



Endometriosis: Are Stem Cells Involved?

Milena Králíčková^{1, 2, 3}, Vaclav Vetvicka^{4, *}

¹Department of Histology and Embryology, Faculty of Medicine, Charles University, Karlovarska, Plzen, Czech Republic

²Department of Obstetrics and Gynecology, University Hospital, Faculty of Medicine, Charles University, Alej Svobody, Plzen, Czech Republic

³Biomedical Centre, Faculty of Medicine in Plzen, Charles University, Plzen, Czech Republic

⁴University of Louisville, Department of Pathology, S. Floyd, Louisville, KY, U. S. A.

Email address:

Vaclav.vetvicka@louisville.edu (V. Vetvicka)

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Abstract: Endometriosis is a benign, but serious gynecologic condition affecting millions of women. This disease is defined by the presence of endometrial tissue outside the uterus. Despite decades of intensive research, the mechanisms of endometriosis are poorly understood. In the last decade, strong evidence seems to suggest the involvement of stem cells. Several possible hypotheses are discussed in this review.

Keywords: Endometriosis, Stem Cells, Tissue, Markers, Menstruation

1. Introduction

Endometriosis represents a serious pathological condition involving adhesion, proliferation and subsequent development of endometrial tissue in regions such as peritoneal cavity and ovary. It is an estrogen-dependent disease,¹ which is characterized by the ectopic presence and growth of ectopic endometrial tissue outside the uterine cavity. In addition to pathological problems, endometriosis results in an infertility rate of 6 to 10%. It is estimated that this disease affects over 176 million women worldwide.² Various mechanisms have been suggested. The most probable hypothesis of the pathogenesis suggests that the adhesion and subsequent growth of endometrial fragments is caused by the retrograde menstruation³ suggesting that the endometriotic implants arise from retrograde menstruation of endometrial tissue through the fallopian tubes. However, the pathogenesis of endometriosis is most likely multifactorial. To make the situation even less clear, the individual theories are not mutually exclusive.

Three major hypotheses supporting the concept of *in situ* development include Mullerian and Wolffian rest theory, coelomic metaplasia theory and metaplasia following endometrial stimulation theory. Mullerian remnant abnormalities are mainly suggested for endometriosis infiltrating the cul-de-sac and uterosacral ligaments. Aberrant migration or differentiation of the Mullerian ducts might influence spreading of cells in the migratory pathways of

normal organogenesis into pelvic floor.^{4, 5} One of the theories gaining the strongest interest, is focused on stem cells and suggests that endometriotic lesions arise from ectopic endometrial stem cell progenitors.⁶ An up-to-date review of individual hypotheses can be found in a review by.⁷

The stem cell theory is based on the fact that the regular monthly regeneration of the endometrium following menstrual shedding strongly suggests the involvement of stem cells. Their involvement might be a result of abnormal translocation of endometrial basalis.⁸ The non-endometrial source of stem cells might explain some origins of endometriosis, which the traditional theories based on retrograde menstruation through the fallopian tubes. This concept suggests that endometriotic lesions may be clonal in origin.⁹ Different concepts emerged regarding the possible role of stem cells in the pathogenesis of endometriosis.

Endometrium is known for its demand for fast and repeated tissue regeneration. This is similar to the situation in highly regenerative tissues such as blood, intestinal epithelium or skin. In all these tissue types, adult stem cell population is required.¹⁰ The possible main source of endometrial stem cells is not surprisingly bone marrow. However, other sources have been suggested, including fetal stem cell reservoir surviving in the adult endometrium (for review see¹¹).

2. Stem Cells and Endometrium

The speculations about fetal stem cells persisting in the

adult uterus and are able to replace both glandular epithelium and stroma shed away by each menstruation are still not fully proven.¹² The cellular source of resident adult stem cell population is hypothesized to be a basalis layer.¹³

Endometrial stem cells serve as a source of cells that subsequently differentiate to form the endometrium. This cyclic renewal is depending on a rather small pool of multipotent stem cells and is under the regulation of systemic hormonal changes.¹⁴

Purified epithelial and stromal cells from endometriotic cysts contain endometriotic progenitor cells. This was demonstrated by their ability to form colonies, have self-renewal capacity and their multipotency. Cells deriving from large colony-forming units (CFUs) differentiated into four mesenchymal lineages.¹⁵ These results showed that ovarian endometrioma contains significant subset of cells with properties of somatic cells.

Gotte et al. analyzed the expression of the pluripotency factors SOX-2, OCT4, KLF-4, and NANOG in the healthy and endometriotic patients.¹⁶ These authors concluded that aberrant expression of SOX-2 might indicate a stem cell origin of endometriosis, whereas the positive expression of all progenitor markers in the endometrial tissue suggests that endometrium might be a potential source for induced stem cells.

3. Mesenchymal Stem Cells

Presence of mesenchymal stem cells (MSCs) in the endometrium has been established. Once there, these cells will proliferate, invade and subsequently differentiate into endometrial cells, resulting in implants generation. In addition, some studies suggest a role of MSCs in angiogenesis promotion.¹⁷ These stem cells were characterized by expression of markers such as CD90 and CD105 and by the ability to differentiate into various cell types. Recently, these cells are isolated as CD146⁺ PDGF-R β ⁺ cells and are found in both basalis and functionalis as perivascular cells (for review see¹⁸). Invasion of ectopic endometrial mesenchymal stem cells is regulated by COX-2 and IL-1 β .¹⁹

Another approach was to study the possible effect of umbilical cord mesenchymal stem cell transplantation on nerve fibers of endometriosis. The study showed that these MSCs strongly reduced nerve fibers density in endometriosis,²⁰ which might provide a potential therapeutic modality.

Some studies tried to directly compare healthy and ectopic MSC. Transcripts of Toll-like receptors, collectins and pro-inflammatory cytokines such as IL-6, MCP-2 and IFN- γ were found to be strongly upregulated in ectopic MSC. Several adult stem cell markers such as bcl-2, c-kit and CD34 have been found in endometrial tissue.²¹ For a review of stem cell markers in human endometrium, see.¹¹

In addition, these cells showed upregulated expression for markers of migration and angiogenesis. These distinct phenotypic differences might be responsible for reduced

immunosuppressive activities of ectopic MSC.²² Targeting stem cells may be beneficial. In a mouse model employing selective estrogen receptor modulator, a strong reduction of bone marrow MSCs to the lesions and subsequent lesion regression have been found.²³

4. Somatic Stem Cells

Somatic or adult stem cells (SSCs) are usually defined as cells able to undergo extensive division and having the potential to differentiate into various cell types. Endometrium undergoes probably the most extensive proliferative changes and remodeling in all adult mammalian tissues with app. 500 complete reconstructions during reproductive lifetime.²⁴ The same author proposed the existence of SSCs. SSCs are known to contribute to endometrium-associated disorders. A recent comprehensive review of available literature strongly supported this hypothesis.²⁵ This hypothesis is supported by analyses of undifferentiating markers suggesting the existence of undifferentiated progenitor cells in endometriosis. Similarly, aberrant telomerase activity has been found in endometriotic lesions.²⁶ Using colony formation assays, Chan et al. found significant colony forming activity among both epithelial and stromal cells.¹⁵ These cells retained their stem cell phenotype of CD146, CD105, CD90, MS11, NOTCH-1, and SOX-2.²⁷

Isolation and subsequent culture of endometrial epithelial or stromal cells revealed cells with adult stem cell properties including self-renewal and clonal differentiation. These cells might be responsible for the immense regenerative capacity of endometrium.²⁸ Later studies suggested the stem cells present in shedding endometrium have a role in the pathogenesis of the early onset of endometriosis via the retrograde neonatal uterine bleeding. Later, under the influence of rising estrogen levels, stem cells divide and establish ectopic endometrial lesions (for review see²⁹).

Migration and invasiveness of endometrial stromal cells are controlled by a complex network of hormones, chemokines, and growth factors. In addition, it includes signaling through Rho GTPases, phosphatidylinositol-3 kinase and mitogen-activated protein kinase pathways.³⁰ Detailed review of the current knowledge of the role of SSCs in human and mouse endometrium can be found in.³¹

5. Bone Marrow-Derived Stem Cells

Recent experiments suggest that bone marrow might be the main source of endometrial stem cells. These cells are known to be circulating and have the ability to fully differentiate into multiple cell types. Bone marrow studies found chimerism in the endometrial glands and stroma after HLA-mismatched bone marrow transplantation, suggesting contribution of bone marrow-originating stem cells in endometrium repopulation.³² Similar conclusions can be drawn from subsequent studies using experimental model of

endometriosis induced by endometrial implantation in the peritoneum of hysterectomized LacZ transgenic mice.³³

While bone marrow-derived cells engraft to the endometrium and may contribute to the development of endometriosis, it is not clear how they are mobilized and directed. A detailed study showed that human endometrial stromal cells produce CXCL12, which binds to the CXCR4 receptor expressed on bone marrow cells. In addition, these expressions are induced by estradiol. The estradiol-CXCL12-CXCR4 signaling pathway helps the bone marrow cells to migrate to the endometrium, which might be used in target-specific inhibition of this migration.³⁴ Mouse model of endometriosis allows the analysis of these bone marrow-derived stem cells in the blood. Their concentration positively correlates with the amount of endometriotic tissue and is reduced by treatment with inhibitor of angiogenesis.³⁵ The ability of bone marrow-derived stem cells to repopulate endometrium was also demonstrated in mouse experiments using bone marrow transplantation.³³ Estrogen receptor modulator caused regression of endometriotic lesions as well as reduction in stem cell recruitment, but at the same time restored uterine stem cell engraftment.²³ A recent summary of the hypothetical role of stem cells in pathogenesis of endometriosis can be found in.¹²

Another possible role of stem cells in the development of endometriosis might be the interaction between misplaced Mullerian-derived stem cells and peritoneal immune dysregulation.³⁶ The authors hypothesize that the misplaced stem cells originating from Mullerian structures acquire new phenotype and functions and subsequently form a functional ectopic endometrial tissue. This might result in a breakdown in the peritoneal homeostasis with subsequent secretion of inflammatory and angiogenic cytokines.

One of the recently found factors in the pathogenesis of endometriosis is microRNAs (miRNAs).³⁷ miRNAs regulate multiple biological processes such as cell proliferation, angiogenesis and metastatic invasion. A study of serum obtained from women with or without endometriosis characterized the miRNA expression profiles. The study showed that miRNA-199a-5p was significantly downregulated in endometriosis. In addition, tumor suppressor gene SMAD4 elevated miRNA-199a-5p expression in ectopic endometrial MSCs. These upregulation inhibited cell proliferation and angiogenesis by targeting the 3' untranslated region of VEGFA.³⁸ This miRNA-199a-5p might provide both diagnostic marker and therapeutic target.

6. Future Prospects

Embracing the stem cell-based hypothesis, it might be possible to integrate most of the older theories regarding the pathogenesis and development of endometriosis into a single comprehensive theory. The last decade found overwhelming evidence for the presence of stem cells in human endometrium (for review see³⁹). The question of how these cells are involved in formation and progression of

endometriosis is less clear. Implants from these cells might not only account for an alternative mechanism of endometriosis, but might also be involved in normal mechanisms such as retrograde menstruation.

Surprising data showing that tobacco use inhibits stem cell migration into endometrium⁴⁰ might explain the low incidence of endometriosis among smokers. These findings might be of therapeutic interests, as tobacco smoke consists of dozens different molecules, often with biological effects. One can speculate that we might be able to isolate the responsible molecule and use it for targeting of the flux of stem cells to endometriotic tissue.⁴¹

To date, no direct evidence of the role of endometrial stem cells in the pathogenesis of human endometriosis has been found. One of these proofs would be the finding of progenitor cells in the menstrual blood.⁴² Our knowledge of stem cells and their role in various biological processes is still in the beginning stages, and the scientific tools are limited. However, the potential advantage of more detailed studies is apparent. Although there is no general agreement about the histochemical markers of SSCs in the endometrium, growing evidence supports the viewpoint that stem cells play an important role in both normal and neoplastic endometrium. Some authors even suggested potential targeting of stem cells for the treatment of endometriosis.⁴³ The question is not if the endometrial cells are involved. Too many groups managed to identify, isolate and characterize putative progenitor cells (for review see⁶). The question is how these stem cells are involved. One problem in answering this question might be the fact that almost each of the methods used produced cells, which strongly differ, from cells demonstrated by another technique.

Out of many theories on the pathogenesis of endometriosis, the stem cell theory recently gained the most attention. With the progress of our knowledge of stem cell biology, it is not surprising that this newest theory is currently the most studied one. However, with so many types of stem cells suggested to be involved in endometriosis progression, it is not possible to reach any lasting conclusion. Similarly, no correlation between the stem cell theory and older theories exist, with some studies even suggesting that the causes of these pathological conditions are multifactorial.

The aim of this short review of the potential role of stem cells in endometriosis was to summarize current knowledge. So far, the full understanding of the role of stem cells in endometriosis is still elusive, mainly due to the technical limitation of stem cell research. However, it is clear that current fundamental studies on endometrial progenitor cells will provide new insights into the pathophysiology of endometriosis.⁴⁴ One can easily envision new therapies targeting key stem cell functions. However, to progress beyond the level of hypothesis, we will need to clearly define and identify endometrial stem cell.

Conflict of Interests

Authors declare no conflict of interest.

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