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MOLECULAR MECHANISMS OF CYCLIC TRANSFORMATION OF THE ENDOMETRIUM

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▪ Structural transformation of the endometrium during the menstrual cycle is a genetically determined process and is provided by complex molecular-biological interactions aimed at the onset and development of pregnancy. Sex steroid hormones play a key role in endometrial morphogenesis, which mediate or directly affect angiogenesis and immunogenesis.

▪ **Keywords:** menstrual cycle; endometrium; estrogen and progesterone receptors; angiogenesis; immunogenesis; chronic endometritis.

МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ ЦИКЛИЧЕСКОЙ ТРАНСФОРМАЦИИ ЭНДОМЕТРИЯ

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▪ Структурная трансформация эндометрия в течение менструального цикла является генетически детерминированным процессом и обеспечивается сложными молекулярно-биологическими взаимодействиями, нацеленными на наступление и развитие беременности. Ключевую роль в морфогенезе эндометрия играют половые стероидные гормоны, которые опосредованно или непосредственно влияют на ангиогенез и иммуногенез.

▪ **Ключевые слова:** менструальный цикл; эндометрий; рецепторы эстрогена и прогестерона; ангиогенез; иммуногенез; хронический эндометрит.

The endometrium where complex molecular interactions of biologically active substances take place, creates optimal conditions for the implementation of the high priority function, namely, the fetal egg implantation and the development of pregnancy. It has been of interest to researchers for many decades, although they still have not managed to reveal its functional activity completely. With advances in medicine, knowledge about the endometrium structure and functional activity was subsequently refined and expanded. The complete proliferative and secretory transformation of the endometrium during the menstrual cycle represents a genetically determined process. It is based on the balance of interactions of steroidogenesis, angiogenesis, and immunogenesis in the endometrium, and starts from the intrauterine development of the fetus.

Embryonic development of the uterus begins in an 8–9-week-old fetus. The endometrium glandular component originates from the epithelium lining the Muller ducts, and the cells of the adjacent

mesenchyma serve as a source of endometrial stroma and myometrium of the uterus. At the beginning of development, the endometrium is represented by low cylindrical epithelium; however, as the gestation period increases, the height of the endometrium increases, and starting from week 18, the first glands of the endometrium are formed. The uterus actively grows from week 20 of pregnancy, which is associated with the development of receptors and the organ sensitivity to the sex hormones of the mother, in particular to estrogens. By week 24 of pregnancy, the first signs of subnuclear vacuolization are noted in the endometrial epithelium, and the endometrium becomes secretory-like. Well-defined signs of secretion in the endometrium and the endocervical epithelium are found from week 28, with a peak by weeks 35–36 of gestation, when the placenta secretes maximum amounts of estrogen and progesterone.

Regardless of age, the endometrium has a thickness of 0.5 to 1.5 mm, contains a significant number of cells (lymphocytes, fibroblasts, plasmocytes) and a few fibers. In the neonatal period, the glandular component of the endometrium is represented by gland-like "immersions," and only starting from the first year of life, the glands obtain the typical structural features and their number increases. By the time of puberty, there is significant growth and branching of the glands without an increase in the thickness of the endometrium [1].

With the onset of sexual maturation, in the endometrium, a complex cyclic cascade of molecular and neuroimmunoendocrine interactions occur under the control of the hypothalamic-pituitary-ovarian relationship, and a genetically determined menstrual cycle is generated. The endometrium is a complex and interconnected system consisting of the luminal, glandular epithelial, stromal, and vascular components.

From the early stage of the proliferation phase to the late stage of the secretion phase, the glandular epithelium and stromal cells are characterized by heterogeneity, which provides the cell transformation processes. With the onset of the proliferation phase, the endometrium re-epithelialization starts with the migration of epithelial cells from the growing glands until the proliferative activity of stromal and epithelial cells begins. This process covers the entire surface of the uterus completely, and the functional layer is restored quickly [2–4].

The use of scanning electron microscopy of the menstrual endometrium showed that epithelial cells arise from stromal mesenchymal cells in desquamated sites, and not only from epithelial glands, which suggests reprogramming of endometrial stromal cells even in the phase of menstrual decay [5, 6]. In this case, mesenchymal cells change their characteristics and become epithelial cells; this process is known as the mesenchymal-epithelial transition (MET). Evidence for this hypothesis was obtained in a mouse experiment using the cytoskeleton protein pancytokeratin, and vimentin, a stromal cell marker. Significant changes in MET were revealed in endometrial cells 24 hours after progesterone withdrawal [7].

The work of Cousins et al. (2014) showed the activation of proliferation processes in sites of damaged endometrial stroma in women under the influence of cytokeratin and osteopontin, were similar to the MET process [8]. Therefore, it can be assumed that the endometrium basal layer promotes re-epithelization of the desquamated surface.

There is also a reverse MET process, namely the epithelial-mesenchymal transition (EMT), which is necessary for wound healing and the development of fibrosis [9]. The role of EMT in the endometrium remains unclear, but the balance of EMT and MET is likely of great importance for the processes of full repair of the endometrium in the desquamation phase. The strict control of these factors in the endometrium enables the tissue to heal without scarring [10].

Perfusion of growing tissue requires adequate angiogenesis. By days 5–6 of the menstrual cycle, estradiol synthesis increases because of growing follicles, which stimulate endometrial neovascularization directly by expressing angiopoietin-2 (Ang-2) in the endothelium. Estrogen does not significantly affect the repair of the endometrium in the early stage of the proliferation phase. However, during the middle and late stages of the proliferation phase, when the primary mechanism of angiogenesis is an increase in vessel length, estrogen, together with VEGF (vascular endothelial growth factor) synthesized by stromal cells, provides estrogen-dependent regeneration, and increased vascular permeability [11–13].

In an experiment on animals undergoing ovariectomy, three peaks of VEGF effects on the endometrium were demonstrated, namely on the surface epithelium in the early stage of the proliferation phase, on stromal fibroblasts in the middle stage of the proliferation phase, and the

glandular component during the late stage of the secretion phase [14].

The significance of the vascular component in endometrial regeneration has been confirmed by studies of stroma-derived growth factor (SDF-1) through pro-fibrotic CXCR4 or pro-regenerative CXCR7 receptors. The stroma-derived growth factor (SDF-1) is present in all phases of the menstrual cycle, and CXCR4 expression is expressed in the early proliferative phase in both epithelial and endothelial cells [15].

It is known that cyclic transformations of the endometrium occur through the implementation of hormonal effects of sex steroid hormones (estrogen and progesterone) on the mucous membrane of the uterine body when bound to the corresponding specific nuclear cell receptors. Sex steroid hormone receptors are ligand-dependent transcription factors consisting of a specific sequence of amino acids and forming ligand-receptor complexes in which a specific gene is activated or deactivated by coactivators or cosuppressors [16, 17].

Currently, two types of estrogen receptors (ER) are known. They are ER-α associated with proliferative changes in cells and ER-β associated with the phase of secretion of the menstrual cycle and the preparation of the vascular bed for adequate blood flow and decidualization of the endometrial stroma [18]. The progesterone receptor (PR) is also represented by two main isoforms, PR-A and PR-B. The progesterone receptors A and B are identical in structure, but differ in the presence of 164 amino acid residues on the N-terminal sequence of PR-B, which is absent in the progesterone receptor A [19, 20].

Estradiol is characterized by an increase in the synthesis of its receptors, as well as PRs and androgen receptors, while androgens can enhance the synthesis of their own receptors only. It should be noted that PRs in the endometrium are present both in the proliferative phase and in the secretory phase of the cycle and have a different ratio of isoforms. Progesterone not only does not enhance the synthesis of its receptors but also inhibits them, and also inhibits the synthesis of ER receptors. During the menstrual cycle, the content of PR receptors in the basal layer of the endometrium remains almost unchanged, whereas receptors in the functional layer have different temporal and local expression. In the phase of secretion, the number of PRs decreases in the nuclei of the glands of epithelial cells of the functional layer, whereas the amount of PRs in the stroma remains the same, especially in the perivascular region. In addition, progesterone exerts a short-term proliferative effect on stromal cells [21–24]. Low expression of PR in the endometrium may be due to mutations in the receptor gene, despite normal serum progesterone levels, which may be the cause of spontaneous miscarriages in trimester I [25].

A decrease in the expression of the receptors of sex steroid hormones ER and RP in the endometrium, regardless of the phase of the menstrual cycle, indicates the presence of a chronic inflammatory process in several gynecological diseases that subsequently determine endometrial dysfunction in patients with infertility, miscarriage, and ineffective ancillary reproductive technology programs [26–28].

Long-term clinical and morphological studies of the endometrium, conducted at the D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductology using confocal laser scanning microscopy, immunohistochemical, and immunofluorescence methods, and a method for endometrial cell culturing, showed that during the full ovulatory cycle, sex steroid hormone receptors (ER and RP) in the endometrium are characterized by the following expression patterns:

- Dynamic, which is characteristic of ER in the glands and stroma with maximum values in the middle stage of the proliferation phase and subsequently decrease to minimum values in the early stage of the secretion phase; for PRs in glands with maximum values from the middle stage of the proliferation phase to the early stage of the secretion phase, with a decrease in expression to minimum values in the middle secretory phase of the cycle;
- Constant, which is registered in all phases of the menstrual cycle, and is characteristic of the expression of PRs in the stroma [29, 30]. Following the menstrual cycle, it is the glandular component of the endometrium that undergoes maximum remodeling. The endometrial stromal component is a relatively stable structure. It is characterized by significant fluctuations in the level of ER expression at relatively constant and high levels of PR expression during all phases of the menstrual cycle, which is because of the main functional ability of the endometrium, namely blastocyst invasion and the development of pregnancy.

The onset and development of pregnancy are inextricably linked to physiological and pathological inflammatory immune reactions in the endometrium, and directly in the nidation

zone. The constancy of the physiological microbial population and the prevention of inflammatory reactions represent one of the essential aspects of a woman's reproductive tract. The immune components of the mucous membrane of the female reproductive tract in different parts of the genital tract are represented by the predominant pool of T cells, macrophages/dendritic cells, natural killer cells (NK), neutrophils, and mast cells [31, 32]. Macrophages (CD68+), plasmocytes (syndecans), and B cells are present in the endometrium at all stages of the menstrual cycle in small quantities. In addition, during the proliferative phase, syndecans induce angiogenesis [33–35].

The basal layer of the endometrium contains true lymphoid follicles, formed from germinal centers with light zones consisting of B cells surrounded by T cells and an external halo of macrophages (CD14+). In the late stage of the proliferation phase and the secretion phase, lymphoid follicles increase in size, with B cells expressing CD19+, and T cells expressing almost solely CD8+, and extremely rarely CD4+ [36].

In the functional layer of the endometrium of the proliferation phase, there are predominantly cytotoxic T-lymphocytes (CD8+) that have increased cytolytic activity compared with the secretory phase of the cycle. Moreover, the suppression of the CD8+ cytolytic activity is noted only in the secretory endometrium and fallopian tubes, in contrast to the cervix [37]. The content of the number of cytotoxic T-lymphocytes (CD8+) and T-helpers (CD4+) in the normal endometrium is up to 10 cells in the field of view, whereas the number of B-lymphocytes (CD20+) is up to three cells in the field of view [38]. An increase in the number of cells of cytotoxic T-lymphocytes, B-lymphocytes, and the presence of plasmocytes (CD138+) indicates the presence of chronic endometritis [29, 38].

The process of decidualization of the endometrial stroma is characterized by a limiting effect on inflammatory processes in the functional layer, whereas the basal layer remains intact, which is crucial for effective reparative processes in the endometrium. In addition, progesterone blocks the activation of metalloproteinases (MMP) during the secretory phase of the cycle [41, 42].

The endometrial immunological cell composition of the secretory phase is represented by NK cells that express surface receptors CD56+, CD16+, CD3+, and are phenotypically different from peripheral blood NK cells. An increase in CD56+ during the middle stage of the secretion phase, with predominantly periglandular and perivascular localization, is associated with maintaining the immune tolerance of the mother's body to the onset and development of pregnancy [39, 40].

By the end of the secretion phase, in the endometrium, the population of neutrophilic leukocytes, which contain high MMP levels for initiating endometrial decay, increases significantly (up to 7%–15%). Leukocytes do not have estrogen and PRs and penetrate the endometrium by chemotaxis in response to physiological and pathological inflammatory reactions in the tissue [43, 44]. In this period, neutrophils are characterized by resistance to apoptosis and hypoxia under the influence of inflammatory mediators, which increases tissue damage [45, 46].

In addition to secretory transformations of the endometrium, progesterone also affects the contractility of the myometrium. A decrease in PR expression in the late stage of the secretion phase leads to activation of the myometrium and an increase in contractile activity in the menstrual decay phase. In contrast, the level of progesterone in the blood serum does not correlate with progesterone concentration in the myometrium [47, 48].

In the desquamation phase, an excessive or prolonged inflammatory response can lead to significant tissue damage and polymenorrhea, whereas the level of tumor necrosis factor and pro-inflammatory cytokines increases, and expression of cyclooxygenase-2 (COX-2) mRNA also increases [49]. The reparative processes start in the endometrium 36 hours after the onset of menstruation.

Thus, the combination of molecular, endocrine, and biochemical and immunological factors leads to a complete transformation of the endometrium during the menstrual cycle. Secretory transformation of the endometrium with an appropriate ratio and distribution of estrogen and PR expression, complete angiogenesis, and immunological balance determine the implantation, placentation, and development of pregnancy.

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