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Review

Stem cell therapy in Asherman syndrome and thin endometrium: Stem cell-based therapy

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ABSTRACT

The endometrium is one of the essential components of the uterus. The endometrium of human is a complex and dynamic tissue, which undergoes periods of growth and turn over during any menstrual cycle. Stem cells are initially undifferentiated cells that display a wide range of differentiation potential with no distinct morphological features. Stem cell therapy method recently has become a novel procedure for treatment of tissue injury and fibrosis in response to damage. Currently, there is massive interest in stem cells as a novel treatment method for regenerative medicine and more specifically for the regeneration of human endometrium disorder like Asherman syndrome (AS) and thin endometrium. AS also known as intrauterine adhesion (IUA) is a uterine disorder with the aberrant creation of adhesions within the uterus and/or cervix. Patients with IUA are significantly associated with menstrual abnormalities and suffer from pelvic pain. In addition, IUA might prevent implantation of the blastocyst, impair the blood supply to the uterus and early fetus, and finally result in the recurrent miscarriage or infertility in the AS patients. It has been evidenced that the transplantation of different stem cells with a diverse source in the endometrial zone had effects on endometrium such as declined the fibrotic area, an elevated number of glands, stimulated angiogenesis, the enhanced thickness of the endometrium, better formed tissue construction, protected gestation, and improved pregnancy rate. This study presents a summary of the investigations that indicate the key role of stem cell therapy in regeneration and renovation of defective parts.

1. Introduction

Stem cells are known as undifferentiated cells that have the potential to be multiplied as a stem cell in undifferentiated form (self-renewal) and to mature and differentiated cells. Stem cells can be classified based on their capability to produce various types of cells: totipotent, pluripotent, multipotent, and unipotent [1]. Considering the self-renewal and the capacity of multi-lineage differentiation, stem cells therapy can be useful in the treatment of many degenerative diseases and situation that therapeutic choices are limited or do not exist. Stem cells have the potential of substituting damaged cells in the endometrium. Cell replacement strategies have been suggested and examined in some models of endometrium pathology across decades of investigation in animal models. In addition, multipotent and pluripotent stem cells have displayed beneficial paracrine effects, which can decrease cell death and provide growth/trophic support to host cells

Abbreviation: ART, assisted reproductive treatment; ASC, adult stem cell; BMSC, bone marrow stem cell; EA, endometrial atrophy; EnSC, endometrial stem cell; ER, estrogen receptor; ERC, endometrial regenerative cell; ESP, endometrial side population; ESC, epithelial stem cells; FET, frozen embryo transfer; GFP, green fluorescent protein; GMCSF, granulocyte macrophage colony stimulating factor; hAMSC, human amniotic membrane mesenchymal stem cell; HRT, hormonal replacement therapy; hUCMSC, human umbilical cord mesenchymal stem cell; IUA, intra uterine adhesion; Lgr-5, leucine rich repeat containing G protein-coupled receptor-5; menSC, menstrual blood-derived stem cell; MMP, matrix metalloproteinase; MNC, mononuclear Cells; MSC, mesenchymal stem cell; OCT-4, octamer-binding transcription factor-4; PDGF, platelet derived growth factor; PR, progesterone receptor; PROM, preterm premature rupture of membrane; RPL, recurrent pregnancy loss; SP, side population; SSEA-4, stage-specific embryonic antigen-4; UDC, uterine derived cells; VEGF, vascular endothelial growth factor

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Table 1
Some resources and features of stem cells which contribute in endometrium regeneration.

Stem cell	Major Resource	properties	Reference
BMDSC	Bone Marrow	-Low quantity in bone marrow - Declined differentiation potency with age -Aggressive seclusion methods	[27]
CD45 + HPS	Bone Marrow	They are derived from mesoderm and located in the red bone marrow. They are also found in umbilical cord blood and in small numbers, in peripheral blood. HPS have a higher potential than other immature blood cells to pass the bone marrow barrier. HPS numbers were similar in the endometrial samples from fertile and infertile women.	[86]
hESP cell	Endometrium	ESP cells produce endometrial endothelial, epithelial, and stromal cells in vitro and in vivo, and are placed in both basalis and functionalis. ESP cells most ample during the menstrual and proliferative phases of the cycle. ESP cells exhibit greater cloning efficiency that non side population cells.	[112]
Autologous Adult Stem Cell	Bone Marrow	These cells, regardless of their foundation, may serve as a source of compensatory cells for the generative tract. Both stromal and epithelial cells were derived from bone marrow origin. These evidences display the potential for stem cells to have a role in the regeneration or repair of this tissue after damage.	[106]
MSC	Adipose Tissue	-Easy separation -Plentiful proliferation capacity in vitro without any change in their biological features -Injured tissues tropism -Weakly immunogenic effect -Contains much larger volumes of mesenchymal stem cells than bone marrow does -Lowest hurt to normal cells/tissues.	[15]
eMSC	Endometrium	These cells are multipotent and have vastly proliferative potential. They could be used clinically to renew endometrium or other tissues. The functional layer of endometrium (which includes eMCSs) can be sampled by biopsy as a routine procedure thus, eMSCs can easily be collected, purified, expanded in culture and differentiate.	[113]
hESC	Embryonic	Human embryonic stem cells (hESCs) have limitless capacity and are able to differentiate into cell types of all three germ layers both in vivo and in vitro; therefore, hESCs are a candidate for cell replacement therapy.	[114]
hUCMSC	Umbilical Cord	Unlike the other stem cells, hUCMSCs appear to suggest the best clinical tool since they are non-controversial, easy accessing, having faster self-renewal properties and can be gathered by non-invasive procedures in abundance. More importantly, HLA class I are weakly expressed or not detectable in hUCMSCs, representing the useful outcome on allograft transplantation without immunological suppression.	[90]
menSC	Menstrual Blood	menSCs are directly isolated from menstrual blood of women, which characterize its comfort of noninvasive attainment. MenSCs show classical stem/progenitor cell features of clonogenicity, multipotency and high proliferative potential.	[104]
hAMSC	Amniotic	-High Frequency -Easily harvesting -Having great proliferative capacity -Immune modulating effect.	[101]

BMDSC: Bone Marrow Derived Stem Cell. **HPS**: Hematopoietic Progenitor Stem cell. **hESP**: human Endometrial Side Population. **MSCs**: Mesenchymal Stem Cell. **eMSCs**: Endometrial Mesenchymal Stem Cell. **hESC:** human Embryonic Stem Cell. **hUCMSC**: human Umbilical Cord Mesenchymal Stem Cell. **HLA:** Human Leucocyte Antigen. **menSCs**: menstrual blood-derived Stromal Cells. **hAMSCs**: Human Amniotic Mesenchymal Stromal Cell.

and reformative activities in the host tissues. It is commonly approved that transplanted cells can provide morphological and functional benefits through multiple mechanisms including, but not restricted to, trophic support, cell replacement, regeneration of endogenous cells, immunosuppression/anti-inflammation, stimulation, and regulatory interactions with endogenous cells [2]. The scope of stem cell therapy is quickly developing and, to date, clinical trials have begun to investigate the use of stem/progenitor cells in the therapy of degenerative diseases, cancer, and the renovation of damaged or lost tissues [1]. One of the increased risk factors for pregnancy complications is Asherman syndrome. Treatment of AS is only recommended if the patient has clinical indications or reproductive problems. Common Treatments for AS include Hysteroscopic lysis of adhesions, hormonal therapy, and physical barrier. Despite advances in a surgical procedure and numerous approaches for inhibition of recurrent adhesive disease, the treatment of AS remains challenging [3]. Thin endometrium occurs is a cause of worry since it is related to lower implantation and pregnancy rates. A number of treatments have been tried to increase endometrial development, but none has been validated up to now. The most popular ongoing treatments such as intra-uterine granulocyte colony-stimulating factor, extended estrogen support, human chorionic gonadotropin priming in the follicular phase, and drugs that increase endometrial blood flow include Pentoxyfilline, tocopherol, sildenafil, and l-arginine [4]. Cell-based therapies using endometrial stem/progenitor cells hold promise for coming use in restoring poor endometrium. As a result, a concise review of the current clinical applications will be provided and the treatment aspects of stem cell therapy in endometrial disorders will be discussed in the present work.

2. Endometrium

Human's endometrium is a highly regenerative tissue, experiencing more than 400 cycles of formation, developing, and shedding during woman's reproductive ages. The regeneration of endometrial tissue also follows wide resection, parturition, and takes place in postmenopausal women who receive estrogen substitution therapy [5]. The lining of endometrial tissue demonstrates structural and regenerative similarities to the intestinal villus. The endometrium widely consists of two cell types; i.e., epithelial cells (including luminal and glandular cells) and supporting mesenchymal cells [6]. From a functional point of view, the endometrium is composed of two different layers; i.e., the outer functionalis layer and the inner basalis layer. The functionalis is composed of compact glandular tissue and a slack connective stroma, whereas the stroma is the main part of inner basalis layer. Leukocytes and vasculature are the foundation of the glands. Embryologically, Mullerin is the source of all these components [7]. In the menstrual period, the functionalis and a small part of the basalis are shed during each cycle [8]. The rebuilding of the functional layer is crucial for the expanding of a tissue, which is responsible for implantation and menstruation [9].

The regeneration of surface epithelial in endometrium was displayed to occur as a result of stromal cells that differentiated, but not a direct development of the remains basal epithelial glands [10,11].

2.1. Stem cell

Generally, we can divide stem cells into two groups: embryonic stem cells (ESCs) and adult stem cells (ASCs). The origin of embryonic stem cells is blastocysts [12]. Depending on the ability to differentiate into