Austin Journal of Invitro Fertilization

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Mini Review

Isolation, Culture and Characterization of Human Endometrial Mesenchymal Stem/ Stromal Cells (EnMSCs): A Mini Review

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Received: February 25, 2016; **Accepted:** April 23, 2016; **Published:** April 25, 2016

Abstract

The endometrium is an extraordinary tissue with the dynamic remodeling capacity in each menstrual cycle for the purpose of embryo implantation. These preparing undergone consecutive changes of sex hormones during monthly periods. Endometrial basal layer cells could proliferate and differentiate into various cell types. This ability of endometrium confirmed the appearance of specific population of cells could regenerate functional is layer, known as, stem cells. The progression of infertility treatments with novel therapies for the patient with endometrial dysfunction requires an appropriate understanding of the role of endometrial stem cells in regenerative medicine and subsequent cell therapy.

Keywords: Cell Therapy; Endometrial Stem/Stromal Cells; Regenerative Medicine; Uterus

Abbreviations

ASCs: Adult Stem Cell; EnMSCs: Endometrial Mesenchymal Stem/ Stromal Cells; CFU: Colony Forming Unit; MSCs: Mesenchymal Stem Cell; MS: Multiple Sclerosis

Introduction

Adult Stem Cells (ASCs) have functional properties including: self-renewal, proliferation and differentiation capacity into one or more lineage [1,2]. These cells could be isolate from different tissue origins such as: intestines [3], muscles [4], skin [5], blood [6], nervous system [7-9], and endometrium [10].

The human endometrium is a unique model with considerable regenerative potential during women's reproductive life. The endometrium undergoes dynamic remodeling including regeneration, differentiation, tissue break down and shedding of upper functional in different phases of each menstrual cycle. As we all aware, regeneration of the new functional is part for subsequent cycle could performed with remaining germinal portion in the lower basalis layer [11]. Consequently, It has been hypothesized basal layer of human endometrium remaining to regeneration potential contain epithelial and stromal adult stem cells, which after shedding of top two-third at menstruation, these cells population facilitated regeneration of endometrial glandular tissue which protected by vascularized stroma [12,13]. Therefore, in this mini-review we briefly focused on the identification and characterization of Endometrial Mesenchymal Stem/Stromal Cells (EnMSCs) population according current studies and use their regeneration potential in future medical therapeutics.

Resembling to other ASCs, EnMSCs have Colony Forming Unit (CFU) activity, which could determine adult stem cell characteristics like: self-renewal, differentiation, and high proliferative potency *in vitro* [14]. This confirmed their ability to response to the monthly steroid hormonal changes and differentiation the endometrium for fertilized egg receptivity. Regeneration process after shedding of the functionalis layer during each menstrual cycle, emphasized to reside of epithelial and stromal CFU in the basalis layer [14]. Another study reported that post-menopausal endometrium, whether atrophic with low level of estrogen circulation, or after estrogen treatment, contains a small population of stromal cells with Mesenchymal Stem Cell (MSCs) characteristics [15].

Cloning assays shows the efficiency of each potential stem cell marker to enrich for endometrial stromal CFU. CD146 could be as a potential marker enriching for endometrial stromal CFU, and detection of $CD90^{hi}$ versus $CD90^{lo}$ stromal cells in all samples may be of value for further investigation as a potential marker [16]. The identification of STRO-1 and CD133 as negative markers of endometrial stromal CFU validates the importance of undertaking functional stem cell assays to demonstrate the utility of the stem cell markers for isolation of purified stem cell populations. The same study shows which endometrial stromal colony-forming cells were identified in perivascular space, even near the microvasculature [16]. Isolation of EnMSCs from human endometrial tissue after *in vitro* culture showed expression of MSCs markers CD90, CD105 but hematopoietic markers like CD34. CD45 did not express [17]. Another group reported same results. In this study isolated cells after flow cytometry analysis showed positive MSCs markers (CD146, CD90 and CD105), but hematopoietic and endothelial markers CD34 and CD31 respectively, were negative [18,19] (Figure 1).

Regenerative medicine is a hopeful policy for human cells, tissues, organs replacement or regeneration and finally reestablishment of normal function [20,21]. To prevention the limitation of *in vivo* study, endometrium generally has been studied *in vitro* with cell culture and tissue engineering techniques to demonstrate physiological and disorders of the endometrium [22]. For evaluation of regenerative potential of EnMSCs in Immunodeficient mice with Duchenne

Citation: Akyash F, Sadeghian-Nodoushan F and Aflatoonian B. Isolation, Culture and Characterization of Human Endometrial Mesenchymal Stem/ Stromal Cells (EnMSCs): A Mini Review. Austin J In Vitro Fertili. 2016; 3(1): 1025.

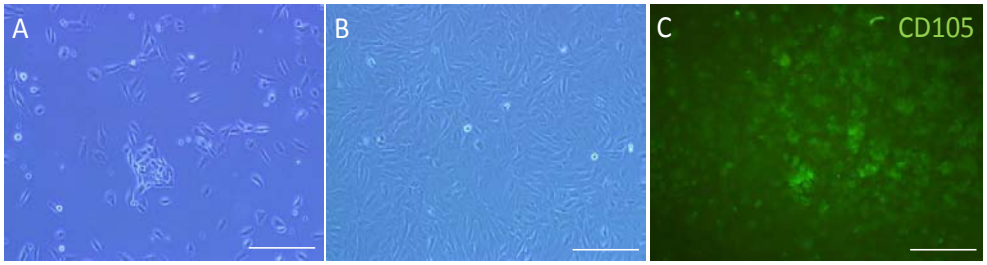

Figure 1: CFU assay (A), culture (B) and characterization (C) of human EnMSCs.

muscular dystrophy, these cells after transplantation into atrophied skeletal muscle fibers, contributed to muscle repair [23]. However, exact mechanism of repair has not been clear, it was claimed that fusion and in situ differentiation of cells might have been involved, and because of transplanted EnMSCs could stimulated angiogenesis in peri-muscle fibers regions [23]. Furthermore, in patient that suffering from Duchenne muscular dystrophy, EnMSCs injected into muscles and reported improvement in muscle strength and reduction of respiratory infections [24]. Other report supported the role of EnMSCs in angiogenesis procedure, which showed these cells improved limb ischemia by femoral artery ligation [25]. Hida and co-workers used EnMSCs for treatment of murine with myocardial infarction [26]. In this study, comparison between treated infarct area with EnMSCs and bone marrow MSCs was evaluated and results showed, grafted EnMSCs into the infarct area differentiated into α-actinin$^+$, troponin$^+$ striated cardiac muscle cells and more improvement in this area was observed rather than control bone marrow MSCs group [26]. Another study that used EnMSCs for tissue engineering, reported reconstruction of women urinary bladder wall with constructed nano fibrous silk-collagen fibers and cultured EnMSCs, these cells could differentiate into smooth muscle cells [27] Zhong *et al*, demonstrated the application of EnMSCs that derived from menstrual bleeding and role of these cells in reduction of immunological reactions after intravenous and intrathechal injection for patient with Multiple Sclerosis (MS) disease [28].

Conclusion

Endometrial tissue is a part of uterus that undergoes a cyclical regeneration every month in normal women's life span. Endometrial regeneration after delivery even in postmenopausal women after estrogen therapy indicates that EnMSCs could proliferate and differentiate into different cell types and confirmed the stemness potential of these cells. Hence, based on current studies, EnMSCs can be used in the future for novel therapeutic methods in regenerative medicine such as treatment of uterine-factor infertile female that suffering from infertility.

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Austin J In Vitro Fertili - Volume 3 Issue 1 - 2016
ISSN : 2471-0628 | www.austinpublishinggroup.com

Citation: Akyash F, Sadeghian-Nodoushan F and Aflatoonian B. Isolation, Culture and Characterization of Human Endometrial Mesenchymal Stem/ Stromal Cells (EnMSCs): A Mini Review. Austin J In Vitro Fertili. 2016; 3(1): 1025.