Commentary

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The Role of Stem Cells of the Basal Layer of Endometrium in Gynaecological Diseases

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Abstract

Stem cells of the endometrium belong to epithelial and stromal cells, capable of self-reproduction *in vitro*. Epithelial cells differentiate into cytokeratin-positive iron-like structures, and stromal cells are multipotent and can differentiate into adipocytes, chondrocytes and osteoblasts. Epithelial progenitor and mesenchymal stem cells have a regenerative ability to restore the endometrium during the menstrual cycle. These cells can participate in the development of diseases such as endometriosis, adenomyosis, endometrial hyperplasia, endometrial cancer, and also provide a resource for cell therapy.

Keywords: Epithelial progenitor cells; Endometrium; Mesenchymal stem cells; Endometrial hyperplasia; Adenomyosis; Uterine myoma

Commentary

Hyperplasia of the endometrium (GGE) is a disease that arises from the prevalence of proliferation over apoptosis in the background of enhanced angiogenesis and altered receptor status of the endometrium. This disease occupies one of the leading places among all diseases of female genital organs along with other benign proliferative processes of the uterus (uterine myoma and adenomyosis) [1].

GET is the most frequent form of pathological changes in the uterine mucosa and is treated as a nonphysiological proliferation of the endometrium, accompanied by structural rearrangement of the glandular and, to a lesser extent, stromal component of the tissue. Despite a large number of studies, the mechanisms of the development of endometrial hyperplastic processes have not been sufficiently studied so far.

Recent studies have examined the expression in the endometrium of normal and pathological growth factors and their receptors, as well as the proliferation factors (PCNA, Ki-67) required for the replication of genomic DNA. However, the data obtained in this case are contradictory. Numerous studies have established the relationship between foci of adenomyosis and autologous hyperplastic endometrium. Compelling evidence confirming the pathogenetic community between the focus of adenomyosis and hyperplastic endometrium has been obtained [2].

According to I.S. Sidorova uterine myoma in 76% is combined with hyperplastic processes of the endometrium, in connection with which the clinical manifestations of myoma are largely dependent and determined by the form of endometrial hyperplasia [3]. The basis of these diseases is violations of proliferation and apoptosis, which are regulated by cellular and extracellular components at the molecular level. Many authors note a high frequency (85%) of the combination of uterine fibroids and adenomyosis, often occurring against the background of hyperplastic endometrial processes. Despite the fact that the concepts of pathogenesis, morphogenesis, clinics, tactics of adenomyosis and uterine fibroids have been discussed for decades, many issues devoted to this problem remain controversial and insufficiently studied [3-5]. At the current stage, it is important to open new approaches to the treatment of these diseases in order to reduce the risk of recurrence, progression and malignancy.

The progress of fundamental science in the field of cellular and molecular biology, molecular genetics and biotechnology allows us to look with optimism in the near future. Numerous studies in this field lead to the discovery of ever new sources of stem cells, the development of new approaches to the use of regenerative and differentiating potential of stem cells in practical medicine. Approaches to the application of stem cell transplantation in the treatment of diseases that until recently were considered incurable by traditional methods have been actively developed [6]. The use of stem cells is of great interest as a new model of treatment in reproductive medicine that arose when human embryonic stem cells were first cultivated as a stem cell has a potential for growth of diseases [7]. Stem cell research is currently in the development phase and has the potential to dramatically affect the therapeutic potential of human embryonic and adult stem cells in reproductive medicine and gene therapy [8]. The best example of such research is Doctor Panos Zavos and his team that can be used for numerous medical purposes, from burn victims to people who are suffering from infertility issues and gynecological diseases [9].

Stem cells are characterized by their ability to self-reproduce by symmetrical division and the ability to differentiate into

different types of tissues through asymmetric division. Adult stem cells repair the tissue in which they develop. They are found in various tissues, including the human bone marrow, lungs, prostate, brain and liver [10]. These Cells may also be found in the endometrium a highly proliferative, cyclically changing tissue. In the initial studies, the content was revealed. An insignificant population of epithelial and stromal cells that *in vitro* exhibited traits of progenitor stem cells (clonogenic activity) [11-13]. Many gynecological diseases are associated with abnormal endometrial proliferation, and it is possible that endometrial stem cells can play a role in the pathophysiology of gynecological diseases such as endometrial hyperplasia, endometrial cancer, endometriosis, adenomyosis, and also a potential resource for cell therapy [8,9,11]. Thus, at this stage, it is important to identify endometrial progenitor stem markers for more detailed characterization and to determine the role of these cells in the pathogenesis of proliferative endometrial disorders. In the current studies, it is suggested that stem cells can be of clinical importance in the treatment of various gynecological diseases [7,8,10].

Attempts to isolate, characterize and localize endometrial stem cells were undertaken only a few years ago, while experimental studies on identification of adult stem cells in other tissues actively developed. The evidence of the existence of adult stem cells in the endometrium of humans and mice is due to the peculiarities of stem cells, which can now be determined in endometrial cells.

Endometrium is a highly dynamic tissue that undergoes more than 400 cycles of proliferation, differentiation, rejection and regeneration during the reproductive period of a woman. It is assumed that in the basal layer of the endometrium there are cells responsible for the regeneration of the endometrium. Studies are underway to identify the key properties of stem cells among individual epithelial and stromal cells of the endometrium. It is assumed that adult stem cells are responsible for the regenerative capacity of the human endometrium, and their dysfunction can lead to proliferative disorders in the endometrium and, as a consequence, to gynecological diseases [8-10]. Kato and colleagues (2007) isolated such cells from human endometrium and showed that they can be classified as stem cells because they are able to differentiate into both epithelial and stromal endometrial cells [14].

Mesenchymal stem cells (MSCs) are multipotent somatic cells that can differentiate into different types of mesodermal and non-dermatological organs. First, MSCs should be adhered to the plastic upon isolation under standard culture conditions. Secondly, they must express the markers CD 105, CD 73, CD 90 and ignore the expression of surface molecules: CD34, CD45, CD14, CD16, 56 or CD11 and HLA-DR; and thirdly, MSCs must differentiate into osteoblasts, adipocytes and chondrocytes *in vitro* [15]. MSCs are found in various tissues of the human body: adipose tissue, umbilical cord blood and peripheral tissue, postpartum tissues (umbilical cord and placenta), amniotic fluid, fetal liver, skin, in the pulp of dairy teeth. Since the content of MSC does not exceed a few parts of a percent, working with them implies isolation and cultivation *in vitro*. The most accessible sources of mesenchymal stem cells are fatty tissue, umbilical cord blood and placenta [16-18].

Human endometrium contains a small number of cells with characteristics of endometrial stromal progenitor cells, which belong to the family of mesenchymal stem cells. These cells are responsible for the restructuring and remodeling of the human endometrium during the month [19,20]. According to Musina and co-workers (2008), menstrual blood can be considered the most accessible source of MSCs. Morphology MSC is typical for MSCs from menstrual blood. Comparison of MSCs from various sources has shown that a specific feature of endometrial MSC is a lower ability to differentiate into adipocytes compared to cultures from bone marrow, adipose tissue, and skin [21-23]. By the ability to differentiate into osteoblasts, endometrial MSCs do not differ from cultures isolated from other sources [24]. The discovery of these cells is a solid result, which can influence the solution of gynecological problems associated with many diseases [25]. Epithelial and stromal colony-forming cells demonstrated the defining characteristics of adult stem cells: self-renewal, high proliferative activity, *in vitro* differentiation [26].

Epithelial endometrial and stromal stem cells have been identified in vivo in the endometrium of mice [27-30]. It is established that these cells can play a key role in the development of Gynecological diseases associated with abnormal proliferation of endometrium: endometriosis, adenomyosis, and endometrial hyperplasia [31-33]. Transplantation of isolated human endometrial epithelial cells with murine mesenchymal or human endometrial stromal cells inserted under the capsule of the spleen immune-deficient mice rebuilt endometrial tissue, reproducing human gland and mouse or human stroma. Structures of glandular epithelium expressed progesterone receptors and proliferated under the influence of estrogens, while stromal cells differentiated into prolactin-producing decidual cells [34].

In the future, these achievements make it possible to provide an excellent system for detecting in vivo the ability of mouse or human stem progenitor cells to reconstruct endometrial tissue. Difference in the number, functions, regulation, and localization of endometrial stem progenitor cells can become a determining link in the pathogenesis of diseases such as endometrial hyperplasia, adenomyosis, uterine myoma, endometrial cancer [35-38].

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