Research in Molecular Medicine

New Insights and Perspectives on Human Menstrual Blood-derived Stem Cells as a New Cell-based Delivery Technology in Regenerative Medicine

Atefeh Hojjat[1], Seyed Ehsan Enderami[2*], Reyhaneh Nassiri Mansour[2], Mohammad Kabi[1], Mohamadfoad Abazari[3], Keyvan Mehdipour Chari[1], Amirali Khodashenas[1], Vahid Kia[4], Amir Maleksabet[1]

1. Department of Medical Biotechnology, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Medical Biotechnology, Immunogenetics Research Center, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Department of Neurosciences, University of British Columbia, Vancouver, Canada.
4. Department of Medical Biotechnology, School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.

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ABSTRACT

Background: Menstrual blood has been identified as an important source for the isolation of mesenchymal stem cells (MSCs). These stem cells can easily and non-invasively be harvested from menstrual blood during menstrual shedding. There has been extensive research on the differentiation potential of menstrual blood-derived stem cells (MenSCs) and their application in regenerative medicine and the treatment of diseases.

Materials and Methods: The aim of this paper was to review the current and future application of MenSCs in the field of regenerative medicine and cell therapy based on an electronic search in various databases, like Scopus, PubMed, and Google Scholar for English-language studies. The application of MenSCs in regenerative medicine can be the window of hope for the treatment of various diseases and disabilities, such as female infertility, type 1 diabetes, myocardial infarction, wound healing, neurodegenerative diseases, and many other conditions that were thought to be incurable in the past.

Conclusion: Nowadays, the use of MenSC as a novel source of MSCs has garnered special interest among scientists due to two important factors: Non-invasive accessibility and the immunomodulatory potential of these cells, which have historically posed significant obstacles in the field of stem cell therapy. To date, there has been substantial research on these cells, and many studies are ongoing, as scientists seek to leverage their differentiation potential and optimize differentiation conditions and protocols for their application in regenerative medicine.

*** Corresponding Author:**
Seyed Ehsan Enderami, Assistant Professor.
Address: *Department of Medical Biotechnology, Immunogenetics Research Center, School of Advanced Technologies in Medicine, Mazandaran University of Medical Sciences, Sari, Iran.*
E-mail: *ehsan.enderami@gmail.com, ehsan.enderami@strc.ac.ir*

Introduction

Cell transplantation therapy is one of the promising methods to cure a wide range of diseases. To date, scientists have found stem cells as an unlimited source for cell replacement therapies. Mesenchymal stromal/ stem cells (MSCs), due to their multipotency and high proliferative rate, have become an excellent option for cell therapy and regenerative medicine. MSCs can be isolated from all adult tissues in the body [1] and they share several common characteristics, including (a) adherence to plastic, (b) expression of surface markers such as CD73, CD90, and CD105, while lacking hematopoietic surface markers including CD34, CD45, CD133, and human leukocyte antigen DR (HLA-DR), (c) the ability to differentiate into mesodermal lineage cells (osteoblasts, adipocytes, chondrocytes), and (d) low immunogenicity [2].

Among all the adult tissues that can be used for the isolation of MSCs, bone marrow (BM) [3], adipose tissue [4], placenta [5], and umbilical cord blood [6] are used more frequently than other tissues. BM-MSCs are the most prevalent source for the isolation of MSCs, as they have a high proliferation capacity and can yield a large number of cells during the isolation process. However, the isolation of cells from the BM requires invasive methods and must be performed during a surgical operation. On the other hand, the number of MSCs and their differentiation capacity decline with the age of the donor [7]. Adipose tissue is another source of AD-MSCs, which can be isolated during liposuction surgery; this method is less invasive than BM extraction, but both sources share MSC characteristics [8].

Since the most important issue in the use of MSCs is the invasiveness of isolation methods, scientists have been searching for a suitable alternative that is non-invasive, ethically uncontroversial, and low-cost. For the first time in 2007, Meng et al. reported menstrual blood-derived stem cells (MenSCs) as a novel source of adult stem cells [9]. MenSCs are located in the endometrium and can be obtained during menstrual shedding in every menstrual cycle; therefore, their isolation is completely non-invasive. MenSCs are highly proliferative, possess stable chromosomal karyotypes [10], and are multipotent cells that can differentiate into all three germ layer cell types [9], making them significant for regenerative medicine. In this review, we aim to investigate the differentiation and regenerative potential of menstrual blood-derived MSCs for cell-based therapy.

Endometrial stem cells

During every menstrual cycle, the endometrium thickens to about 7 mm to prepare for the nesting and development of a fetus. If pregnancy does not occur, this endometrial layer begins to shed through menstrual blood, and the thickness of the endometrium starts to increase again for the next month. In this process, endometrial stem cells play a key role in the regeneration of the endometrium [11].

Over 30 years ago, the presence of stem cells in the endometrium was proposed [12]. For the first time, cloning of human endometrial stem cells confirmed the existence of endometrial epithelial progenitor cells. It was also shown that endometrial stem cells (EnSCS) are located in the superficial layers accessible by endometrium biopsies, and some researchers have reported the isolation of EnSCs from menstrual blood or endometrium biopsies [10]. EnSCs reside in the basalis and functionalis layers of the endometrium, and while these cells leave the body through menstrual blood, they are referred to as MenSCs. Like other types of MSCs from other sources, MenSCs exhibit characteristics such as self-renewal, clonogenicity, and multipotency. Furthermore, they demonstrate higher extraction efficiency and longer passaging capacity with shorter doubling times [13].

Another advantage of MenSCs is their isolation procedure. The most convenient method for collecting the MenSC, which involves no complications or harm to the donors, is to collect the deciduous endometrium from menstrual blood using a menstrual cup during the first several days of menses [13, 14]. Additionally, there are some other methods for obtaining these cells, including diagnostic curettage, first-trimester deciduas [15], menstrual cup [14], and hysteroscopy [13]. The isolation and culture methods for MenSCs are listed in Table 1, and the isolation of MenSCs from the endometrium is illustrated in Figure 1.

Markers and identification of MenSCs

Investigations by various research groups have reported that MenSCs are positive for the expression of CD44, CD29, CD9, CD73, CD90, CD105, OCT-4, CD166, and MHCI CXCR-4. Among these markers, CD29, CD73, CD90, and CD105 are common markers of MSCs that can also be expressed by BM-MSCs [16]. However, the expression of hematopoietic markers, such as CD34, CD45, CD133, and HLA-DR, is negative in MenSCs [16]. Another study highlighted the negative expression of hematopoietic lineage markers such as

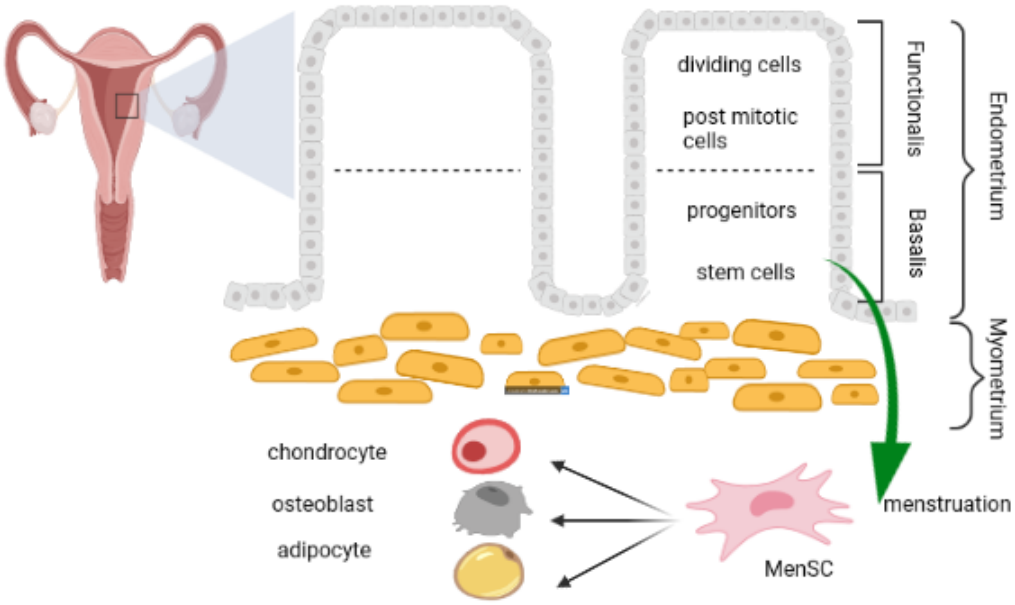

Figure 1. Isolation of MenSCs from the endometrium

Note: Stem cells are located in the basalis layer of the endometrium, and during menstrual shedding, these stem cells leave the body and are thereafter referred to as menstrual blood-derived stem cells. MenSCs are multipotent and can differentiate into three lineages: Adipogenic, osteogenic, and chondrogenic.

CD34 and monocyte-macrophage antigens like CD14 (a marker for macrophages and dendritic cells [DCs]) and CD45 (leukocyte common antigen). The low immunogenicity, which is one of the advantages of MenSCs in regenerative medicine, is due to the very low expression of HLA-ABC and HLA-DR [17]. Verdi et al. used the co-expression of CD140b and CD146 for the isolation of MenSCs [18]. Another study reported that MenSCs can be directly isolated from the endometrial shedding mixture using CD146, PDGFRβ, and SUSD2 markers [19].

MenSCs also exhibit telomerase activity, accompanied by the expression of human telomerase reverse transcriptase (hTERT) [20]. Furthermore, MenSCs express embryonic stem cell markers such as OCT-4. In some studies, scientists observed that MenSCs expressed embryonic and intracellular multipotent markers, including the C-Kit proto-oncogene (c-kit)/CD17, OCT-4, and SSEA4, while these markers were not expressed in MSCs from other sources [21].

Differentiation potential of MenSCs

MenSCs demonstrate the potential to differentiate into three lineages: Adipogenic, osteogenic, and chondrogenic. They can be differentiated into ectodermal and mesodermal cell lineages, specifically into bone, fat, cartilage, nerve, and endothelial cells in vitro [22].

MenSCs express embryonic stem cell markers, like OCT-4, c-kit, and SSEA-4, suggesting that MenSCs are more primitive and have a stronger multi-directional differentiation capacity than MSCs from other sources. In a study examining the effects of human MenSCs (hMenSCs) on bleomycin-induced pulmonary fibrosis, Wu et al. reported that MenSCs exhibited a spindle and fibroblast-like morphology and could be successfully differentiated into osteogenic, chondrogenic, and adipogenic cells [23]. A comparative study of MenSCs from healthy volunteers and patients with fertility disorders reported that MenSCs from both groups were able to differentiate into chondrogenic and osteogenic lineages, but they had a low potential for adipogenic differentiation [24].

Considering all these studies, there remains a contradiction regarding the differentiation potential of MenSCs. A study by Uzieliene et al. demonstrates that MenSCs and BM-MSCs both can differentiate into adipogenic and osteogenic lineage cells. However, BM-MSCs exhibit a stronger adipogenic differentiation capacity [25]. Darzi et al. reported that compared to BM-MSCs, MenSCs have a lower capacity to differentiate toward osteoblast lineage, but using human platelet release instead of FBS in the culture medium can compensate for this limitation and increase the osteogenic differentiation capacity of MenSCs [26]. MenSCs can also differentiate into hepatocytes, but this differentiation relies on the concentration of hepatocyte growth factor, oncostatin M, and the elimination of serum from the induction medium [27].

Therapeutic applications of MenSCs in various diseases and wound healing

hMenSCs possess a broad range of properties, such as pluripotent or multipotent differentiation, strong paracrine activity, and immunomodulatory capacity, which make them promising candidates for regenerative therapy [28]. These unique properties have inspired extensive research into their potential therapeutic applications across diverse diseases. In the following section, we summarize current evidence on the use of MenSCs in various diseases and wound healing, highlighting both in vitro and in vivo studies that support their regenerative and reparative capabilities.

Asherman's syndrome (AS)

The major cause of uterine infertility could be a thin endometrium, which is often found in women with AS or intrauterine adhesion (IUA) [29]. In this case, the basal layer of the endometrium is destroyed, and the functional layer fails to respond to hormonal stimulation. There are many treatment options for AS or IUA, including hysteroscopic adhesiolysis, oral hormones, and biological barriers; however, despite their beneficial effects, each of these methods has limitations [30]. Stem cell therapy is one of the promising therapies for the future treatment of AS. In a study involving the transplantation of spheroids of human endometrial stem cells from menstrual blood into rats with AS, Tan et al. reported that MenSCs could increase the synthesis of anti-inflammatory and angiogenic factors. Therefore, they could preserve all properties in a monolayer. Autologous MenSC transplantation was shown to increase the endometrium thickness in 7 women with AS according to a non-controlled prospective clinical study. Of the seven patients, five achieved an endometrial thickness of 7 mm, which is the optimum thickness for embryo implantation. Four of the patients underwent frozen embryo transfer (FET), and after the second MenSC transplantation, one of them became pregnant, with none of the seven patients experiencing transplantation complications. Therefore, it can be concluded that autologous MenSC transplantation is an alternative treatment for AS [31]. The results of studies have shown that MenSCs are a safe and promising source of cells that could be used for IUA and other types of endometrial damage.

COVID-19

In December 2019, coronavirus disease 2019 (COVID-19) spread around the world and caused a coronavirus pandemic. Major lung-associated diseases in COVID-19 patients are acute respiratory distress syndrome (ARDS) and respiratory failure [32]. Preclinical studies have proven that one of the promising therapeutic strategies for refractory and non-life-threatening pulmonary illness is cell therapy, and MSCs appear to have beneficial effects for COVID-19 [33]. Furthermore, by secreting trophic factors, cytokines, and chemokines, MSCs can exhibit immunomodulatory and tissue-repairing abilities [34]. Chen et al., for the first time, used MenSCs as a treatment for COVID-19. Due to their immunomodulatory properties, MenSCs could reduce the inflammatory effects associated with cytokine storms, thereby improving patients' conditions [35].

Myocardial infarction (MI)

MI is a type of coronary artery disease in which excessive ischemic conditions lead to the apoptosis of cardiomyocytes. Despite developments in medical and surgical strategies for treating cardiac disease, it remains the major cause of morbidity and mortality worldwide. Many clinical and preclinical studies have proposed that stem cell therapy can restore cardiac function and regenerate damaged cardiac tissue. hMenSCs, due to their paracrine effect, immunomodulation, and transdifferentiation, can promote both these conditions [36]. MenSCs can differentiate into cardiomyocytes both in vivo and in vitro [14]. After testing the use of hMenSCs in MI in rats, it was shown that the in vivo transplantation of MenSCs could lead to greater improvements in cardiac function compared to BM-MSCs. In a study using the nude rat model with MI, the in vivo transplantation of MenSCs could lead to greater improvements in cardiac function compared to BM-MSCs [37]. In a study by Jiang et al. on an immunological MI rat model, it was observed that MenSCs could significantly reduce apoptosis, promote cell proliferation, and recruit c-kit$^+$ cells [38].

Liver fibrosis

The last stage of most chronic liver diseases leads to liver fibrosis, which causes a huge burden with high rates of mortality and morbidity worldwide. Every year, liver diseases are responsible for 3.5% of all deaths [39]. The most effective method for fibrotic liver treatment is orthotopic liver transplantation; however, despite its efficiency, it usually faces some limitations, like organ donor shortage, surgical complications, and the need for lifelong immunosuppression. To overcome these limitations, new approaches for the treatment of liver fibrosis have been suggested based on MSC therapy [40]. For the first time, a study using a carbon tetrachloride-induced mouse model of liver fibrosis demonstrated that the

Table 1. Isolation and culture methods of MenSCs

Isolation Method	MenSC Extraction Protocol
Endometrial biopsy	Novak curettes or a pipette device were used to collect samples on days 19-24 of the menstrual cycle from females with fertility problems. Full-thickness samples were washed in Hanks' buffer (penicillin, streptomycin, and amphotericin B) after isolation. Collagenase I was used for tissue digestion. Stem cells were separated from RBCs using Ficoll and centrifugation for 20 minutes, and then they were cultured in Dulbecco's modified eagle medium (DMEM) with 10% FBS in tissue culture bottles [11].
Hysteroscopy	Endometrial specimens were isolated in sizes of 1x1x1 cm^3 and transferred to Hanks' buffer containing 1% streptomycin, 1% penicillin, 1 µg/mL amphotericin B, and 5% FBS at 5 °C. After that, pre-warmed Hank's media were used to wash samples, and then they were incubated with collagenase I at 37 °C for 30-45 minutes for tissue digestion. After centrifugation at 300 x g for 5 min, the passed cells were gently added to Ficoll and centrifuged again at 400 x g for 20 min to separate the stem cells. The RBC sediment was disposed of, and the cellular layer was transferred to the culture medium [15].
Injection syringe	A 3 mL menstrual blood sample was collected on day 2 of menses from healthy donors. The menstrual blood was transferred to Ficoll and then fractionated using density gradient centrifugation. Mononuclear cells located in the central layer were separated and cultured in a 25 cm^2 tissue culture bottle with DMEM, 1% streptomycin, and 1% penicillin [17].
First-trimester decidual	Young healthy women undergoing elective vaginal surgical termination of early pregnancy were chosen for sample collection. Sterile PBS (pH: 7.4) was used for transferring the samples, which were then washed three times in a large volume of DMEM with 100 IU/mL P/S. Decidual tissue was isolated from the trophoblast and ground into 1-2 mm^3 pieces. Collagenase was then added to the sample, and they were incubated for tissue digestion. DMEM supplemented with FBS was also used for enzyme deactivation, and nylon mesh was employed for the filtration of samples. The mixture was centrifuged at 200 x g for 10 minutes, and the pellet was resuspended and cultured [18].
Menstrual cup	Menstrual blood samples were collected from healthy females during the first few days of menses using a menstrual cup. The samples were transferred into an equal volume of PBS containing 100 U/mL penicillin, 100 U/mL streptomycin, 0.25% mg/mL amphotericin B, and 2 mM EDTA. The sample was added gently to Ficoll and then centrifuged. After that, karyocytes and deciduous endometrial cells suspended in the Buffy coat were isolated and transferred to a Falcon tube. Following another centrifugation, the pellet was resuspended and cultured in DMEM medium [16].

transplantation of MenSCs had positive effects on liver function, decreased collagen deposition, and inhibited activated stellate cells up to two weeks after the transplantation of MenSCs [41].

Type 1 diabetes mellitus (T1DM)

T1DM is an autoimmune condition caused by an attack of insulin-producing β cells by the immune system, leading to their destruction. In this case, β cells lose their ability to respond to blood glucose, resulting in hyperglycemia. The transplantation of the whole pancreas or islets is the most effective treatment for T1DM [42, 43]; however, it is often limited by donor shortages, and patients must take immunosuppressive drugs for the rest of their lives. To address the issue of donor shortages, scientists have suggested using an unlimited source of cells and differentiating them into mature insulin-producing β cells [44, 45].

MenSCs can increase the expression of neurogenin-3 (*NGN3*), forkhead box protein A2 (*FOXA2*), pancreatic duodenal homeobox-1 (*PDX1*), NK homeobox factor 6.1 (*NKX6.1*), and paired-box (*PAX*) genes after transplantation of MenSCs in T1DM mice. Therefore, they can promote β-cell differentiation and increase the number [46]. In vivo models of T1DM have shown that human menstrual blood progenitor cells (MBPCs) display remarkable potential to enhance pancreatic function through indirect regenerative pathways. MBPC administration can ameliorate hyperglycemia, enhance metabolic properties, and increase insulin generation, while also promoting recovery of islet structure. Interestingly, rather than directly differentiating into beta-like cells, MBPCs appear to home to injured pancreatic tissue and stimulate resident endocrine progenitors, as demonstrated by increased *NGN3* expression across islet, ductal, and exocrine compartments. This activation is accompanied by the upregulation of genes involved in embryonic β-cell development, suggesting that MBPCs exert their therapeutic effects primarily via paracrine signaling and modulation of the local microenvironment. Such findings position MBPCs as a promising, noninvasive candidate for future regenerative strategies in T1DM [47]. Furthermore, a study of diabetic animals showed that treatment with repeated doses of hMenSC-derived exosomes could increase β-cell mass and insulin production in a diabetic animal model [48].

Wound healing

Regarding the multipotency and self-renewal ability of stem cells, as well as their capacity to secrete pro-regenerative cytokines, they could be suitable options for tissue regeneration. Wound healing refers to the process by which skin or other tissues regenerate and repair themselves after injury [49, 50]. The interaction of different cells, including inflammatory cells, keratinocytes, fibroblasts, and endothelial cells at the site of injury, plays a crucial role in cutaneous wound healing. MSCs, due to their ability to promote angiogenesis and decrement scarring, can reduce inflammation and facilitate wound healing [51]. Compared to other sources, like BM-MSCs, MenSCs have a higher potential for migration and angiogenesis; thus, MenSCs are an appropriate candidate for wound healing [52]. These cells can alleviate the wound healing process by releasing some cytokines, including platelet-derived growth factor (PDGF), elastin (Eln), angiopoietin (ANGPT), matrix metalloproteinases 3 (MMPs3), and matrix metalloproteinases 10 (MMPs10) [53]. Furthermore, MenSCs can release exosomes that have a beneficial effect on non-healing wounds in diabetic mice. These exosomes upregulate VEGF, thereby enhancing neo-angiogenesis [54].

Female infertility

Infertility is a condition in which couples cannot achieve pregnancy after one year or more. The number of people suffering from infertility exceeds 186 million around the world [55]. Several in vivo and clinical studies have further illustrated the regenerative properties of MenSCs in female infertility, such as premature ovarian failure and thin endometrium [56]. MenSCs can promote endometrial repair by enhancing angiogenesis, modulating inflammatory responses, and secreting paracrine factors that stimulate proliferation and differentiation of endometrial epithelial cells. Transplantation of MenSCs into animal models of infertility has resulted in improved endometrial thickness, increased vascular density, and restoration of normal estrous cycles. Early-phase clinical trial results have also displayed that intrauterine infusion of MenSCs may enhance endometrial receptivity and pregnancy outcomes in patients with refractory infertility. These reports suggest that cell-based therapy could represent a novel, minimally invasive approach for restoring reproductive function and improving fertility in women. Several clinical studies have investigated the therapeutic potential of MSCs for treating female infertility [57]. Zheng et al. claimed that MenSCs have the potential for the regeneration of the reproductive system for the first time [58]. After directing MenSCs into epithelial differentiation lineage, it was observed that the expression of decidualization-related genes (including *PRL*, *ESR*, *IGFBP*, and *FOXO1*) and angiogenesis-related genes (*HIF7*, *VEGFR2*, and *VEGFR3*) increased. After analyzing the characteristics and potential of MenSC isolated from both healthy donors and women with fertility issues, it was demonstrated that only some epigenetic and stemness gene expressions were lower in women with infertility, while the expression of other genes was similar in both groups [24].

Duchenne muscular dystrophy (DMD)

In muscle tissue, the interaction of cells is facilitated by a protein named dystrophin. DMD is a genetic disorder in which dystrophin is changed, leading to progressive muscle degeneration and weakness. Scientists have been investigating the application of stem cell therapy for the treatment of DMD. MenSCs can increase the expression of the muscle-like proteins in immunodeficient DMD model mice, thereby enhancing muscle regeneration and repairing skeletal muscle. Furthermore, after co-culturing with mouse myoblast cells, MenSCs were able to differentiate into myoblast/muscle cells, which can express anti-atrophy muscle proteins [59].

Neurodegenerative disease

MenSCs, being a rich source of stem cells that are easily accessible and have the potential to differentiate into neurons, can be an ideal tool for the treatment of neurodegenerative disorders [60]. The administration of MenSCs has a therapeutic effect on tissue regeneration and the function of the central nervous system, as well as in the heart and ischemic limbs [61]. Under glucose deprivation conditions, MenSCs can provide protection to primary neural cultures. MenSC media can secrete factors that have neuroprotective effects on neurons, such as vascular endothelial growth factor (VEGF), brain-derived growth factor (BDNF), and neurotrophin-3 (NT-3) [62]. In a study on Alzheimer's disease, Zhao et al. examined the effect of MenSC treatment after intracerebral transplantation in APP/PS1 transgenic mice. They observed that amyloid-beta (Aβ) deposition and tau hyperphosphorylation were reduced, and cognitive decline improved. Additionally, the treatment modulated microglial activation and restored Aβ clearance in the transgenic mouse model [63]. In a clinical study of multiple sclerosis, no adverse effects or immune rejection were noted during a one-year follow-up after the intravenous and intrathecal administration of MenSCs, demonstrating the feasibility of clinical use [64].

The multilineage differentiation potential of MenSCs is illustrated in Figure 2.

Immune modulatory

In 2002, the first report on the immunomodulatory effect of MSCs was published [65]. MSCs have the potential to modulate the immune system; therefore, they can be used as a promising tool for the treatment of inflammation. As mentioned above in connection with the immune-modulatory properties of MenSCs, their interaction with different immune cells includes hindering the proliferation of B cells, T cells, natural killer (NK) cells, and DCs, while promoting regulatory T cells (Treg). MenSCs can modulate both innate and adaptive immune responses [66]. The immunomodulatory effects of MenSCs on the immune cells are illustrated in Figure 3. MenSCs play an important mediating role in immunomodulation by inhibiting the generation and maturation of DCs and by secreting IL-6 and IL-10 [67]. Scientists have been investigating the effect of MenSCs on T cells in mixed lymphocyte reactions involving a mixture of MenSCs and allogenic human peripheral blood mononuclear cells (PBMNCs). It was observed that while the production of interleukin 4 (IL-4) increased, cellular proliferation, as well as interferon gamma (INFγ) and tumor necrosis factor alpha (TNF-α) levels, were suppressed, indicating that MenSCs exert this effect in a dose-dependent manner [68].

MenSCs also have a dose-dependent effect on cytokine levels, which reduces anti-inflammatory IL-4^{+}, IL-10^{+}, and CD_4^+ T cells at a low MenSC: PBMC ratio compared to BM-MSCs [69]. This may be a result of a higher number of HLA-DR molecules on the MenSC surface and a lower number of IFNγ receptors. Additionally, compared to BM-MSCs, MenSCs exhibit less production of indoleamine (IDO), cyclooxygenase-2 (COX2), and activin A [69]. Intravenous administration of MBPCs resulted in the restoration of islet structure and an increase in the number of B cells in the T1DM mice model [47]. Several studies have demonstrated the effect of MenSCs in different models of inflammation, including experimental colitis [70], lipopolysaccharide (LPS)-induced injury [71], and polymicrobial sepsis. The survival of mice undergoing experimental colitis improved after treatment with MenSC. There was also an increase in the production of regulatory B cells (Breg) and the expression of IL-10 and CXC chemokine receptor-4 (CXCR4) by MenSCs as an immune-modulatory agent, resulting in fewer changes in colon tissue [72].

MenSCs can exert an immune-modulatory effect through the suppression of lymphocytes and the pro-

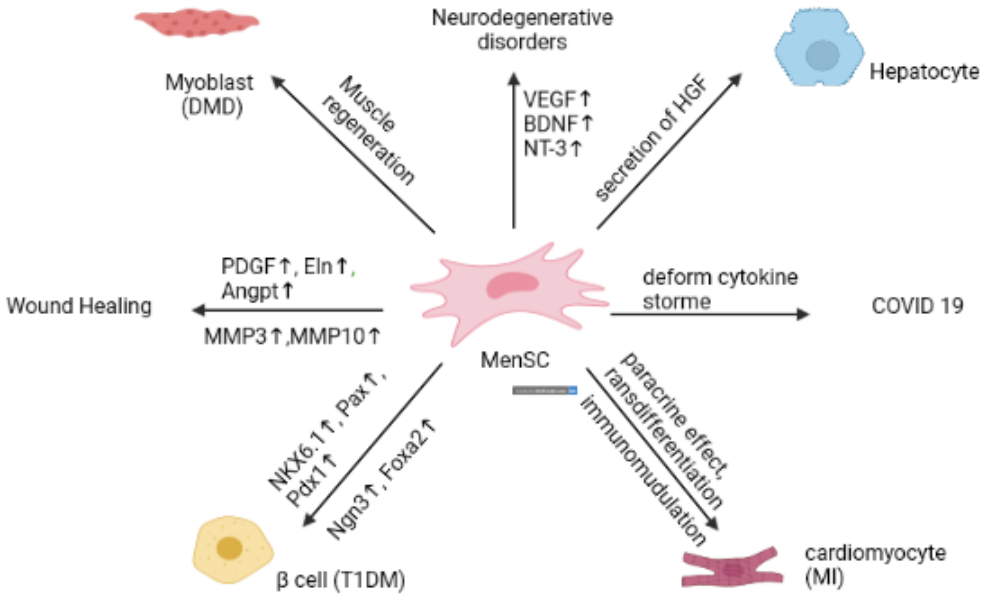

Figure 2. Multilineage differentiation potential of MenSCs

Note: MenSCs can be directed into different cell lineages, including adipocytes, myocytes, β cells, and neurocytes in vitro, and as such, they could be used for the treatment of a wide range of diseases. MenSCs can also enhance or inhibit some gene expression or release exosomes that may promote disease conditions.

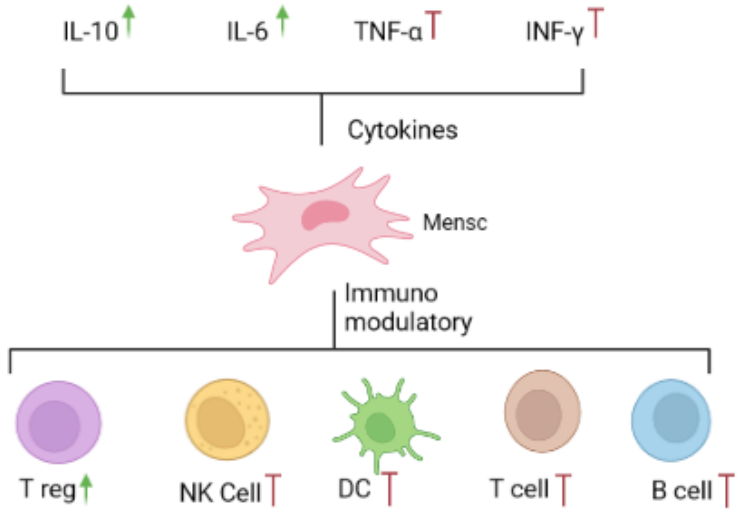

Figure 3. Immunomodulatory effects of MenSCs on immune cells

Note: MenSCs can suppress B cells, T cells, DCs, and NK cells, but they cause upregulation and proliferation of regulatory T cells (Tregs). MenSCs can also increase the anti-inflammatory cytokines, such as IL-6 and IL-10, while inhibiting pro-inflammatory cytokines, like TNF-α and INFγ.

liferation and secretion of inflammatory cytokines, like INFγ and TNFα. They also suppress neuroinflammation by decreasing the recruitment of Th_1 and Th_{17} cells to the nervous system, upregulating anti-inflammatory cytokines, like IL-10 and IL-27, and downregulating pro-inflammatory cytokines, such as IL-1β [36]. Lv et al. indicated that endometrial regenerative cells (ERC) can have anti-inflammatory and immunosuppressive effects, thus potentially ameliorating colitis in mouse models. In this study, treatment of DSS (dextran-sulfate-sodium)-induced mice with ERCs resulted in a decrease in the disease activity index (DAI) and in levels of intracolonic IL-2 and TNFα. Conversely, the expressions of IL-10 and IL-4 increased. In contrast, the untreated group of DSS-induced mice exhibited severe colitis, characterized by body weight loss, mucosal ulceration, bloody stool, and colon shortening. Also, it was observed that ERC-treated mice had decreased MHC II expression, higher levels of $CD4^+CD25^+$ and $FOXP3^+$ T-reg cells, and fewer $CD3^+CD25^+$ active T cells [73]. ERC can also decrease the amount of IgG deposition in the colon and the number of immature plasma cells in the spleen. Therefore, they can improve the survival of colitis mice. It can be concluded that ERC increases B-reg and IL-10 production, resulting in therapeutic effects on colitis in mice [70].

In a study on LPS-induced lung injury, the levels of inflammatory cells and IL-1β expression significantly decreased after the transplantation of MenSCs. It was assumed that MenSCs hinder the T cell function through cell contact, thereby inhibiting inflammation in the injured lung [17]. There has been some research on the combination of MenSCs with agents, like antibiotics, and evaluating their efficiency in the treatment of sepsis. Alcayaga-Miranda et al. investigated the direct and indirect effects of MenSCs on sepsis. In the direct method, they incubated a bacterial mixture with MSCs derived from BM and menstrual blood for 6 hours. Compared to the control group, both MSCs significantly inhibited bacterial growth. They also studied conditioned medium (CM) to determine whether the anti-bacterial effects of MSCs are related to soluble factors. Compared to BM-MSCs, the non-stimulated CM of MenSCs had a stronger inhibition of bacterial growth. After 40 hours post-CLP, the serum levels of TNFα, IL-6, and MCP-1 decreased in the group treated with MenSCs, both with and without antibiotics, compared to the saline group. The group treated with antibiotics and MenSCs also showed decreased levels compared to untreated mice. In conclusion, they observed that only the MenSC-treated group, regardless of antibiotic treatment, could reduce pro-inflammatory and inflammatory cytokines. Overall, it can be emphasized that MenSCs were effective in rescuing mice from uncontrolled systemic inflammatory response following CLP-induced sepsis [74].

Jin et al. demonstrated that pretreatment of ERC with stromal cell-derived factor-1 (SDF-1) plays a crucial role in alleviating sepsis-related models. They reported that

SDF-1-pretreated ERCs could significantly reduce pro-inflammatory cytokines (TNFα, IL-1β) while increasing levels of the anti-inflammatory factors IL-4 and IL-10 [71]. The immunosuppressive ability of BM-MSCs increased after their pre-treatment with an anti-inflammatory stimulus. IFN-γ-pretreated BM-MSCs can have an anti-proliferative effect on CD_4^+ T cells; however, the pretreatment of INF-γ and INF-g with MenSCs demonstrated a milder immunosuppressive response. Compared to BM-MSCs, the in vitro effect of MenSCs on T cell proliferation is weaker, and it can be influenced by factors, such as cytokine milieu, T cell-stimulating factors, the MenSC/ T cell ratio, and the culture system [75].

NK cells play a substantial role in the innate immune system of the endometrium. Although it has been acclaimed by reported that MenSCs could induce the proliferation of NK cells, pretreatment of MenSCs with INFγ/IL-β has anti-proliferation potential through the mediation of the IL-6 and TGFβ pathways. MenSCs could impair the cytotoxicity of NK cells on K562 cells [76]. The concentration of MenSCs can have a significant effect on immune system cells; for example, they can stimulate or inhibit the mixed lymphocyte reaction (MLR) and may also inhibit the complete and optimal maturation of monocyte-derived DCs in a dose-dependent manner [67]. In the case of NK cells, this dose-dependent effect remains, with MenSCs exhibiting maximum suppression at a ratio of 1:4. As the MenSC/NK cell ratio increases, NK cell proliferation decreases [76].

By affecting innate immune cells (human blood monocyte-derived DCs (MoDCs)), NK cells, and tissue macrophages) and the secretion of monocyte-to-DC differentiation inhibitory factors (IL-6 and IL-10), MenSCs can affect the innate immune system. Uterine NK cells (uNK), as an important part of the endometrial innate immune system, play a crucial role in hindering allorejection, which contributes to maintaining a successful pregnancy. Any dysfunction of uNK cells may result in the pathogenesis of recurrent pregnancy loss; therefore, the cytotoxic function of uNK cells must be tightly regulated [77]. MenSCs, through the production of IL-6 and TGF-β, can have inhibitory effects on NK cell proliferation. MenSC treatment with INF-γ/IL-β can decrease the expression of granzyme A, granzyme B, and perforin, leading to a prevention of NK cell cytotoxicity [78]. In a model of allograft heart transplanted mice, it was observed that 24 hours after the injection of MenSCs, the ingraft deposition of donor-specific IgG and IgM antibodies was reduced, and donor-specific antibody-secreting B cells also declined, resulting in an improvement in graft survival in recipient mice [79]. Cabezas et al. examined the intravenous injection of MenSCs into a murine model of colitis. After 2-8 days, they observed that levels of IL-4 and IL-10 increased, while IL-2 and TNF levels decreased. Also, compared to the untreated control group, the MenSC-treated group exhibited higher expression levels of MHC II from splenic DCs [80].

Translational potential and clinical considerations of MenSC-based therapies

Given their unique biological potentials, MenSCs are emerging as a promising cell type for the treatment of many human diseases, ranging from reproductive disorders and cardiovascular diseases to autoimmune and inflammatory conditions. Early-phase clinical studies, particularly on AS, premature ovarian failure, and liver cirrhosis, have indicated encouraging safety profiles and preliminary efficacy, highlighting their potential for broader clinical use. However, the translation into routine clinical practice faces several challenges, including the need for standardized isolation and expansion protocols, large-scale good manufacturing practice (GMP)-compliant production, and rigorous long-term safety evaluations. Potential risks, such as unwanted immune responses, ectopic tissue formation, and tumorigenic potential—though currently considered low—must be systematically addressed through well-designed preclinical and clinical trials. Furthermore, regulatory hurdles, cost-effectiveness analyses, and ethical considerations will play critical roles in shaping the future clinical landscape of MenSC therapies. By bridging current laboratory findings with clinically applicable protocols, MenSCs could become a versatile and minimally invasive platform for regenerative therapy [81, 82].

Conclusion and Future Research

In conclusion, the application of stem cells in regenerative medicine can be the window of hope for the treatment of various diseases and disabilities, such as female infertility, type 1 diabetes, MI, wound healing, neurodegenerative diseases, and many other conditions that were once thought to be incurable. Nowadays, the use of MenSCs as a novel source of MSCs is gaining special interest among scientists due to two important factors: Non-invasive accessibility and the immunomodulatory potential of these cells, which have historically posed significant obstacles in the field of stem cell therapy. To date, there has been extensive research on these cells, and many studies are ongoing, as scientists seek to harness their differentiation potential and optimize differentiation conditions and protocols for their application in regenerative medicine. Future research on MenSCs

should focus on addressing the current gaps in clinical trial evidence, particularly through well-designed, large-scale clinical trials to survey their long-term safety and efficacy. Advanced strategies, such as exosome extraction from MenSCs, could enhance their therapeutic potential and enable targeted delivery in regenerative therapy. Moreover, comparative studies with other adult stem cell sources are needed to better define their unique advantages and limitations.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran.

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Authors contribution's

Conceptualization and study design, data collection, statistical analysis, and writing the original draft: Atefeh Hojjat and Seyed Ehsan Enderami; Data interpretation: Mohammad Kabi, Mohamadfoad Abazari, Keyvan Mehdipour Chari, Amirali Khodashenas, Vahid Kia, and Amir Maleksabet; Review and editing: Atefeh Hojjat, Reyhaneh Nassiri Mansour and Seyed Ehsan Enderami; Project administration, Seyed Ehsan Enderami.

Conflict of interest

The authors declared no conflict of interest.

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