

Menstrual Blood Mesenchymal Stem Cells: Boon In Therapeutics

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Abstract

Side effects of drugs are well known. Recently adopted cell therapy is the perfect alternative to this problem. In order to promote cell therapy, scientists were in look out for easy, abundant, hassle free resources of stem cells. We have reviewed the applications of menstrual blood mesenchymal stem cells (MenSCs) in the tissue repair technique. A novel stem cell population that can be used for tissue repair in almost all organs which are structured by mesenchymal cells was established a decade ago, still in infancy for human use. So far, many successful applications were performed in animal models and a few on humans; however, menstrual blood mesenchymal stem cell therapy has a bright future in therapeutic sciences.

INTRODUCTION

After knowing well that almost every drug has side effect(s) researchers wanted to find a therapeutic procedure where side effects are eliminated. Cell therapies instead, inject, graft or implant into a patient the compatible viable cells, which effectuates a medicinal effect without any chemical drug. In the present scenario, a flourishing research field, cell-based therapy involves modifying a patient's own cells or cells from a donor to fight a disease and alleviate medical conditions.

STEM CELLS THERAPY

Cells which are capable of regeneration and differentiation into a wide range of specialized cell types are used for stem cell therapy. They are of following types

- Foetal stem cells (FSCs).
- Aadult stem cells (ASC).
- Pluripotent stem cells (PSC).

Stem cells are immature or undifferentiated cells with the capacity to self-renew differentiate and repopulate a host *in vivo* (1). Remarkable plasticity or potency is hierarchical ranging from totipotent (differentiating into all cell types including placenta), pluripotent

(differentiating into cells of the three germ layers, but not trophoblastic cells), multipotent (differentiating into cells of more than one type but not necessarily into all the cells of a given germ layer) to unipotent (differentiating into one type of cell only, *e.g.* muscle or neuron).

They fall into three categories *i.e.* **a.** Foetal stem cells (FSCs), **b.** Adult stem cells (ASC) and **c.** Pluripotent stem cells (PSC). FSCs appear to be more primitive and have greater multi-potentiality than their adult counterparts. Foetal stem cells (FSCs) can be isolated during gestation from many different tissues such as blood, liver and bone marrow as well as from a variety of extra-embryonic tissues such as amniotic fluid and placenta. They have been observed to differ on many biological aspects such as growth kinetics, morphology, immuno-phenotype, differentiation potential and engraftment capacity *in vivo*.

Adult stem cells can be found in almost all tissues such as brain, dental pulp, muscle, bone marrow, skin and pancreas with their therapeutic potential. The adult stem cell could be multipotent (*e.g.* haematopoietic stem cells (HSCs) giving rise to all blood cells and adherent stromal/mesenchymal stem cells (MSCs) that give rise to bone, fat, cartilage and muscle) or unipotent (*e.g.* progenitor cells). Adult MSCs have the problem of being difficult to extract in sufficient

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numbers for therapy and/or presenting restricted plasticity and limited proliferative capacity compared with FSCs cells.

Pluripotent stem cells can be derived from the inner cell mass of the pre-implantation embryo (*i.e.* Foetal stem cells (FSCs)) or isolated from the foetal primordial germ cell pool (PGC) above the allantois (*i.e.* embryonic germ (EG) cells and embryonic carcinoma (EC) cells (2, 3). Induced pluripotent stem cells have unique abilities to self-renew and to recreate functional tissues. The destruction of the blastocyst or early foetus necessary for their derivation /isolation raises ethical concerns (4), although recent work has shown that FSCs can be derived from single blastomeres isolated using procedures similar to those routinely used for pre-implantation genetic diagnosis(5,6). Stem cells can keep dividing as long as they are alive and they have two important features: a. they can create other stem cells and/or they can become multiple types of more specialized cells. b. These cells or their derivatives when transplanted or infused, promote the repair response of diseased, dysfunctional or injured tissues.

Nowadays, stem cell therapy has become an effective strategy for SCI (Spinal cord injury) (7,8) The most promising stem cells are neural stem cells (NSCs), because of their ability to differentiate into neural and glial cells when transplanted in the site of injury (9). However, some drawbacks also shadowed with NSCs such as non availability of adult NSCs for autologous cell transplant, and ethical concerns of the fetal-derived NSCs.

MESENCHYMAL STEM CELLS (MSCs)

In the recent past, MSCs have been explored as vehicles for cell therapy. Mesenchymal stem cells (MSCs) are multipotent adult stem cells which can

be differentiated into multiple cell types (10). These cells can be isolated from the bone marrow, umbilical cord blood, adipose tissue, muscle, and dental pulp. Transplantation of MSCs into the injured spinal cord promoted tissue preservation by directly replacing the damaged cells, decreasing the cyst and injury area, stimulating axonal sprouting, producing neurotrophic factors, as well as inhibiting inflammatory cytokines in rats. In comparison with NSCs, MSCs show a high degree of genomic stability during culture and typically do not result in tumour formation. Centre for Genomic Regulation (CRG) in Barcelona are developing a stem cell treatment for retinal degeneration by using engineered mesenchymal stem cells (from bone marrow) to have an excessive amount of Ccr5 and Cxcr6 and transplanted them into models of retinal degeneration which preserved the function of degenerating retinal tissue. Mesenchymal stem cells could offer several advantages for the treatment of eye diseases, including an ability to differentiate into retinal cells and to be grown outside the body. When the altered cells were transplanted into models of human and mouse retinal diseases, the cells migrated in high numbers to deteriorating retinal tissue and prevented the death of retinal cells (11).

MENSTRUAL BLOOD-DERIVED MESENCHYMAL STEM CELLS (MENSCs)

Menstrual blood-derived mesenchymal stem cells (MenSCs) are boon in therapeutics and a list of diseases is treated and more are in pipeline undergoing clinical trials. Approximately a decade ago, Meng *et al.* (12) and Cui *et al.* (13) discovered a novel source of MSCs from human menstrual fluid, named menstrual blood-derived stem cells (MenSCs) (14). These SC have high rate of proliferation and possess multi lineage differentiation potency as well as its differentiation into epidermal lineage is remarkable.

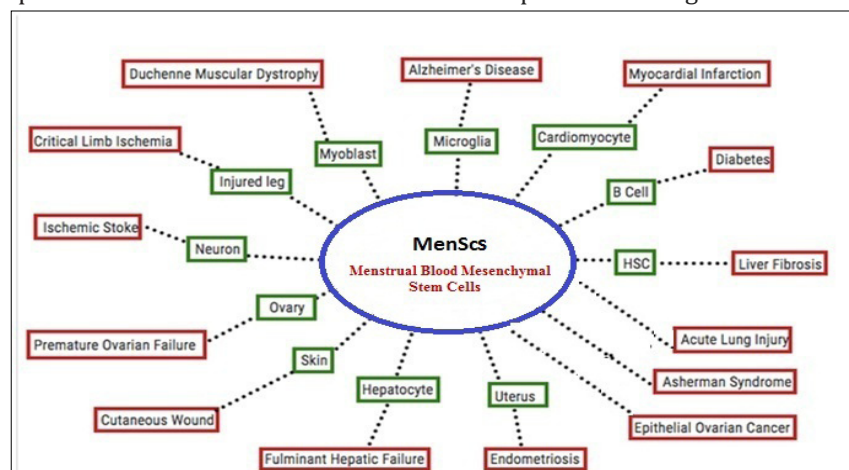


Fig1. Different diseases treated with MenSCs.

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MenSCs are giving rise to hopes in clinical application that can be harvested from human menstrual blood shedding of endometrium monthly. Period blood is a highly dynamic and powerful substance. Scientists in Japan have found that cells taken from menstrual blood can be cultured in the laboratory and used like SC, which can even repair damaged heart tissue (Fig.1). Scientists devoted to researching SC found that the lining of the uterus, which is a main constituent of period blood, have an abundance of these cells. MenSCs proliferate faster than the stem cells from umbilical cord and can be manipulated to transform into all kinds of cells, including those found in fat, muscle, bone, and nerves.

Menstrual fluid consists of blood as well as extra tissue from the uterine lining. It also can contain the remnants of the egg that travelled down the fallopian tube into the uterus during ovulation and was not fertilized. Women felt better about their periods after being made aware of the ability to donate menstrual fluid, meaning that MenSC therapy can be beneficial for donors and patients alike. The average volume of menstrual fluid during a monthly menstrual period is 35 milliliters (2.4 tablespoons of menstrual fluid), with 10–80 milliliters (1–6 tablespoons of menstrual fluid) considered typical. About half of menstrual fluid is blood. This blood contains sodium, calcium, phosphate, iron, and chloride, the extent of which depends on the woman. In addition to blood, the fluid consists of cervical mucus, vaginal secretions, and endometrial tissue. Vaginal fluids in menses mainly contribute water, common electrolytes, organ moieties, and at least 14 proteins, including glycoproteins.

To collect, bring a jar with you to the toilet, and when you have removed the cup from inside your body, transfer the contents of it into the jar and close the lid. Always store your period blood in the fridge and use it quickly. Menstrual fluid may have an unpleasant odour, but given how period blood isn't exactly a rare substance, there is no need to 'save it for later' and let it get stale (15, 16).

With the potential of multi-directional differentiation,

MenSCs are able to undergo adipogenic, chondrogenic, osteogenic, myogenic, and neurogenic differentiation *in vitro* (17, 18). Compared with other sources of MSCs, MenSCs can be easily selected in a periodic manner and obtained by a noninvasive method, avoiding the ethical issues (19), do not form teratomas (20), and can be expanded by at least 20 passages without genetic abnormalities (21). Recently, MenSCs showed potential therapeutic applications in a variety of animal disease models, such as stroke (22), type 1 diabetes (23,24), myocardial infarction(25) and so on. Co-culture experiments showed that MenSCs restrained the proliferation of LX-2 cells (HSC line) through secretion of paracrine cytokines, including interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein 1 (MCP-1), growth-related oncogene (GRO), osteoprotegerin (OPG), hepatocyte growth factor (HGF) by promoting hepatocellular regeneration or inducing the apoptosis of stellate cells and antifibrotic function by inducing G₀/G₁-phase arrest in stellate cells.

THERAPEUTIC APPLICATIONS OF (MENSCS)

In this section we are mentioning the diseases where MenSCs are used for repair the tissue injury.

Uterine Endometriosis

Inactive endometrium contains hormone independent, clonogenic epithelial and stromal cells which do not vary from the proliferative to secretory stage of the menstrual cycle, or between active, cycling and inactive endometrium for both epithelial and stromal cells (26). Activation of the Hippo/TAZ pathway is required for menstrual stem cells to suppress myofibroblast and inhibit transforming growth factor β signalling in human endometrial stromal fibrosis (27).

Fulminant Hepatic Failure

Human menstrual blood-derived stem cells alleviate fulminant hepatic failure (FHF). Parekkadan et al. (28) for the first time have shown that Mesenchymal Stem Cell-Derived Molecules (Exosomes) can also reverse FHF in mice *in vitro and in vivo*.

Microvesicles arises by budding of the plasma

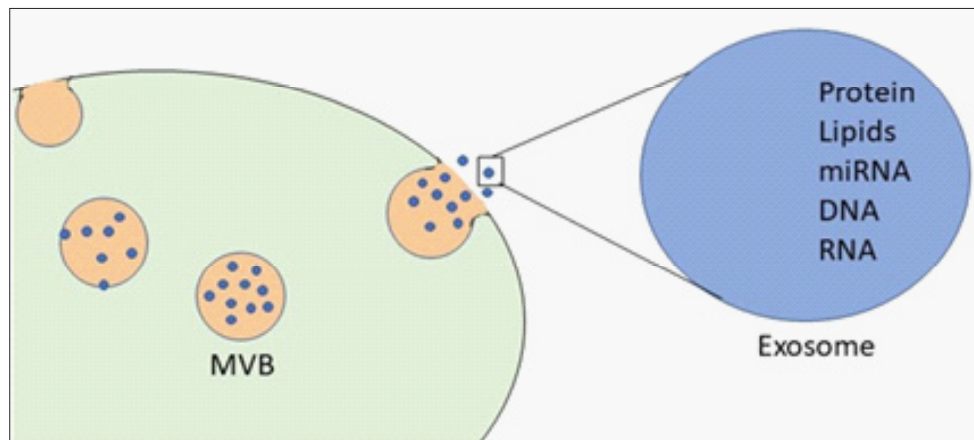


Fig2. showing the origin of microvesicles and exosomes from cells.

membrane are more irregular in shape and size and can contain cytoplasmic materials. Microvesicles express surface markers such as integrin- β , CD40 and selectins such as plasma selectins and/or proteins from the cells they originate from. Exosomes originate from the endosomal trafficking system (therefore, are more regular in shape and size), easily identifiable via cell surface markers such as CD81, CD9 and CD63 and may contain materials such as mitochondrial DNAs, mRNAs and miRNAs. miRNA: microRNA; MVB: multi-vesicular bodies.

Skin disease

Inflammatory skin disorders resulting in serious deterioration of the quality of life have become one of the major public concerns. Unfortunately, despite their significance, there is no fundamental cure to date. Only BM (bone marrow) derived MSCs possess unique immunomodulatory properties which make them a promising tool for the treatment of various inflammatory diseases especially within the skin due to the suppressive effect on T cell proliferation till today. MSCs from menstrual blood can be successfully used for the treatment of atopic dermatitis (AD), dermatitis and psoriasis. In addition, it has been proposed that cell priming or gene transduction can be novel strategies for the development of next-generation high-efficacy MSCs for treating inflammatory skin diseases (29).

Premature Ovarian Failure (POF)

The incidence of premature ovarian failure (POF) has been increasing in recent years. Many researchers have reported that MenMSCs, were tracked in ovarian tissues within 2 months after transplantation, and they differentiated into granulosa cells (GCs). Therefore, the use of these cells can be a practical and low-

cost method for the treatment of POF patients.

Several studies have shown that MenMSCs, reduce apoptosis in granulosa cells and fibrosis of the ovarian interstitium, there by improving folliculogenesis and rescuing overall ovarian function in an animal model of POF (30), including restoring fertility (31). In addition, Wang et al. demonstrated that MenMSCs, produced a high level of fibroblast growth factor 2, which enhanced cell survival, proliferation, and function to repair tissue damage (32), hence, we can safely conclude that the mesenchymal stem cells and in vivo survival of MenMSCs, make them ideal seed cells for stem cell transplantation in the treatment of POF.

Ischemic Stroke

Transplantation of MenSCs, either intracerebrally or intravenously and without immunosuppression, after experimentally induced ischemic stroke in adult rats also significantly reduced behavioral and histological impairments compared to vehicle-infused animals. MenSCs exemplify a source of "individually tailored" donor cells that completely match the transplant recipient, at least in women. Autologous menstrual-blood-derived cells previously collected, expanded up to third passage and cryopreserved would still benefit from the use of allogeneic cells which, being stromal cells, present low immunogenicity and, therefore, tolerable rejection rates (33,34).

Critical Limb Ischemia

De novo angiogenesis based on MenSCs therapy is considered as a promising treatment for acute limb ischemia. MenSCs significantly improved hind limb ischemia helped the recovery of the ischemic tissue with combinatorial therapy returned to normal

mice. These results indicate that menstrual blood is a promising source to isolate stem cells for hind limb ischemia treatment (35, 36).

Duchenne Muscular Dystrophy

Umezawa's team (37,38) successfully trans differentiated MenSCs into myoblasts/myocytes in vitro and restored sarcolemmal expression of dystrophin in dystrophied muscle of DMD mice. Cellular fusion between adipocytes and dystrophied myocytes expressed dystrophin (39) providing a positive results for the treatment of Duchenne muscular dystrophy.

Alzheimer's Disease

Intracerebral transplantation of MenSCs dramatically improved the spatial learning and memory of APP/PS1 mice as well as significantly ameliorated amyloid plaques and reduced tau hyperphosphorylation in APP/PS1 Alzheimer's disease in mouse model. MenSCs markedly increased several A β (amyloid-beta) degrading and anti-inflammatory impact of MenSCs in the brains of APP/PS1 mice. Similar results could be anticipated in humans also by clinical trials yet to be done (12, 40).

Myocardial Infarction

Transplanted MenSCs significantly restored the damaged cardiac function, reduced apoptosis, promoted cell proliferation; stimulate angiogenesis which rescued the myocardium in the infarct region, and recruited c-kit⁺ cells. Expression of some specific cytokines to activate AKT/extracellular signal-regulated kinases 1 and 2 (ERK 1/2) /signal transducers and activator of transcription 3 (STAT 3) and suppress p38 signaling pathway also was noticed (41,42), Wang's team found that MenSCs inhibited endothelial cell to mesenchymal transition (EMT), which helped to reduce the total number of cardiac fibroblasts and tissue fibrosis progression (43). The secreted exosomes of miR-21 mediated and enhanced the paracrine and cytoprotective effects through a transwell co-culture system in vitro. MenSCs transplantation decreased fibrosis area and restored the LV systolic function in the MI (myocardial infarction)-model in vivo. Engrafted MenSCs transdifferentiated into cardiomyocyte within MI area. MenSCs can be a major cell source for stem cell therapy to achieve cardiomyogenesis.

Diabetes

Intravenous injection of human menstrual blood

progenitor cells (MBPCs) can reverse hyperglycemia and weight loss, prolong lifespan, and increase insulin production in diabetic mice. Histological and immunohistochemistry analyses indicated that T1DM mice with MBPCs transplantation recovered islet structures and increased the β -cell number. *In vivo* distribution of MBPCs when analysed a majority of MBPCs migrated into damaged pancreas and located at the islet, duct, and exocrine tissue. MBPCs did not differentiate into insulin-producing cells, but enhanced neurogenin 3 (ngn3) expressions, which represented endocrine progenitors that were activated. Ngn3⁺ cells were not only in the ductal epithelium, but also in the islet and exocrine tissue. MenSCs could facilitate β -cell regeneration and enhance the number of β cells by increasing the expressions of neurogenin 3 (ngn 3), forkhead box A2 (foxa 2), pancreatic and duodenal homeobox 1 (pdx 1), NK homeobox factor 6.1 (nkx 6.1), and paired box gene (pax) to activate endogenous progenitor cell differentiation post MenSC transplantation in T1DM mice (44). The levels of these gene expressions all increased after cell transplantation.

Hsc Liver Fibrosis

Liver function was improved by MenSCs via targeting activated hepatic stellate cells (HSCs). MenSCs significantly reduced collagen deposition and improved liver function within 2 weeks of transplantation in a mouse model. These stem cells underwent hepatocyte differentiation based on CK18 expression. Moreover, tracking of green fluorescent protein-expressing MenSCs demonstrated that transplanted cells migrated to the sites of injury, but few differentiated into functional hepatocyte-like cells. Results provide preliminary evidence for the antifibrotic capacity of MenSCs in liver fibrosis (45,46, 47).

Acute Lung Injury

MenSCs promoted the repair of injured lung by inhibiting the inflammatory response in LPS (lipopolysaccharide)-induced ALI (acute lung injury in mice (48). Furthermore, MenSCs not only improved pulmonary microvascular permeability, reduced histopathological injury, downregulated the expressions of IL-1 β and caspase-3, upregulated the levels of IL-10 in bronchoalveolar lavage fluid (BALF) in the damaged lung, proliferating cell nuclear antigen (PCNA), and keratinocyte growth factor (KGF) in bronchoalveolar lavage fluid (BALF). MenSCs could

also increase the survival rate of BEAS-2B cells (human normal lung epithelial cells) (49).

Asherman Syndrome

Asherman's syndrome is an uncommon, acquired, gynecological disorder characterized by changes in the menstrual cycle caused by the formation of adhesions in the uterine cavity. Patients experience reduced menstrual flow, increased cramping and abdominal pain, eventual cessation of menstrual cycles (amenorrhea), and, in many instances, infertility, (including amenorrhea, less menstruation, or dysmenorrhea), and repeated pregnancy loss (50). This can be treated by autologous MenSC transplantation that significantly increased endometrial thickness (ET) in Asherman syndrome women in 7 patients (51). They showed that the ET of 5 women was significantly increased to 7 mm (a thickness to ensure embryo implantation). Four of these patients were subjected to frozen embryo transfer (FET). Surprisingly, one patient developed a spontaneous pregnancy only after the second MenSCs transplant.

Epithelial Ovarian Cancer

Epithelial ovarian cancer develops from the cells that cover the outer surface of the ovary. Most epithelial ovarian tumors are benign (noncancerous). EOC has been found to be advanced in most cases, with a combination of extensive abdominal metastasis, high recurrence, and chemoresistance (52). This benign tumour can be treated successfully with MenSCs due to its intrinsic anti-tumor properties. EOC cells *in vivo* and *in vitro* provide a strategy for MenSCs -based anti-cancer therapy against epithelial ovarian cancer (53).

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