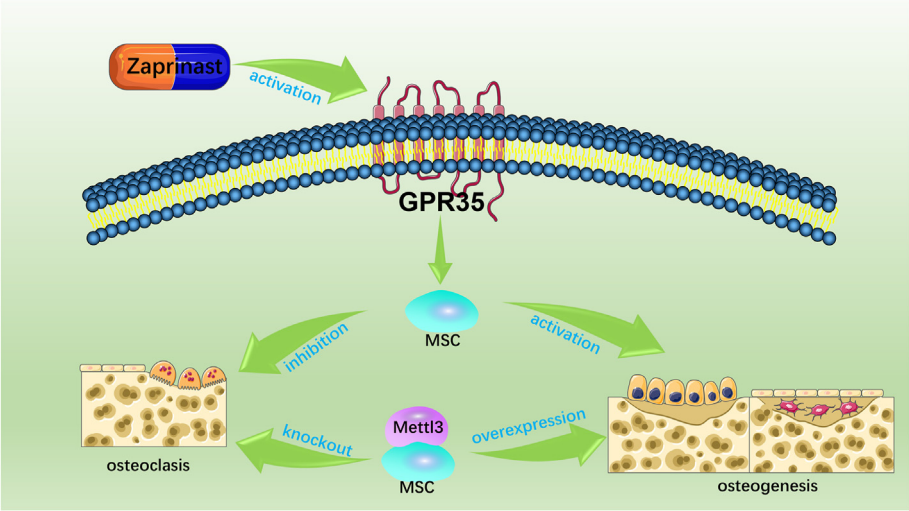

Fig. 3. Mechanisms of MSC application in postmenopausal osteoporosis.

while no such vessels were found in the control scar, suggesting that the autologous BM-MSCs injected into the scar differentiated into endothelial cells and pericytes to form blood vessels [89]. By combining UCMSCs with gelatinous degradable collagen fiber scaffolds and injecting them into rat uterine scars, researchers discovered that the scaffold/UCMSC system enhanced the degradation of uterine scars by increasing MMP-9 secretion from transplanted UCMSCs. Additionally, it facilitated regeneration of the endometrium, myometrium, and blood vessels within the uterine scars. Importantly, fertility was almost completely restored in uterine scars treated with scaffolds/UCMSCs in rat model [90]. All of these findings suggest that MSCs have great potential in the treatment of CSD.

6. Application of MSCs to postmenopausal osteoporosis

Postmenopausal osteoporosis (PMO) refers to osteoporosis that occurs in women after menopause (including natural menopause and unnatural menopause). Decreasing estrogen levels lead to and exacerbate osteoporosis. After menopause, ovarian function is significantly reduced, and the estrogen level is significantly decreased, which significantly increases osteoclast activity, accelerates bone resorption, and reduces bone matrix synthesis. Moreover, a decrease in estrogen increases the sensitivity of bone tissue to parathyroid hormone; this hormone promotes bone resorption and decomposition so that the bone metabolism balance favors bone decomposition over bone synthesis, resulting in osteoporosis [91–93].

Several studies have shown that another major cause of osteoporosis is a decrease in the number of MSCs and their preferential differentiation into adipocytes rather than osteoblasts in aging bones [94,95]. Thus, in theory, we can treat osteoporosis by transplanting and modulating MSCs to increase osteogenic differentiation [96,97]. Studies have discovered that the transplantation of MSCs not only decelerates bone trabecular loss caused by PMO but also restores cortical and overall bone mass. Additionally, autologously derived MSCs can persist in vivo for an extended period after transplantation, thereby achieving long-term enhancements in bone density. These findings suggest the potential utility of MSCs in ameliorating age-related osteoporosis. Moreover, utilizing MSCs for treatment can circumvent the adverse effects associated with prolonged administration of high-dose anti-osteoporotic medications [98–100].

In animal experiments, bone BM-MSCs from mice with conditional knockout of the m6A methyltransferase Mettl3 exhibited pathological features of osteoporosis. Mettl3 overexpression in BM-MSCs protects mice from estrogen deficiency-induced osteoporosis. Further studies have shown that a significant downstream pathway for m6A regulation in BM-MSCs is the parathyroid hormone (PTH)/PTH receptor-1 (PTHR-1) signaling axis. Knocking down Mettl3 expression reduced the translational efficiency of PTHR-1 in the MSC spectrum and disrupted the PTH-induced osteogenic response in vivo [101]. Other studies have shown that after the transplantation of MSCs, the number, volume and bone mineral density of bone trabeculae increase in ovariectomized mouse models. These findings suggest that MSCs may be effective at preventing PMO, which may be related to the involvement of MSCs in rebuilding microcirculation in bone [102]. G-protein-coupled receptor 35 (GPR35) expression in BM-MSCs was found to be inhibited in both osteoporosis patients and osteoporotic mice, and GPR35 gene knockout was shown to inhibit the proliferation and osteogenesis of BM-MSCs. Zaprinast, a GPR35 agonist, has been shown to ameliorate ovariectomy-induced bone loss and promote bone formation in mice. Together, these findings suggest that GPR35 may be useful as a new target for the treatment of PMO and that its agonist zaprinast may be useful as a new therapeutic agent for the treatment of PMO [103] (Fig. 3).

Exosomes derived from MSCs have the potential for tissue regeneration, and they have been reported to promote bone tissue regeneration and reduce bone cell apoptosis [104–106]. Exosomes derived from hUCMSCs activate the AKT signaling pathway to regulate cell proliferation and osteogenesis [107]. Moreover, microRNA-218-5p alleviates PMO by promoting osteoblast differentiation in BM-MSCs [108].

In conclusion, the use of MSCs and their exosomes in the treatment of POM is a promising therapeutic approach. Although no MSC drugs for osteoporosis are currently available, preclinical and clinical studies are ongoing. It is believed that with the deepening understanding of MSCs, the currently unresolved issues will be gradually resolved.

7. Application of MSCs to pelvic floor dysfunction

Pelvic floor dysfunction (PFD) refers to a group of diseases in which pelvic floor tissue is weakened due to injury, degeneration or

other factors, leading to a decrease in pelvic floor support or pelvic floor muscle function, resulting in pelvic organ displacement and pelvic organ functional abnormalities. PFD is a common and frequently occurring condition in women of middle age and older. Pelvic organ prolapse, difficulty urinating and defecating, pelvic pain, stress urinary incontinence (SUI) and sexual dysfunction may occur in women with PFD [109], seriously affecting the normal social activities of patients and increasing their psychological stress.

Research on the application of MSCs in the field of pelvic floor gynecology is lacking, and there is currently no effective method for stimulating the homing of MSCs in vivo in order to improve PFD. MSCs are safe for the treatment of pelvic diseases [110], and MSC-based treatment of SUI is a new method [111]. A new injectable and self-healing hydrogel derived from beta-chitin has been developed by scientists. It promotes MSC homing in vivo, thereby improving the local microenvironment, increasing collagen deposition, repairing periurethral tissue, and ultimately improving SUI [34] (Table 1). This treatment may be an effective nonsurgical therapy for the prevention and treatment of SUI. Regarding surgical treatment, sling implantation is an important procedure for SUI treatment [112,113]. Several studies have reported that ADMSCs can be seeded on polyglycolic acid (PGA) fibers and cultured for 4 weeks to form tissue-engineered slings. Two months following the implantation of the sling into the SUI rat model, the mean leak point pressure (LPP) increased significantly [114] (Fig. 2c). The results of this study indicate that ADMSCs may be a promising novel cell source for tissue sling engineering. Furthermore, ADMSCs have the potential to enhance the therapeutic outcomes of SUI patients [115].

Nerve damage is a recognized cause of PFD [116]. The ability of MSC transplantation to repair pelvic floor nerve injury is good, and MSC-loaded gelatin scaffolds are more effective because they may promote and enhance nerve repair at an early stage [35] (Table 1). Other studies have shown that MSCs and their secreted factors, such as brain-derived neurotrophic factor, improve regenerative capacity in animal models of neuromuscular injury [117,118]. These observations are expected to lead to a new type of treatment for postpartum pelvic neuromuscular injury.

8. Controversies and prospects

Although MSCs have shown great potential in the treatment of many diseases, their use in cancer therapy remains controversial [119]. Several studies have reported that MSCs may play a role in promoting ovarian cancer cell proliferation, metastasis and invasion. For example, one study revealed that MSCs isolated from the greater omentum promote the growth and metastasis of ovarian cancer cells [120]. Exosomes secreted into ascites have been demonstrated to promote the growth and metastasis of epithelial ovarian cancer [121]. ADMSCs increase the proliferation of ovarian cancer cells by upregulating the expression of paired box 8 in ovarian cancer cells and maintaining the stability of the PDZ-binding motif (TAZ). This finding suggests that PAX8 may be involved in regulating cancer progression [122,123]. Other studies have shown that MSCs in the ovarian cancer microenvironment can promote epithelial–mesenchymal transition in ovarian cancer cells through the secretion of IL-6 so that ovarian cancer cells can take on the characteristics of MSCs and increase the secretion of matrix metalloproteinases, thus promoting the invasion and metastasis of ovarian cancer cells [124]. Cancer-associated MSCs can promote ovarian cancer stem cell resistance to chemotherapy through platelet-derived growth factor (PDGF) signaling. PDGF-BB/PDGF-β is an important signaling pathway between cancer-associated MSCs and cancer stem-like cells in ovarian cancer [125–127]. These findings have implications for the development of specific ovarian cancer prevention therapies in the future. In the treatment of endometrial cancer, a small number of BM-MSCs in the blood circulation can be recruited and can infiltrate the lesion site, leading to the occurrence of deep infiltrating endometriosis [128]. It has also been reported that the proliferation of endometrial stromal cells increases after BM-MSCs are cocultured with endometriosis cell lines in vitro [129]. These findings suggest that MSCs may contribute to the growth of endometriotic lesions. Stem cell-derived nutritional factors can induce the proliferation of endometrial cells, leading to the occurrence and development of endometriosis. Targeted blockade of specific signaling molecules secreted by stem cells may be able to control the growth of endometriotic lesions. This provides a new therapeutic strategy for the treatment of endometriosis. In animal experiments, intraperitoneal injection of UCMSCs was shown to aggravate endometriosis in macaque models of endometriosis [130]. Moreover, studies have shown that EMSCs may participate in the formation of endometriotic lesions by changing the body's metabolic pattern and generating immune tolerance [131]. This information will help us to identify new therapeutic targets for endometriosis.

Initially, the therapeutic effects of MSCs were mostly attributable to their homing and differentiation abilities [132]. However, multiple in vivo studies have suggested that the number of MSCs colonized locally in injured tissue is low in the natural state and that the duration of colonization is usually very short [133]. Importantly, MSCs cannot be efficiently transformed into parenchymal cell components of organs under noninducing conditions. This finding suggests that the main therapeutic effects of MSCs may be mediated mainly by paracrine mechanisms [134,135]. As one of the main paracrine mechanisms of MSCs, exosomes play a very important role in the therapeutic effects of MSCs [136–138].

In the future, we should focus on the use of formulation technology to combine therapeutic factors with MSCs, such as the combination of a microparticle system loaded with therapeutic factors and a biological scaffold loaded with stem cells, to achieve better therapeutic effects [139].

9. Conclusions

With the deepening of research on MSCs, their functional value in gynecology and obstetrics diseases will gradually emerge. However, what we know is only a small part of the whole. Further research on the underlying mechanism of action is still needed, and resolving these controversial issues is needed to safely extend the use of MSCs from the laboratory to the clinic. We believe that with the continuous efforts of scientists and clinicians, there will be more MSC-based applications in clinical treatment and that more patients will benefit from these methods.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Author contributions

Changzhong Li conceived the work. Guanwen Gao wrote and drafted the manuscript. Li Li, Changling Li, Degao Liu, and Yunfei Wang discussed and edited the manuscript. All authors read and approved the final version of the manuscript.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics approval

Not applicable.

Funding

This work was supported by the China Shenzhen High-level Hospital Construction Fund (YBH2019-260), the China Shenzhen Key Medical Discipline Construction Fund (No. SZXK027), the Sanming Project of Medicine in China Shenzhen (No. SZSM202011016), and the General Project of China Shenzhen Science and Technology Innovation Commission (No. JCYJ20220531094012027).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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