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Review Article

Stem cell and endometriosis: new knowledge may be producing novel therapies

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Abstract: The human endometrium is a dynamic tissue, which undergoes cycles of growth and regression with each menstrual cycle. Adult progenitor stem cells are likely responsible for this remarkable regenerative capacity; these same progenitor stem cells may also have an enhanced capacity to generate endometriosis if shed in a retrograde fashion. The progenitor stem cells reside in the uterus, and, however, may also travel from other tissues such as bone marrow to repopulate the progenitor population. Mesenchymal stem cells are also involved in the pathogenesis of endometriosis and may be the principle source of endometriosis outside of the peritoneal cavity when they differentiate into endometriosis in ectopic locations. The present short review mainly summarizes the latest observations contributing to the current knowledge regarding the presence and the potential contribution of stem cells in the etiology of endometriosis. All these data can have clinical implications and provide a basis for new potential therapeutic applications.

Keywords: Endometriosis, endometrial progenitor/stem cells, etiology, therapeutic applications, telomerase

Introduction

Endometriosis is a common, benign, chronic estrogen-dependent disease characterized by the presence of ectopic endometrial implant [1]. This disease affects approximately 10% of reproductive-aged women and 20% to 50% of infertile women [2, 3]. Despite its frequency and its impact on quality of life, our understanding of the pathogenesis of endometriosis remains incomplete. Endometrial lesions are primarily located on the pelvic peritoneum and ovaries but can also be found in the pericardium, pleura, lung parenchyma, and even the brain [4]. Implants can result in substantial morbidity, including pelvic adhesions, pain, fatigue, bowel disorders, and infertility requiring extensive and sometimes ineffective medical and surgical treatments [5]. This disease is not only costly but also physically and psychologically debilitating. To date, the leading theories are retrograde menstruation, coelomic metaplasia, embryonic cell rest, and lymphatic and vascular dissemination Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated [6]. Current research involving stem cells should shed some light on the puzzling mechanisms of this disease [7-9]. However, data on stem or progenitor cell function in endometriosis are scarce due to the technical limitations to stem cell research.

Stem cells within the uterus

The human uterine endometrium is one of the most dynamic human tissues. It consists of a glandular epithelium and stroma that are completely renewed in each monthly menstrual cycle. Endometrial stem cells are thought to reside in the basalis layer and serve as a source of cells that differentiate to form the endometrium Cyclic endometrial renewal depends on a small pool of tissue-specific multipotential stem cells [10, 11]. Under systemic hormonal changes, stem cells migrate and give rise to a group of progenitor cells that become committed to specific types of differentiated cells, e.g. epithelial, stromal and vascular cells. These endogenous stem cells allow the rapid regeneration of the endometrium necessary to support pregnancy [12, 13]. To date, the mesenchymal ori-

gin for endometrial stem cells is the most accepted statement [14, 15]. Noteworthy, putative endometrial SSCs have been successfully differentiated into other mesodermal lineages including adipose, chondrogenic, and osteogenic tissues [16-18].

On the other hand, there is an increasing trend suggesting that endometrial regeneration arises from bone marrow derived cells. Different groups have shown endometrial chimerism in endometrial glands and stroma of women who were given male or HLA-mismatched bone marrow transplants [19-21]. Another recent study from Du and coworkers [22] has shown that, after uterine ischemia or reperfusion injury, the amount of bone marrow-derived cells recruited to the endometrium went through a 2-fold increase. In this sense, whether bone marrow cells are recruited for endometrial regeneration under physiological conditions or only after injury or special needs remains to be clarified. Moreover, if bone marrow derived cells could be transformed and give rise to endometriosis or in which stage of their differentiation should they be transformed is still an unresolved question.

Stem cells in endometriosis

The presence of stem progenitor cells in endometrium and in menstrual blood led to the hypothesis that these cells could be at least in part responsible for the development of endometriosis. Lots of studies in the last decade have contributed to the consolidation of this hypothesis, through different approaches. In one study, it was suggested that the basal layer of the endometrium was significantly shed in menstrual flow in women with endometriosis, in comparison with control women [23]. Interestingly, endometrial stem cells are particularly frequent in endometrial tissue during menstruation. It has been speculated that endometrial stem cells may play an important role in the development of endometrial implants [24].

Epithelial cells in some endometriosis lesions are monoclonal, suggesting a single cell origin, possibly by an endometrial stem/progenitor cell. Other endometrial lesions are polyclonal, suggesting contamination with polyclonal stromal cells, repeated seeding of the lesion with cells from other sources, such as bone marrow, Cindy M.P. Duke, et al [25] has provided novel evidence of endometrial regeneration in bone marrow transplant recipients who received marrow from a single-HLA (single-human leukocyte antigen) antigen mismatched bone marrow transplant for leukemia. Donor-derived endometrial epithelial cells and stromal cells were detected in endometrial samples of bone Marrow recipients by RT-PCR (real time-PCR) and immunohistochemistry. Cyclic mobilization of bone marrow derived stem cells may be a normal physiologic process [26]. These findings define a new theory for the etiology of endometriosis ectopic trans-differentiation of stem cells. We have shown that bone marrow derived stem cells can contribute to endometriosis, perhaps explaining the occurrence of disease outside of the peritoneal cavity. Leyendecker et al. showed that significantly more basalis layer was shed in the menstrual flow suggesting an increased number of stem cells in this layer that can result in a propensity for endometriosis [27].

Laschke et al [26] devoted further to the knowledge of the role of stem/progenitor cells in endometriosis with an elegant study based on a model of intraperitoneal endometriosis surgically induced in irradiated FVB/N mice that were reconstituted with bone marrow from FVB/N-TgN (Tie2/GFP) 287 Sato mice These transgenic mice express the reporter gene GFP under the transcriptional control of the Tie2 promoter. Tie2 is a vascular-endothelial-cell-specific receptor tyrosine kinase controlling numerous signaling pathways that are involved in endothelial cell migration and proliferation. The analysis conducted by intravital fluorescence microscopy and immunohistochemistry over 4 weeks after surgery clearly revealed the presence of GFP-positive cells in the vasculature of the ectopic endometrium of mice, thus indicating the contribution of bone-marrow-derived EPCs (endothelial progenitor cells), originating CD31-positive endothelial cells. These cells were accompanied by local tissue-resident EPCs, co-expressing CD34 and VEGFR2 (vascular endothelial growth factor receptor2) [26]. As expected, Laschke et al [28] also showed that the homing of bone marrow-derived GFP-positive EPCs in ectopic endometrium in mice was mediated by the SDF-la (stromal-cell-derived factor la)/CXCR4 (CXC chemokine receptor 4) axis, with an increased expression of SDF-la in developing endometrial lesions. These observations are in accordance

with others revealing an up-regulation of circulating EPCs in a mouse model of endometriosis, where they are incorporated in the growing vasculature of the endometrial lesion and whose concentration positively correlated with the amount of endometrial tissue [29].

Yong Song et al [30] focus on stemness-related genes, such as the transcription pluripotency factors SOX2 (sex-determining region Y-box 2), NANOG (Nanog homeobox), and OCT4 (octamer-binding protein 4) in the endometrium of reproductive-age women with and without ovarian endometriosis, which play a crucial role in the regulation of self-renewal and pluripotency in embryonic stem cells and primordial germ cells, in comparison with the control group, SOX2 mRNA and protein expression was significantly higher in the eutopic endometrium of participants in the endometriosis group. In the endometriosis group, SOX2 and NANOG mRNA and protein expression were markedly increased in ectopic endometrium compared with eutopic endometrium; there was a trend towards lower OCT4 mRNA expression and higher OCT4 protein expression in ectopic endometrium, thus supporting a role for stem cell origin of endometriosis.

It is well known that cigarette smoking leads to a reduction in female infertility, but also to a decreased incidence of endometriosis and of endometrial cancer, through the protective effect played by the increased expression of homeobox A 10 and of progesterone receptor [31, 32]. A recent study provided novel insights into this previous observation, demonstrating in a murine model that both leucocytes and bone-marrow-derived endometrial cells were reduced by 60% and 73%respectively, after 4 weeks exposure to cigarette smoke [28]. Smoking inhibited the recruitment of bone-marrow-derived stem cells to uterus, as well as stem cell differentiation, suggesting that the inhibition of stem cell recruitment might be a general mechanism by which smoking leads to long-term organ damage though the inability to repair or regenerate multiple tissues [33]. These data indirectly support a role for stem cells in endometriosis progression.

Stem cells attempt to compensate for telomere attrition through the action of telomerase. Since circulating stem cells may contribute to endometriosis, longer telomeres could be consistent with a stem cell origin of endometriosis.

Endometriosis has been reported to be characterized by the presence of endometrial cells with capacity to avoid apoptosis beyond the uterine cavity [34]. Apoptosis plays an important role in maintaining tissue homeostasis by striking a balance between proliferation and cell death [34]. Endometrial cells have been described to show the peculiar biological characteristics of resistance to apoptosis with the inability to transmit apoptotic signal and the ability to avoid cell death [34, 35]. Recently, endometriosis has been correlated with aberrant endometrial expression of telomerase and survivin implying modifications in cell fate [34, 35]. Telomerase is a specialized transcriptase that can prevent telomere shortening [35]. Telomeres are noncoding tandemly repeated DNA sequences that are vital for maintaining chromosomal integrity and cell stability [35]. The critical shortening of telomeres is linked to cell division and their senescence and death [35]. Consequently, telomerase activation allows cells to overcome apoptosis acquiring immortal capacity.

Dracxler RC et al [36] compared telomere content in lymphocytes of patients with (n = 86) and without endometriosis (n = 21). Patients with endometriosis had longer telomeres than that of matched, endometriosis-free controls (telomere to single copy gene ratio [T/S ratio] of 1.62 vs 1.34, respectively, P = 00002). Patients with endometriosis were 8.1-fold more likely to have long telomeres (Odds ratio = 8.1, 95% confidence interval: 1.28-51.57, P = 0264).

Novel therapies targeting stem cell

The study summarized so far demonstrating an increase in circulating progenitor cells after the induction of endometrial lesion; it will be of great interest to test whether the circulating progenitor cells and the elevated expression of telomerase in patients could serve as diagnostic makers or as indicators of therapeutic efficacy.

Owing to a lack of full understanding of the pathogenesis of endometriosis, the treatment options success rates of endometriosis are limited, a better comprehension of the pathogenesis of endometriosis could help in developing

new, more effective, non-hormonal medication, which can inhibit disease development and alleviate pain or infertility without inhibition of ovulation and menstruation [32]. The identification of the different stem cell populations in ectopic endometrium could provide a potential therapeutic target for this frequent and invalid-ing disease. For example, a recent study conducted on MSCs (mesenchymal cells) isolated from eutopic human endometrium and from ectopic endometrium revealed that ectopic endometrial MSCs from patients with endometriosis showed a higher proliferation, migration and angiogenic ability in comparison with eutopic MSCs from the same patient or with control MSCs from patients without endometriosis. Treatment with sorafenib, a tyrosine kinase inhibitor, was able to revert the increased proliferative, migratory and angiogenic phenotype of ectopic endometrial MSCs [37]. Similarly, Pittatore G et al. [38] also revealed that once in the abdominal cavity, these MSCs could proliferate, invade, and differentiate into endometrial cells, finally generating ectopic implants. In more detail, As only differentiated endometrial cells, and not endometrial MSCs, possess steroid hormone receptors, MSCs could be responsible for the high rate of persistence/recurrence of the disease after hypoestrogenism-inducing therapies. MSCs play an important role in the survival and proliferation of endometrial tissue through the formation of new blood vessels. In fact, inhibition of angiogenesis represents a new, promising therapeutic approach for the disease. Further, medications directly targeting endometriosis MSCs could be effective, alone or in association with hormonal treatments, in increasing the success of medical treatment.

Current research centers on elucidating the factors that enable these cells to engraft an ectopic site and drive them toward endometrial differentiation. Preliminary data are providing several pathways to target in order to prevent stem cell flux and the initiation and progression of endometriosis. For example, Laschke et al. [28] in a marine model of surgically induced intraperitoneal endometriosis, where the treatment with AMD3100, an antagonist of the SDF-la/CXCR4 axis, significantly decreased the number of recruited EPCs and the vascular ration of endometrial lesions.

On the basis of previous studies, tobacco use inhibits stem cell flux to endometrium and endometriosis [33]. While we would not advocate tobacco use in the treatment of endometriosis, it may explain the lower incidence of this disease in smokers. Individual components of tobacco smoke may prove useful in the treatment of this disease. Of therapeutic interest, the molecular targeting of deregulated signaling pathways by these cells and their local microenvironment, blocking key self-renewal pathways and pro-survival-signaling pathways, preventing cell recruitment, flux and adhesion through interference with chemokines, and adhesion molecules that regulate these processes, as well as inhibiting abnormally activated pathways within the cells or surrounding niche cells, represent new potential strategies for the development of more effective clinical treatments.

Similarly, Sakr et al. [39] demonstrate that the selective estrogen receptor modulator bazedoxifene (BZA), administered with conjugated estrogens (CEs), leads to regression of endometriosis lesions as well as reduction in stem cell recruitment to the lesions. Female mice underwent transplantation of male bone marrow. Endometrium was transplanted in the peritoneal cavity of half to create experimental endometriosis. Mice with or without experimental endometriosis were randomized to BZA/CE or vehicle treatment. Endometriosis lesions, bone marrow-derived mesenchymal stem cell engraftment of the lesions, and eutopic endometrium as well as ovarian stimulation were assessed. BZA treatment significantly reduced lesion size, gland number, and expression of proliferation marker proliferating cell nuclear antigen. Ovarian weight was not affected. Stem cells were recruited to the endometriosis lesions, and this recruitment was dramatically reduced by BZA/CE treatment. Stem cell engraftment was reduced in the uterus of animals with endometriosis; however the number of stem cells engrafting the uterus was completely restored by treatment with BZA/CE. Competition between endometriosis and the eutopic endometrium for a limited supply of stem cells and depletion of normal stem cells flux to the uterus is a novel mechanism by which endometriosis interferes with endometrial function and fertility. BZA/CE not only treats lesions of endometriosis, it also dramatically reduces stem cell recruitment to the lesions and restores stem cell engraftment of the uterine endometrium.

Given the key role of telomerase in the regulation of stem cell in endometrial lesions, down-regulating telomerase expression, may be candidate as a new therapeutic target for endometriosis [40].

In conclusion, all of these approaches represent good concrete examples of the novel potential therapeutic strategies possibly arising from the unequivocal identification of stem cell populations contributing to the development of endometrial lesions. Further, endometrial derived stem cells have been demonstrated to be useful in the treatment of several chronic and often debilitating diseases, including Parkinson's disease [41] and diabetes [42]. They demonstrate that the uterus is a dynamic organ permeable to fetal stem cells capable of trans-differentiation as well as a renewable source of multipotent stem cells. While we still have much to understand about stem cells, their potential applications in reproductive biology and medicine are countless.

Disclosure of conflict of interest

None.

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