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*Review Article*

# Endometrial stem cells: clinical application and pathological roles

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**Abstract:** Adult stem cells occur in human endometrium. Menstrual-blood derived stem cells (MenSCs) are mesenchymal stem cells that can be obtained in a non-invasive manner. Due to their rapid proliferation rate, low immunogenicity, and low tumorigenicity, MenSCs are used extensively in tissue engineering. They can be induced into multiple cell lineages under certain conditions. MenSCs contribute to tissue repair via several different mechanisms, highlighting their great promise in clinical applications. Endometrial stem cells may also be used to shed light on the pathogenesis of endometriosis and endometrial carcinoma. This review will cover recent progress in this field.

**Keywords:** Endometrial stem cells, menstrual blood-derived stem cells, molecular mechanisms, endometriosis, endometrial carcinoma, cancer stem cells

## Introduction

Adult stem cells, also referred to as tissue-specific stem cells, have the ability to self-renew. They proliferate by asymmetric cell division, eventually differentiating into specific cell lineages. The ability of stem cells to produce other cell lineages is called potency. Adult stem cells play important roles in tissue repair and reconstruction.

Adult stem cells were first isolated from the endometrium in 2004 [1]. It had long been speculated that endometrial stem cells existed, based on several properties of the human endometrium. For instance, the human endometrium, an extremely dynamic tissue, undergoes approximately 400 cycles of periodic proliferation, differentiation, and shedding [2]. In addition, the endometrium can grow up to 7 mm in one week [3]. Finally, in the clinical setting, it was demonstrated that the human endometrium could regenerate, even following successful resection [4].

### *Characteristics of endometrial stem cells*

The human endometrium comprises the functionalis and basalis. The functionalis is shed monthly with menstrual blood arising from changes in hormones and it is quickly reconstructed after menstruation. Endometrial stem cells were initially thought to be located only in the basalis [5]. During the menstrual phase, endometrial stem cells migrate to the functionalis in a stromal cell-derived factor-1 (SDF-1)/CXCR4 axis-dependent manner, contributing to the reconstruction of the endometrium. Elshekh et al. reached a similar conclusion on the relationship between SDF-1 and endothelial progenitor cells [6]. The proliferating endometrium is thought to recruit endothelial cells to cover the new vasculature, and because SDF-1 is expressed more highly in the proliferative phase, it is an ideal marker to study endothelial progenitor cell migration during menstruation. Mounting evidence has confirmed that there are stem cells in both the functionalis and basalis of the human endometrium [7].

Three kinds of stem cells exist in the human endometrium: epithelial stem cells, mesenchymal stem cells, and endothelial stem cells [8]. The subpopulation of endometrial stem cells that express CD146 and CD140b/PDGFR-β are the mesenchymal stem cells. They are mainly located near small vessels in the functionalis

and basalis [9], consistent with the conclusion mentioned above [7]. Endometrial stem cells can be obtained non-invasively from menstrual blood, and are referred to as menstrual blood-derived stem cells (MenSCs) [10]. MenSCs have an extremely high proliferative ability, and can maintain a relatively stable karyotype through 40 passages [11]. The doubling time of MenSCs is approximately 20 hours, which is twice as fast as bone marrow-derived stem cells [12]. Differences in telomerase activity may partially explain the highly proliferative characteristic of MenSCs [13]. Telomerase is a transcriptase that allows cells to avoid the shortening of their telomeres. Shortening of telomeres occurs during cell division and eventually leads to cell death. Thus, telomeres are important to sustain the integrity of chromosomes and the genomic stability of cells.

Similar to bone marrow-derived stem cells, MenSCs express mesenchymal-like surface markers, such as CD29, CD44, CD73, CD90, and CD105, but not STRO-1. They also express embryonic stem cell markers SSEA-4 and OCT-4 [12]. In addition, MenSCs express MHC-I, indicating that they are capable of immunomodulation [14]. MenSCs were shown to inhibit the mixed lymphocyte reaction (MLR) in a limb ischemia animal model [15]. They could reduce the production of IFN-γ and TNF-α in a dose-dependent manner. The low immunogenicity of MenSCs might make them attractive for cell transplantation therapeutics.

MenSCs can be induced into multiple cell lineages, including cartilage cells [16], osteoblast cells [17], adipose cells, smooth muscle cells, myocardial cells and hepatocytes. Beating myocardial-like cells expressing myocardial markers (troponin-1 and α-actinin) have been harvested successfully by co-culture of MenSCs with fetal mice myocardial cells [18]. Adult stem cells naturally reside in "niches", or certain sites in tissues with a special microenvironment; therefore, mimicking a "niche" *in vitro* seems to be crucial to induce cell differentiation [19]. Serum is a common medium for inducing cell differentiation *in vitro*, yet it contains numerous growth factors, some of which may interfere with effective differentiation. Ikegami et al. compared the differentiation potential of endometrial mesenchymal cells ECM100 and MenSCs into myocardial cells in serum-free medium and serum-containing medium [20]. The induction potency increased by 36% and 163% in each cell type, respectively, when incubated in serum-free compared with serum-containing medium. Compared with 10% serum-containing medium, the phenotype of induced cells in serum-free medium more closely resembled that in the physiological state. However, determining which growth factors are necessary to induce different cell types is difficult because of the large number of growth factors and their complicated interactions.

For example, Khanmohammadi M compared three different methods for inducing adipose cells in both MenSCs and bone marrow-derived stem cells [21]. The first two protocols involved traditional culture medium, with the second protocol including the addition of retinoic acid. Neither of these two protocols effectively induced MenSCs to differentiate into adipose cells. In the third protocol, in which rosiglitazone was added, oil red O staining confirmed the fat producing ability in the induced cells. MenSCs could be an alternative to bone marrow-derived stem cells for tissue engineering because of their easy accessibility. In addition, Kazemnejad et al. determined that human platelet derivatives (HPDs), rather than serum, could not only promote proliferation of MenSCs, but also increase their osteogenic potency [22]. Moreover, MenSCs could be induced to generate induced pluripotent stem cells (iPSCs) [23], which were first obtained through ectopic expression of four transcription factor genes, OCT4, KLF4, SOX2, and c-MYC. The induction time of iPSCs is usually about 20 days, while MenSCs are capable of inducing iPSCs in just 12 days with high efficiency [24].

*Molecular mechanisms of MenSC-based therapeutics*

MenSCs contribute to tissue repair and reconstruction through a variety of mechanisms. MenSCs can directly differentiate into several different cell types, as previously mentioned. Hepatocyte growth factor (HGF), fibroblast growth factor-4 (FGF-4), and oncostain M (OSM) could induce hepatocyte-like cell differentiation in MenSCs. Mou et al. successfully induced MenSCs into functional hepatocyte-like cells that expressed hepatocyte surface markers ALB, AFP, CK18/19, and CYP1A1/3A4 [25]. Functional tests revealed that these cells could synthesize urea and store glycogen. They repaired a damaged liver effectively in an

injured animal model, suggesting their therapeutic potential in patients suffering from chronic liver diseases. Premature ovarian failure (POF) is a gynecological disease that causes infertility in some women. When transplanted into POF mice, MenSCs survived and expressed ovarian granulosa cell-specific proteins, leading to a remarkable increase in ovarian weight and hormone secretion [26].

In addition, intravenously injected MenSCs improved hyperglycemia significantly in mice with type I diabetes [27]. After being injected into the mice, most MenSCs migrated to the injured pancreas, finally locating near the pancreatic duct and islets. Interestingly, although the number of β cells increased after the injection of MenSCs, no differentiation of MenSCs was detected. Thus, MenSCs might stimulate endogenous pancreatic progenitor cell differentiation in a paracrine manner via the upregulation of neurogenin (ngn3). Likewise, MenSCs were able to secrete neuroprotective factors such as vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF) in a mouse model of stroke. These factors promoted the survival of neurons and mitigated behavioral and histological changes. However, whether Effects of MenSCs involved their direct differentiation into neuronal cells was unclear [28].

Finally, as mentioned previously, MenSCs also have an immunomodulatory effect. Ulcerative colitis is a type of inflammatory bowel disease. MenSCs showed an extensive immunomodulatory effect when injected into mice with colitis. They decreased the infiltration of inflammatory cells, including macrophages and NK cells, and modulated the number of immune cells. In addition, MenSCs mediated the expression of multiple cytokines. In the MenSC-treated mice, pro-inflammatory cytokines IL-2 and TNF-α decreased significantly, while anti-inflammatory factors IL-4 and IL-10 increased dramatically [29]. Notably, the immunomodulatory mechanism of MenSCs is not always the same and depends on interactions with numerous factors. Further research is needed to clarify their specific effects in different disease states [30].

*Endometrial stem cells and endometriosis*

Endometriosis is a condition characterized by progressive dysmenorrhea and chronic pelvic pain that causes infertility in some women. Endometriosis correlates with retrograde menstruation [31]. The theory of endometrial stem cells brought a new perspective to the pathogenesis of endometriosis [32]. Li et al. isolated and identified epithelial stem cells and mesenchymal stem cells in ectopic endometrial tissue [33]. With the discovery of an endometrial side population (ESP), it was speculated that a few ESPs might contribute to the initiation of endometriosis [34]. ESPs in the functionalis might be engrafted ectopically with retrograde menstrual blood, from which they could then promote angiogenesis. This is consistent with endometrial stem cells being located mainly near vessels in the functionalis and basalis, providing support for the role of ESP metastasis via blood vessels [10]. In addition, endometrial stem cells are capable of differentiating into multiple cell lineages [35]. Song et al. compared stem cell-related genes in patients with and without endometriosis. Sex-determining region Y-box 2 (SOX2) and Nanog homeobox (Nanog) were upregulated at the mRNA level, with SOX4 and OCT4 upregulated at the protein level [36]. These pluripotency markers might help explain the etiology of endometriosis.

IPO13, a member of the importin β superfamily, was expressed higher in the ectopic endometrium and in endometrial carcinoma. IPO13 colocated with mesenchymal stem cell marker CD90 [37], which further consolidated the relationship between stem cells and endometriosis.

New vessels are needed for the survival and development of the ectopic endometrium [38]. Tie2 is a vasculature-endothelium-cell specific tyrosine kinase receptor that mediates proliferation and migration of endothelial cells whose expression is upregulated in the ectopic endometrium [39, 40]. Circulating endothelial progenitor cells (EPCs) are modulated by the SDF-1/CXCR4 axis, causing the migration of EPCs into the ectopic endometrium, where they co-express VEGFR2 and CD34. These conclusions may account for the source of angiogenesis in ectopic endometrium.

Finally, microRNAs (miRNAs) may also play a role in the pathogenesis of endometriosis. When miRNA levels in serum were compared between patients with and without endometriosis, miRNA-199a-5p expression was downregu-

lated in patients with endometriosis [41]. Upregulation of miRNA-199a-5p inhibits endometrial stem cell proliferation and angiogenesis in the ectopic endometrium by targeting the 3' untranslated region of *VEGFA*. Expression of miR-199a-5p reduced damage in an endometriosis animal model, suggesting that it might represent a novel therapeutic strategy.

*Endometrial stem cells and endometrial carcinoma*

Local and whole body signaling pathways tightly regulate the proliferation of adult stem cells. The "niche" is important to maintain homeostasis of adult stem cells, and dysfunction of these pathways is likely to cause carcinomas [42]. Cancer stem cells may originate not only from normal adult stem cells with silenced tumor suppressor genes, but also from differentiated adult stem cells with mutations that activate self-renewal pathways [43]. Cancer stem cells are found in many different types of carcinomas [44]. Hubbard et al. confirmed the existence of endometrial cancer stem cells [45]. CD133 is usually considered a marker for isolating endometrial stem cells. *In vitro* experiments showed that CD133-positive cells had a higher proliferation rate and this proliferation activity was monoclonal [46]. SP (side population) cells in endometrial carcinoma could promote metastasis and EMT [47]. Secreted protein acidic and rich in cysteine (SPARC) is upregulated in endometrial carcinoma, which leads to higher expression of fibronectin and the eventual promotion of EMT [48]. However, SPARC plays a dual role in endometrial carcinoma. While SPARC contributes to the metastasis of endometrial cancer stem cells through EMT, its overexpression can inhibit tumor growth [49].

Large intergenic non-coding ribonucleic acids-ROR (Linc-RNA-RoR) is necessary to maintain the pluripotency of embryonic stem cells and interferes with differentiation mediated by miR-145 [50]. Linc-RNA-RoR was found in endometrial carcinoma. Blockage of miR-145 mediated the differentiation of cancer stem cells, which could be a reasonable explanation for the canceration of stem cells. Under *in vitro* experimental conditions, when the concentrations of differentiation factors were high, miR-145 was transcribed. Under such circumstances, however, linc-RNA-RoR promoted the differentiation of stem cells [51]. This interaction provides guidance for targeting therapeutics of endometrial carcinoma in the clinic.

In conclusion, it is well established that endometrial stem cells have extensive applications in tissue repair and engineering. Moreover, endometrial stem cells have helped to reveal the pathogenesis of endometriosis and endometrial carcinoma. Endometrial stem cells have the potential to become a powerful tool for both clinical diagnosis and therapeutics. Preliminary results from endometrial stem cell use in animal models of different diseases suggested a future for endometrial stem cell-based applications in the clinical setting. Further research is needed to advance the development of endometrial stem cells for clinical use.

## Disclosure of conflict of interest

None.

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