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Endometriosis and Stem Cell Trafficking

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Abstract

Adult stem cells have a major role in endometrial physiology, remodeling, and repair, but they also have a critical role in the development and progression of endometriosis. Bone marrow–derived stem cells (BMDSCs) engraft eutopic endometrium and endometriotic lesions, showing stromal and epithelial fate. Nevertheless, circulating BMDSCs are in limited supply, and the presence of endometriosis depletes stem cells from the blood circulation, preventing their homing in the uterus. Furthermore, stem cells migrate from endometriotic lesion into the uterus, leading to a dysfunctional endometrium. Stem cell trafficking is a central feature of endometriosis. Understanding molecular mechanisms regulating cell mobility and engraftment in endometriosis may reveal new targets for treatment.

Keywords

endometriosis, stem cells, cell trafficking, endometrium

Introduction

Adult stem cells are found in numerous human organs including the endometrium that contains populations of stem/progenitors cells responsible for its monthly regeneration during women's reproductive life.[1] These cells have a major role in endometrial physiology, remodeling, and repair, but they also have a role in the generation of endometriosis.[2] Although it is likely that numerous converging factors determine the risk for developing endometriosis, investigators generally accept Sampson's theory of retrograde menstruation as a common contributing mechanism to the development of ectopic endometrial growth. Retrograde menstruation delivers endometrial cells to the peritoneal cavity where they implant and grow. This mechanism likely accounts for some intraperitoneal and ovarian endometriosis. However, it cannot account for the less common locations of endometriosis, including remote areas that are not in communication with the peritoneal cavity. Some of these lesions may arise from vascular or lymphatic spread of endometrial cells; nevertheless, even this mechanism cannot explain the proliferation of endometriosis lesions after hysterectomy or cases reported in men undergoing treatment for prostate cancer. As a result, some endometriosis lesions may arise from stem cells. Stem/progenitor cells that are deposited in the peritoneal cavity by retrograde menstruation may lead to the most common forms of pelvic/abdominal endometriosis. Remote endometriosis is likely derived from differentiation of multipotent stem cells originating from bone marrow (BM) and other sources. Stem cells contribute to development, progression, and spreading of all types of endometriosis. Altered stem cell trafficking and homing contributes to pathophysiology of this disease, and it may represent a target for treatment.

Endometrial and Endometriosis Stem Cells

The human endometrium is a dynamically remodeling mucosa, undergoing monthly cycles of morphologic and functional changes during reproductive life under ovarian steroids influence. Postmenopausal endometrium maintains proliferative properties following estrogen treatment. In the last decade, a number of laboratories have investigated populations of adult stem/progenitor cells in the human and murine endometrium with the identification of epithelium progenitor cells and pluripotent mesenchymal stem cells harboring the functionalis and basalis layer of the human endometrium.[3] The mesenchymal properties of these cells have been clearly demonstrated in vitro differentiation assays to chondrogenic, osteogenic, and adipogenic fates.[4-6] They also differentiate into smooth muscle cells and fibroblasts.[6,7] Similarly, the regenerative properties of endometrium have been documented in several studies.[8,9] Human endometrium-derived stem cells have been differentiated into insulin-producing cells that resemble pancreatic β-cells.[10] These cells produced insulin in a glucose-dependent fashion. When transplanted into diabetic mice, these cells improved glucose control. Similarly, endometrial stem cells have been differentiated into dopamine-producing

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neuron-like cell, increasing the synthesis of dopamine in Parkinson models.[11,12]

The BM-derived cells appear to migrate to many organs and differentiate into tissue-specific cells.[13] Several populations of bone marrow–derived stem cells (BMDSCs) have been also found in the endometrium; these have been identified in BM transplant recipients where the BM origin of the cells could be clearly demonstrated.[14] Women who had received single human leukocyte antigen-mismatched BM transplantation during cancer treatment showed fractions of endometrial stroma and epithelium derived from donor tissue.[14] This finding was confirmed in other studies using a murine model.[15-18] Endometrial BM-derived cells are identified by coexpression of donor and endometrial markers, in the absence of BM-derived immune cell markers. Rates of BM-derived cell engraftment into the endometrium vary from less than 1% to 48% for epithelial cells and from 0.3% to 52% for stromal cells, depending on the context, method of detection, and time since BM transplantation.[8,16] In a study investigating human endometrial samples, the majority of endometrial glands were chimeric, indicating that BM-derived cells are able to differentiate into an endometrial glandular phenotype and contribute to the glands derived from the endogenous endometrial progenitor cells.[18] The BMDSCs also participate to uterine repair.[19,20] Mechanical and ischemic injury was shown to increase recruitment of BM cells to the stromal compartment by 2-fold when compared with sham surgery. The BM-derived cells within the endometrium showed differentiated endometrial phenotype due to the expression of vimentin and loss of CD45 expression.[19,20]

The BMDSCs are also involved in the pathogenesis of endometriosis and may be also the principal source of extra-pelvic endometriosis when they differentiate directly into endometriosis cells at ectopic locations.[2,21] Emerging evidence from murine models suggests that tumor microenvironment factors systemically stimulate quiescent BM compartments, resulting in the expansion, mobilization, and recruitment of BM progenitor cells.[22] These cells have a clear role in tumor development, angiogenesis, and escape from the immune system.[22] It has been demonstrated in murine endometriosis that BM-derived endothelial progenitor cells contribute to lesion vascularization and development.[23,24] Similar to injured endometrium, chronic inflammation and the altered microenvironment within endometrial implants likely stimulate the recruitment of BMDSCs to endometriosis. In order to test this hypothesis, an experimental endometriosis model in mice has been developed to determine the ability of extrauterine cells to engraft to endometriotic lesions.[21] Endometrium from wild-type mice was transplanted into the peritoneal cavities of hysterectomized LacZ transgenic mice to induce endometriosis. After 10 weeks, the ectopic lesions were excised, and frozen sections were stained with 5-bromo-4-chloro-3-indolyl-β-dgalactoside (X-gal) to detect the presence of LacZ-expressing cells. LacZ-expressing cells constituted a small population of epithelial and stromal cells in endometriosis, confirming that extrauterine stem cells contribute to endometriotic lesions.[21]

The contribution of BM-derived cell to the development of endometriosis has been recently further investigated.[25] In a murine experimental model, 4.48% of the endometriosis cells were $CD45^-$ BM-derived cells.[25] Nevertheless, circulating BMDSCs mesenchymal stem cells are in limited supply, and the ability of endometriosis to effectively recruit stem cells depletes the cells from the circulation and prevents their homing in the uterus. As a result, ectopic lesions seem to function as a "sponge," attracting stem cells and preventing their migration to the uterus. Defects in endometrium of women with endometriosis may in part originate from the defective replenishment of endometrial stem cells.

Regulation of Endometrial/Endometriosis Stem Cell Trafficking and Homing

Specific mechanisms regulate BMDSCs trafficking and homing. In a murine model of endometriosis, bazedoxifene (BZA), a selective estrogen receptor modulator (SERM), reduces BMDSC engraftment to ectopic sites, promoting engraftment to the eutopic endometrium.[25] The BZA significantly reduced the mean size of implants, endometrial cell proliferation, and estrogen receptor α expression. The regression of endometriosis likely involved decreased estradiol-mediated stem cell recruitment and engraftment, demonstrating that estrogens are required for recruitment of stem cells to lesions. The BZA treatment led to a significant reduction in the number of BMDSCs engrafting lesions of endometriosis. Similarly, BZA treatment restored stem cell recruitment to the uterus to levels in the range of control groups without endometriosis, confirming that endometriosis affects cell trafficking, and this process may be reversible using a specific SERM.[25]

Selective cytokines, such as vascular endothelial growth factor A, placental growth factor, granulocyte colony stimulating factor, C-X-C motif chemokine ligand 12 (CXCL12), and osteopontin, secreted by a growing tumor can reach the BM stem cell niche via the peripheral circulation.[22] These factors can switch the quiescent microenvironment in the BM compartment to an active state that promotes the expansion and mobilization of stem cells into the circulation toward the gradient of peripheral site of cytokines/chemokines synthesis.

Recently, the role of CXCL12/CXCR4 axis has been investigated in the context of endometriosis lesion. The CXCL12 expression is increased in endometriosis implants and in the peritoneal fluids of affected patients.[26] Similarly, CXCR4 expression, a CXCL12 receptor, is increased in ectopic and eutopic endometrium of patients with endometriosis.[26-28] As a result, the upregulation of CXCL12/CXCR4 may represent a mechanism involved in the increased recruitment and homing of stem cells from the circulation to the endometriosis implants, preventing/limiting the physiological engraftment of the uterus. This hypothesis has been recently investigated in vitro, demonstrating that CXCL12-CXR4 axis efficiently regulates trafficking of BMDSCs to the endometrium.[29] Moreover, the in vitro pharmacological antagonism of CXCR4 blocked this migration in a dose-dependent manner,

identifying a potential target for regulating BMDSCs engraftment into the endometrium.

Gonadal steroids further regulate the CXCL12/CXCR4 axis, driving cell trafficking and homing. Treatment with physiological concentrations of 17 β-estradiol induced CXCL12 expression in normal endometrial stromal cells and CXCR4 expression in BMDSCs and enhanced the chemoattraction of BMDSCs to human endometrial stromal cells.[29] Progesterone antagonized the effect of estradiol on CXCL12 expression in normal human stromal cells in vitro,[29] but it failed to inhibit the expression of this chemokine in a model of endometriosis in vivo.[30] Moreover, both estrogen and progesterone increased CXCR4 expression in BM-derived cells, and this mechanism may be further amplified by the abnormal endocrine microenvironment of endometriosis implants.

Although it is clear that BMDSCs migrate to the uterus and endometriosis, stem cells are also capable of trafficking between locations, likely through the blood circulation. Recently, a population of mesenchymal stem cells that migrate from the endometriotic lesion into the uterus has been identified.[31] These cells were mainly localized in the basal layer of the endometrium often next to blood vessels and never in the epithelial lining of the lumen or within the glands. They showed a distinct gene expression profile compared with the eutopic endometrium, and they produced factors capable of altering uterine receptivity. Following isolation by fluorescence-activated cell sorting, these cells displayed increased expression of SNAI1, SNAI3, goosecoid, and the downregulation of ZEB2.[31] Interestingly, these genes are associated with the endometrial epithelium during uterine development and in epithelial-to-mesenchymal transition. After engraftment of the uterine stroma, these cells, all derived from the endometriosis, displayed activation of the signaling pathways indicating that they had taken on an epithelial identity, although they were not located in the epithelium. The abnormal presence of dysfunctional endometriosis stem cells in the eutopic endometrium may disrupt epithelial–stromal polarity and lead to decreased endometrial receptivity in patients with endometriosis.[32]

Conclusion

Recruitment and homing of BMDSCs in the endometrium is crucial for the physiological remodeling of uterine mucosa during the reproductive life. Circulating stem cells are inappropriately incorporated into endometriosis and play a role in the development and progression of peritoneal and extra-peritoneal implants. Furthermore, endometriosis interferes with the normal BMDSCs to the uterus, leading to a dysfunctional endometrium. Altered stem cell mobility and engraftment is a critical feature of endometriosis and may represent a target for its treatment.

Declaration of Conflicting Interests

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