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STEM CELLS IN ENDOMETRIUM AND THEIR ROLE IN THE PATHOGENESIS OF ENDOMETRIOSIS

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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, however less committed mesenchymal stem cells 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. Finally, besides progenitor stem cells, recent publications have identified multipotent stem cells in the endometrium. These multipotent stem cells are a readily available source of cells that are useful in tissue engineering and regenerative medicine. Endometrial stem cells have been used to generate chondrocytes, myocytes, neurons and adiposites in vitro as well as to replace dopiminergic neurons in a murine model of Parkinson disease.

Keywords

endometrium; endometriosis; stem cells

STEM CELLS IN ENDOMETRIUM AND ENDOMETRIOSIS

Stem cells are undifferentiated cells that have the ability to self-renew as well as to produce more differentiated daughter cells (1,2). Broadly, they can be divided into two categories: embryonic and adult. Embryonic stem cells are found in the inner cell mass of the blastocyst. Adult stem cells, derived from postembryonic cell lineages, have been described in a number of different organ systems and have been best characterized in the hematopoietic system (1,3).

Embryonic and adult stem cells are classified by their ability to differentiate into cells of different cell lineages. Differentiation is defined as a change in cell phenotype because of expression of genes associated with cellular function rather than cell division (4). Totipotent stem cells are fully undifferentiated and able to generate all embryonic germ layers (endoderm, mesoderm, and ectoderm) as well as the extra-embryonic tissues (trophoblast, placenta, and extra-embryonic membranes); the zygote is representative of this cell. The embryonic stem cells, in turn, are pluripotent stem cells, that lie along a spectrum of differentiation and can produce cells of all three germ layers, but not the extra-embryonic tissues. As stem cells undergo differentiation and their cell lineages become more restricted, they are described as multipotent because they can produce multiple cell types within the same germ cell lineage, or unipotent, differentiating into a single cell lineage (5).

Adult stem cells reside in an anatomic structure called the niche (6). The stem cell niche is a microenvironment of surrounding support cells that signal to the stem cell population. The niche cells provide signals that maintain stem cells in an undifferentiated state, protecting them from differentiation, proliferation, and apoptotic cues. But also they sense the need for tissue replacement and communicate proliferative and differentiation signals to resident stem cells (7)

Maintenance of the stem cell population requires cellular self-renewal, i.e. the capacity to generate identical daughter cells, which can happen through asymmetric or symmetric division. In an asymmetric division, one stem cell produces an identical daughter cell and a more differentiated daughter, whereas in a symmetric division it produces two daughter stem cells or two transit amplifying progenitors (TA). TA cells undergo repetitive cycles of cell divisions to increase in number while progressively acquiring markers of the differentiated cell type; consequently, they lose the ability for self-renewal.

Structure of the human endometrium

The human endometrium of the uterus comprises the endometrial mucosal lining which is a highly regenerative tissue. It is composed primarily of two cell types – the epithelial cells (luminal and glandular) and the supporting mesenchymal cells (stromal cells) (8) as well as endothelial cells and leukocytes (9). The endometrial–myometrial junction is irregular with no submucosal tissue to separate endometrial glandular tissue from the underlying smooth muscle of the myometrium (10)

Functionally, the endometrium is composed of two layers—the outer functionalis layer and the inner basalis layer. The functionalis, comprising the upper two thirds, is composed of dense glandular tissue surrounded by a loose connective stroma. The inner basalis layer rests on the muscular subendometrial myometrium and contains primarily the base of the glands, dense stroma and large vessels. This layer serves as a germinal compartment for generating the new functionalis each month (8).

Evidence for progenitor stem cells in human endometrium

Adult stem cells are found throughout the whole body after embryonic development (11). They have the potential for self-renewal, playing a critical role in replenishment and regeneration of damaged tissues, thereby contributing to the structural and functional maintenance of the organs and tissues. Similar events occur in the endometrium. During each menstrual cycle there is a vast growth of tissue and blood vessels (12). Thus, following menstruation, the proliferative stage begins under the influence of increasing circulating estrogen levels. This in turn is followed by the secretory phase in which progesterone levels rise as the endometrium prepares for the possibility of fertilization and an implanting embryo. If this does not occur, then the functionalis and a small portion of the basalis endometrium are shed{Maruyama, 2010 #170}. The shed blood and tissue contain a heterogeneous population of cells including some with regenerative capacity. It has been hypothesized that adult stem or progenitor cells are responsible for the cyclical regeneration of the endometrial functionalis (13)

The first evidence of stem cells regenerating the endometrium was based on functional assays (14–16). In 2004, using purified single cell suspensions obtained from hysterectomy tissues, it was shown that 0.22 ± 0.07% of endometrial epithelial cells and 1.25 ± 0.18% of stromal cells formed individual colonies within 15 days when seeded at clonal density (14). Two types of colonies were generated by both epithelial and stromal cells-large and small colonies. Large putative stem/progenitor cell colonies were rare; occurring at 0.08% and 0.02% for epithelial and stromal cells, respectively. These colonies displayed significantly

greater self-renewal capability compared with the small, loose colonies that failed to serially clone and displayed limited proliferation potential. These investigators hypothesized that the large colonies were derived from putative endometrial stem/progenitor cells with a greater potential for self-renewal. By contrast, the small colonies are presumably derived from TA cells that lack the ability for self-renewal and thus display a diminished proliferative potential.

Schwab et al. performed a similar analysis of clonogenicity using samples collected from proliferative, secretory, and inactive endometrium (16). This work demonstrated that the frequency of clonogenic epithelial and stromal cells did not vary in different phases of the menstrual cycle or in inactive endometrium. Because inactive endometrium contains only a basalis layer and not an endometrium functionalis, these data would suggest that putative endometrial stem/progenitor cells reside in the basalis layer and persist beyond menopause.

There are no specific known markers for endometrial progenitor stem cells that distinguish them from their mature progeny. In fact, recent studies have been evaluating candidate markers and until now, no specific markers have been identified. These studies, while valuable, require further analyses to validate whether cells expressing these markers function as endometrial stem/progenitor cells. The transcription factor Oct-4 is crucial for the maintenance of cell pluripotency and is known to be expressed in embryonic stem cells, germ cells and whole embryos at various stages of development and, more recently, in adult stem cells (17). In 2005, the expression of Oct-4 was first demonstrated in human endometrium tissue, but the cell types and their location were nor determined (18). More recently, in a prospective cohort study, endometrial samples of 98 women in follicular or luteal phase of the menstrual cycle were obtained during hysteroscopy (19) OCT-4 mRNA was detected in all samples, but it was not differentially expressed during the menstrual cycle.

Several general adult stem cell markers, bcl-2, c-kit (CD117) and CD34, have also been identified in endometrial tissue (20) The importance of these markers, however, cannot be determined since they were expressed in many more endometrial cells than the numbers of clonogenic or side population cells identified in functional studies (14,21). Recently, flow cytometry analysis identified cells with a hematopoietic stem cell phenotype (CD34þCD45þ) in human endometrial cell suspensions that co-expressed CD7 and CD56 and appear to be lymphoid progenitors (22).

Another study evaluated the expression and localization of Musashi-1 in endometrial, endometriotic and endometrial carcinoma tissue specimens of 46 patients (23). Musashi-1 is a RNA-binding protein and an epithelial progenitor cell marker that regulates self-renewal signaling pathways (23). Musashi-1 protein expression was found in endometrial glands and stroma. In proliferative endometrium, the proportion of Musashi-1-positive cells in the basalis layer was significantly increased 1.5-fold in the stroma, and three-fold in endometrial glands compared to the functionalis. The number of Musashi-1 expressing cell groups was significantly increased in proliferative compared to secretory endometrium, suggesting their possible stem/progenitor cell function. Interestingly, Musashi-1 is expressed at high levels in endometriosis and endometrial cancer (23).

Identification of “side population” cells has been used to isolate and characterize somatic stem cells from multiple tissues (24–26) SP cells constitute a small fraction of cells possessing a unique ability to efflux intracellular DNA-binding dye Hoechst 33342 via the multi drug resistance (MDR) genes, such as the ATP-binding cassette transporter G2 (ABCG2) (11,27). After incubation with Hoechst 33342, they are determined as a Hoechst-understained and/or -unstained fraction by dual wavelength flow cytometric analysis. This

technique was used in the endometrium study. Putative endometrial stem/progenitor cells are believed to reside in the basalis layer of the human endometrium. Immunofluorescence staining of human cycling endometrium showed that ABCG2+ was expressed in the endometrial progenitor cells (28). ABCG2+ cells were distributed across the functionalis and basalis layers of the endometrium and they were located mainly in the perivascular region of these layers (29).

Epigenetics of the endometrium—Investigation of methylation patterns in individual endometrial glands is one of the retrospective approaches for studying the activity of endometrial stem/progenitor cells. It is believed that there are epigenetic markers that arise during adult stem cell division and are inherited by all the daughter cells, whereas other markers arise in transit of amplification or more mature cells are lost when the functionalis layer is shed during menstruation. One way of identifying these markers is studying the methylation in the endometrial glands. The extent of gene methylation in endometrial glands increased with age until menopause, and then remained relatively constant, indicating that the number of epigenetic markers was a reflection of the mitotic activity of endometrial stem/progenitor cells (30). Kim et al. found similar results in the methylation patterns of individual glands, re-enforcing the idea that stem cells are still present in the niche -of individual glands.

Evidence for endometrial multipotent cells in human endometrium

In 2007, two studies showed the existence of a small population of multipotent cells in endometrium (31–34). Schwab and Gargett collected human endometrial tissue from reproductive-aged women, and prepared human endometrial stromal cell cultures(31). Then endometrial stromal cells were incubated with adipogenic, osteogenic and myogenic differentiation induction media for 4 weeks. The results showed that a subset of endometrial stromal cells differentiated into cells of adipogenic, osteogenic, myogenic and chondrogenic cell lineages. Wolff et al. also collected tissues from endometrium, myometrium, fallopian tube, and uterosacral ligament tissue (34). These cells were cultured in a defined chondrogenic media for 21 days and then were analyzed for markers of human articular cartilage. Only cells derived from the endometrium were able to differentiate into a heterologous cell type: chondrocytes, thus demonstrating the presence of multipotent stem cells.

In the first study the authors could isolate endometrial MSC by the co-expression of two perivascular cell markers, CD146 and PDGF-receptor-β (PDGF-Rβ) (31). It was the first time that markers were used to identify mesenchymal stem cells. The CD146+PDGF-Rβ+ cells were found in the perivascular region in both functionalis and basalis layer of endometrium. These cells expressed typical MSC surface markers (CD29, CD44, CD73, CD90 and CD105), were negative for haemopoietic and endothelial markers and also underwent differentiation into adipogenic, myogenic, chondrogenic and osteoblastic lineages when cultured in appropriate induction media. In 2009, another study evaluated a bone marrow-derived MSC surface marker, MSCA-1, called Tissue Nonspecific Alkaline Phosphatase (TNAP). This marker is able to identify the MSCs, but also identifies endometrial cells. Then, a second marker is necessary to exclude these endometrial cells and isolate the mesenchymal ones (35).

As mentioned above, the possibility that endometrial stem cells can migrate and repair tissues makes these cells an attractive potential treatment for several diseases. Thus, endometrial tissue obtained from nine women who did not have Parkinson’s disease was utilized to isolate endometrial stem cells and were transformed into dopamine-producing nerve cells like those in the brain. Likewise, when these cells were transplanted into the

brains of mice with a Parkinson's-like condition, endometrial stem cells developed into dopamine-producing cells restoring functioning of brain cells damaged by the disease (32,36). Thus, it can be envisioned that these cells could be coaxed to differentiate into cells involved in multiple diseases such as diabetes.

Possible Sources of Endometrial Stem Cells

Fetal stem cells were speculated to persist in the adult uterus to replace the glandular epithelium and stroma that are shed with each menstrual cycle (37). However, these multipotent cells in the endometrium can arise from another source, and recent studies have suggested that the bone marrow may be the other source of endometrial stem cells (38–41). Bone marrow stem cells (BMDCs) develop into hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC). It is possible that these cells migrate to damaged tissues and are responsible for the angiogenesis and trans-differentiation into the cells of the new tissue. Trans-differentiation is the process whereby cells of a lineage lose their tissue-specific markers and function to then differentiate into a cell from a new lineage, with different functions and markers (36). This phenomenon is also called stem cell plasticity. This hypothesis is appealing as BMDCs have been shown to circulate and to be able to differentiate into multiple cell types, including endothelial cells, hepatocytes, neurons, skin, cardiomyocytes, and gastrointestinal epithelium (42–44). In 2004, Taylor provided evidence of endometrial regeneration in bone marrow transplant (BMT) (38). Each recipient had a bone marrow donor with an HLA type that enabled determination of the origin of any cell. Donor-derived endometrial epithelial cells and stromal cells were detected in endometrial samples of recipients by RT-PCR and immunohistochemistry. The study identified the presence of chimerism in the endometrial glands and stroma of the four women who received the transplants. These data suggest that bone marrow–derived stem cells contributed to the repopulation of the endometrium in these patients. The extent of chimerism ranged from 0.2%–48% and correlated with the length of time between transplantation and biopsy; however, the sample size in this analysis was too small to determine a clear time course for the repopulation of the uterus with bone marrow–derived stem cells. Blood derived cells localized to focal areas, suggesting local proliferation of a donor-derived stem cell.

A follow up study irradiated female mice which subsequently received a bone marrow transplantation from male donor mice (39). It was observed that bone marrow-derived stem cells engraft the murine endometrium. Both stromal and epithelial cells were derived from bone marrow origin. Although present in a small fraction (<0, 01%), these cells could differentiate into endometrial epithelial cells.

Furthermore, a new study showed that bone marrow-derived endothelial progenitors contribute to the formation of new blood vessels in the endometrium (40). Recently a group from Japan also reported that bone marrow-derived cells from human male donors can differentiate into endometrial glands in female transplant recipients (41).

Endometrial stem cells and Endometriosis

Pathogenesis of Endometriosis—Endometriosis is a chronic benign gynecological disease characterized by the presence of endometrial glands and stroma outside the uterine cavity. The consequences of endometriosis often include pelvic pain and infertility. The incidence of the disorder is between 6% and 10% of all women and 35%–50% of women with pelvic pain and infertility (37).

The origin of endometriotic implants and the pathogenesis of endometriosis has long been an area of active investigation. Multiple hypotheses have been explored, including:

Retrograde Menstruation Theory—This theory is the most widely accepted and postulates that endometriotic implants arise from retrograde menstruation of endometrial tissue through the fallopian tubes into the peritoneal cavity (45,46).

Coelomic Metaplasia Theory—This theory proposes that endometriosis develops from metaplasia of the cells lining the visceral and abdominal peritoneum (47). Some undetermined stimulus is believed to induce metaplastic changes in the peritoneal lining, resulting in endometrial implants.

Embryonic Rest Theory—This theory proposes that the presence of cells of mullerian origin within the peritoneal cavity could be induced to form endometrial tissue when subjected to the appropriate stimulus (48).

Lymphovascular Metastasis Theories—Sampson suggested that endometrial cells could spread to ectopic sites via lymphatic and hematogenous spread (45,46).

Although there is evidence for each theory, the clinical manifestation of endometriosis and the presence of endometrial tissue outside the uterine cavity is probably the end point of a combination of several aberrant biological processes. For instance, retrograde menstruation may occur in a woman with an improper immune response and a genetic predisposition to develop endometriotic lesions, possibly in the setting of an aberrant environmental milieu (37).

Briefly, the mechanisms required include attachment of endometrial cells to the pelvic peritoneum, invasion into the mesothelium, and survival and proliferation of the ectopic endometrial cells (49). Extensive investigations have been performed on the molecular biology required for establishment and survival of endometrial implants.

Microarray analysis has demonstrated that in patients with endometriosis the gene expression profile of ectopic endometrial implants differs from the gene expression profile of eutopic endometrium. Furthermore, the gene expression profile from eutopic endometrium of patients with endometriosis differs from that of unaffected controls (50,51). Taken together, these data suggest that the presence of endometriotic implants can alter gene expression profiles within the eutopic endometrium and, by extension, the function of the eutopic endometrial tissue.

The role of stem cells in endometriosis

In combination with the observations that the endometrium basalis contains endometrial/stem progenitor cells and that women have retrograde menstrual efflux, we posit that stem/progenitor cells are present in the blood that achieves the peritoneal cavity. Endometrium-derived stem/progenitor cells residing in the basalis layer can be shed through the fallopian tube to the peritoneal cavity during menses, and establish endometriotic implants (37). It is possible that abnormal endometrial stem/progenitor cells increase their capacity to implant and establish themselves as an ectopic tissue, or that normal stem cells find an abnormal peritoneum a proper implantation site. Another hypothesis is that more severe endometriotic lesions are developed from endometrial stem/progenitor cells, while those that resolve may have established from mature transit amplifying cells (13). To date however, no direct evidence for the role of endometrial stem/progenitor cells in the pathogenesis of human endometriosis has been reported. For instance, it is not known if stem cells shed in the menstrual blood or through the retrograde efflux in higher numbers in patients with endometriosis. However, there is indirect evidence for the role of stem cells in the pathogenesis of endometriosis. Studies have already demonstrated that un-fractionated

human endometrial cells establish ectopic endometrial growth in the many models used for the study of endometriosis(37,52).

Epithelial cells in some endometriosis lesions are monoclonal, suggesting a single cell origin, possibly by an endometrial stem/progenitor cell. Other endometriotic lesions are polyclonal, suggesting contamination with polyclonal stromal cells, repeated seeding of the lesion with cells from other sources, such as bone marrow, or establishment from different fragments of shed endometrium containing several stem/progenitor cells (13). 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 (53).

To explore an alternative hypothesis that extra-uterine stem/progenitor cells function in the pathogenesis of endometriosis, Du and Taylor generated an experimental model to test whether extrauterine-derived cells could track to and populate endometriotic implants (39). Endometriosis was generated experimentally by ectopic wild-type endometrial implantation in the peritoneal cavity of hysterectomized LacZ transgenic mice. LacZ-expressing stem cells of extrauterine origin were incorporated into the endometriotic implants and were capable of differentiating along epithelial and stromal cell lineages at a frequency of 0.04% and 0.1%, respectively. Extrauterine stem/progenitor cells, derived from the bone marrow or an alternative source, are likely to travel to distant ectopic sites via the lymphovascular spaces (37).

CONCLUSION

The biological and clinical implications involving stem cells have recently become a research focus. However, this field is relatively new and still not completely understood. The endometrium has been thought of as a potential source of stem cells. During each menstrual cycle there is a large proliferation of endometrial tissue, which is shed at the end of the cycle. The regenerative potential of this tissue could be a consequence of the presence of stem cells in the endometrium. In vitro and in vivo assays have been developed to isolate and characterize the endometrial stem cells. Two cell types were identified from cultured endometrial cells – epithelial and mesenchymal stem cells (54).

Endometrial stem cells likely play an important role in the physiologic and pathologic uterine biology. Physiologically, they are likely involved in the response to tissue injury and disease. However, they may also be involved in the pathology of the reproductive tract such as endometriosis.

The study of endometrial stem cells is unique as the tissue can be easily obtained from discarded sources and may be an untapped supply for developing new cell based therapeutic strategies.

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