DOI: https://doi.org/10.17816/morph.508661

Морфологические и молекулярные особенности децидуальных клеток эндометрия при невынашивании беременности

Т.А. Гусарова[1], Н.В. Низяева[2], С.А. Михалёв[3], Н.Б. Тихонова[2], Д.А. Оргадеева[2], Л.М. Михалёва[2], О.В. Шарапова[1]

[1] Городская клиническая больница имени В.В. Виноградова Департамента здравоохранения города Москвы, Москва, Российская Федерация;
[2] Научно-исследовательский институт морфологии человека имени академика А.П. Авцына Российского научного центра хирургии имени академика Б.В. Петровского, Москва, Российская Федерация;
[3] Научно-исследовательская лаборатория здоровья женщины, матери и ребёнка Российского национального исследовательского медицинского университета имени Н.И. Пирогова, Москва, Российская Федерация

АННОТАЦИЯ

Децидуализация является динамичным многоэтапным процессом, в результате которого происходит трансформация удлинённых эндометриальных стромальных клеток в округлые эпителиоидоподобные децидуальные клетки в ответ на повышение уровня прогестерона. Децидуальные стромальные клетки играют важную роль на протяжении всей беременности, создавая толерантную микросреду — децидуальную оболочку — для подавления материнского иммунного ответа и предотвращения отторжения аллогенного плода. Считается, что децидуализация важна не только в установлении и поддержании беременности, для предотвращения ранних потерь, модуляции иммунного ответа, но и для контроля начала родовой деятельности, регуляции инвазии трофобласта, а также селекции эмбриона. Децидуальные клетки обладают иммуномодулирующими свойствами в отношении клеток врождённого и адаптивного иммунитета. Для поддержания беременности требуется селективная элиминация провоспалительных стареющих децидуальных клеток активированными маточными NK-клетками.

В обзоре приводятся данные о различных популяциях децидуализирующихся эндометриальных стромальных клеток, выделены их подтипы с различными функциональными характеристиками: предецидуальные, децидуальные и стареющие (сенесцентные), а также переходные. Показано, что повышение количества стареющих децидуальных клеток с провоспалительным фенотипом ведёт к потерям беременности. Проанализированы данные литературы, посвящённой децидуализации и её роли в генезе невынашивания беременности, а также подчёркивается важный вклад децидуальных стромальных клеток в микроокружение и их прямое или косвенное влияние на привлечение, распределение и функцию иммунных клеток, на ремоделирование внеклеточного матрикса и формирование плаценты.

Ключевые слова: децидуальные стромальные клетки; эндометрий; невынашивание беременности; стареющие клетки; хорион.

Как цитировать:
Гусарова Т.А., Низяева Н.В., Михалёв С.А., Тихонова Н.Б., Оргадеева Д.А., Михалёва Л.М., Шарапова О.В. Морфологические и молекулярные особенности децидуальных клеток эндометрия при невынашивании беременности // Морфология. 2023. Т. 161, № 1. С. 37–49. DOI: https://doi.org/10.17816/morph.508661

Рукопись получена: 25.06.2023 **Рукопись одобрена:** 29.09.2023 **Опубликована:** 26.10.2023

DOI: https://doi.org/10.17816/morph.508661

Morphological and molecular features of decidual endometrial cells in miscarriage

Tatiana A. Gusarova[1], Natalia V. Nizyaeva[2], Sergej A. Mikhalev[3], Natalia B. Tikhonova[2], Darya A. Orgadeeva[2], Liudmila M. Mikhaleva[2], Olga V. Sharapova[1]

[1] V.V. Vinogradov Clinical Hospital of the Moscow Department of Health, Moscow, Russian Federation;
[2] A.P. Avtsyn Research Institute of Human Morphology, Petrovsky National Research Center of Surgery, Moscow, Russian Federation;
[3] N.I. Pirogov Russian National Research Medical University, Research Laboratory of Women's, Mother's and Child's Health, Moscow, Russian Federation

ABSTRACT

Decidualization is a dynamic, multistep process that results in the differentiation of elongated endometrial stromal cells into round, epithelioid-like decidual cells in response to increasing progesterone levels. Throughout pregnancy, decidual stromal cells play an important role by creating a tolerant microenvironment, the decidua, to suppress the maternal immune response and prevent rejection of the allogeneic fetus. Decidualization is considered significant not only in the establishment and maintenance of pregnancy, prevention of early losses, and modulation of the immune response but also in the control of the onset of labor, regulation of trophoblast invasion, and embryo selection. Decidual cells have immunomodulatory properties in relation to cells of innate and adaptive immunity. Pregnancy maintenance requires selective elimination of proinflammatory senescent decidual cells by activated uterine natural killer cells. Data on various populations of decidualizing endometrial stromal cells revealed subtypes with different functional characteristics, namely, predecidual, decidual, transitional, and senescent subpopulations. An increase in the number of the latter with a proinflammatory phenotype leads to miscarriages. This paper analyzes the literature data on decidualization and its role in the genesis of miscarriage and highlights the contribution of decidual stromal cells to the microenvironment and their direct or indirect influence on the recruitment, distribution, and function of immune cells, extracellular matrix remodeling, and placenta formation.

Keywords: decidual cells; endometrium; early missed abortion; senescent cells; chorion.

To cite this article:
Gusarova TA, Nizyaeva NV, Mikhalev SA, Tikhonova NB, Orgadeeva DA, Mikhaleva LM, Sharapova OV. Morphological and molecular features of decidual endometrial cells in miscarriage. ***Morphology***. 2023;161(1):37–49. DOI: https://doi.org/10.17816/morph.508661

Received: 25.06.2023 **Accepted:** 29.09.2023 **Published:** 26.10.2023

INTRODUCTION

The female reproductive cycle provides conditions in the mother's body for the development of healthy offspring until birth. After fertilization, the fetal egg penetrates the uterine wall, and further development of the embryo and fetus occurs in close contact with maternal tissues in the uteroplacental area (fetomaternal interface) of the mother–placenta–fetus system. The allogeneity of the embryo causes an immune reactivity problem of the mother to foreign fetal antigens, which must be addressed. The endometrium of the uterine wall, into which the blastocyst implantation normally takes place, undergoes changes, denoted as "decidualization," which ensures the encapsulation of the blastocyst and tolerance of maternal tissues in contact with allogeneic tissues of the embryo. Decidualization changes in endometrial cells are initiated long before implantation. In humans, they are not at all related to fertilization but are evolutionarily embedded in the spontaneous menstrual cycle and depend on the hormonal regulation of the ovulatory cycle. Decidualization can be divided into two main temporal stages [1, 2]. The first stage, often referred to as "predecidualization," is associated with regular cyclic structural, functional, and quantitative changes in endometrial cells during the secretory phase of the menstrual cycle, which aims to prepare the endometrium for unimpeded implantation of the blastocyst. In the absence of fertilization and implantation, menstruation occurs, which involves the detachment and removal of the altered endometrium from the uterine cavity. At the onset of the next secretory phase, the initiation of predecidualization is repeated. In the case of successful fertilization and signals of blastocyst penetration into the uterine wall, the second stage — true "decidualization" — occurs. It involves the formation of a provisional gestational structure that constitutes the maternal part of the placenta – decidual sheath (decidua), and its maturation and maintenance occur until labor [3]. From the structural and functional aspects, the multitude of the cellular and matrix elements of the endometrium undergo changes and provide the main tasks of the process. Thus, this literature review is limited to discussing the changes that endometrial stromal cells (ESCs) undergo and the disorders of ESC decidualization among complications of the first trimester of pregnancy. Other cellular components, such as immune cells, vascular elements, and features of matrix composition changes, are mentioned in the review only when necessary to indicate their importance in ESC decidualization.

RESEARCH METHODOLOGY

In the preparation stage of the review, a search of the underlying publications in the scientific databases RINC, Scopus, PubMed, Web of Science, and Google Scholar for the 2010–2023 period was conducted using the keywords "decidualization," "decidual cells," "first trimester pregnancy complications," "miscarriage," "early pregnancy loss," "decidualization," "decidual cell," "decidua," "early pregnancy loss," "early pregnancy complication," and "early missed abortion".

DECIDUAL REACTION IN THE MENSTRUAL CYCLE AS PREPARATION FOR PREGNANCY

A successful implantation is the result of a complex interaction between two distinct components: the viable blastocyst and the prepared endometrium. The preparation of the endometrium for implantation involves the development of the decidual response, which starts immediately after ovulation in response to hormonal stimuli and involves all cellular components, namely, the epithelium, immune cells, and vascular and stromal cells. In ontogeny, a spontaneous cyclic decidualization in response to hormonal signals is only apparent with the onset of menarche. Endometrial sensitivity to progesterone is established after prolonged estrogen-dependent uterine growth, which begins before mammary gland development in prepubertal girls and continues after menarche [1].

In the proliferative (follicular) phase of the menstrual cycle, estradiol stimulates the transcription of the progesterone receptor in endometrial cells, ensuring their sensitivity to progesterone in the secretory phase [1, 3]. Following ovulation, estrogen-dependent proliferation during the follicular phase controls the division of endometrial epithelial and stromal cells into subpopulations with different functions and responses to decidual stimuli [2, 4, 5]. After ovulation, an increase in progesterone provokes the onset of decidualization, and its high level is maintained throughout pregnancy [6]. Progesterone is an important signal of decidualization and a prerequisite for successful implantation. The dynamics of the ovarian secretion of estradiol and progesterone in the menstrual cycle control decidualization and implantation [6, 7]. Postovulatory progesterone deficiency is associated with infertility and recurrent miscarriages [8].

Estrogen and progesterone receptors are nuclear transcription factors responsible for triggering signaling pathways that regulate decidualization and are organized into a regulatory network. This network consists of sequentially activated transcription factors and transducer proteins that transmit activation or inhibition signals and direct the process along one or the other pathway. Proteins belonging to transcription factors and constituting the chains of signaling pathways can undergo specific phosphorylation, which determines their regulatory function. Signaling pathways triggered by progesterone with the accumulation of cyclic adenosine monophosphate (cAMP) promote the expression of decidual regulators of transcription controlled by epigenetic

DOI: https://doi.org/10.17816/morph.508661

modifications, coordination of signal transduction, and posttranscriptional changes [9]. Thus, in the middle of the secretory phase in stromal fibroblasts, a genetic module is activated, which includes the genes of transcription factors *Dickkopf1* (*DKK1*) and *CRYAB*. The same module contains the decidualization-initiating transcription factor forkhead box protein O1 (FOXO1) and the *IL15* gene. The expression of this module is noticeable already at the beginning of the phase, although in a smaller percentage of cells and at a lower level [5].

Decidualization of ESCs is a multistage differentiation program, which is considered an evolutionarily shaped response to acute cellular stress [10]. After ovulation, the secretory phase of the cycle occurs, which is characterized by an increase in circulating progesterone levels and an initial decidual stress response. The endometrium enters a short period of receptive state (window of implantation [WOI]), which is ideal for blastocyst implantation [5]. Implantation outside this time window results in the failure to establish pregnancy or increases the risk of adverse events [11, 12]. The decidualization of stromal fibroblasts is characterized by a gradual change in their morphofunctional characteristics. Elongated fibroblast-like cells of the proliferative phase are transformed into large, round epithelium-like cells with large nuclei, several nuclei, dense secretory granules near the cytoplasmic membrane, accumulation of lipid droplets and glycogen in the cytoplasm, and enlarged endoplasmic reticulum and Golgi complex [13]. Specialized decidual cells do not appear until a few days following ovulation; however, the process is initiated in a few cells even before the opening of the WOI [5]. In the middle of the secretory phase, stromal cells decidualize around the arteries of the upper two-thirds of the endometrium, and implantation becomes possible approximately 6 days following ovulation. The abundant appearance of morphologically differentiated decidual cells heralds the closure of the WOI [9].

Changes in the morphology of decidualizing cells are associated with sequential functional reprogramming. The activation of the progesterone receptor signaling pathway by progesterone increases intracellular cAMP levels, which induces decidualization, and stimulates the expressions of prolactin (PRL) and insulin-like growth factor binding protein (IGFBP1). Although PRL and IGFBP1 (PP12, placental α-microglobulin 1 [PAMG-1]) are traditionally considered decidualization markers, decidual cells produce many other factors, such as interleukin-15 (IL-15), IL-11, epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), activin A, prokinectin-1, leukemia inhibitory factor (LIF), left-right determination factor 2, tissue factor, and neuropeptides (Fig. 1) [9, 14, 15]. Functional changes in the stromal component during decidualization include the organization of the extracellular matrix, cell adhesion, intercellular interactions, cytoskeleton organization, signal transduction, metabolism, and stress response and affect the cell cycle, differentiation, and apoptosis [9, 14].

During the menstrual cycle, the phenotype of decidualizing stromal fibroblasts changes from the middle to the late secretory phase, with a marked increase in IGFBP1 expression, whereas PRL expression levels remain low. Researchers have identified two types of decidualizing stromal cells: those expressing only IGFBP1 and those co-expressing both IGFBP1 and PRL in smaller numbers [5].

At the functional level, the following subtypes are distinguished in the population of decidualizing ESCs, namely, predecidual (pre-ESCs), decidual (dESCs) and senescent (senDESCs), and transitional forms with signs of mesenchymal–epithelial transition [16]. Moreover, cells that have started the reprogramming of transcription in accordance with the initial decidual phase, characterized by an increase in cAMP [17], a sharp release of reactive oxygen species, and secretion of inflammatory mediators and nuclear alarmins, such as IL-33 and HMGB1 [18-20], and allow complexes of specific transcription factors to gain access to decidual gene networks are designated as pre-ESCs. In parallel, massive chromatin remodeling, involving the opening and closing of numerous DNA loci, allows access to promoter and enhancer regions that control the expression of specific decidual gene networks [21, 22]. DESCs

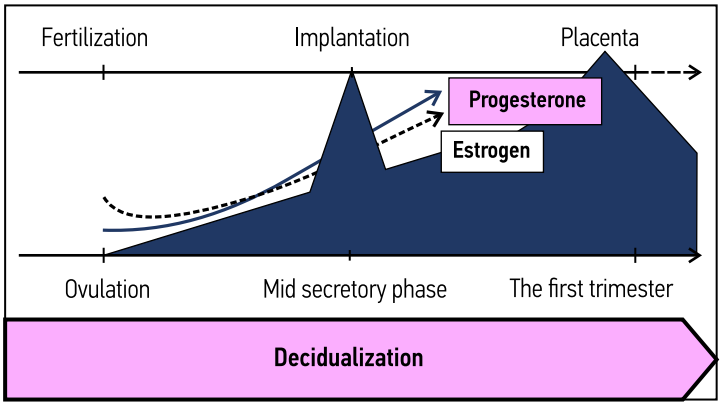

Fig. 1. Scheme of the decidualization process begining after the ovulation phase of the menstrual cycle and before the first trimester of pregnancy (cited from [15] with modifications).

are characterized by progesterone dependence, activation of defense mechanisms, suppression of oxidative and metabolic stress, activation of cellular defense mechanisms, and selective suppression of stress-responsive signaling pathways. Consequently, decidual stromal cells (DSCs) are not only protected from oxidative and metabolic stress but are also largely immune to harmful environmental influences [23]. These cells become the basis for the formation of the decidual membrane during gestation [24]. They produce large amounts of CXCL14 and IL-15, which are required for chemotaxis and activation of uterine natural killer cells (uNKs) [3, 25], and epigenetically inhibit chemokines that attract cytotoxic T lymphocytes [26]. Functionally opposite to dESCs are sendESCs, which acquire a secretory phenotype that is associated with aging [27]. Such phenotype includes proinflammatory cytokines, chemokines, growth modulators, angiogenic factors, extracellular matrix proteins, and proteases [28]. These cells are involved in tissue remodeling (including during fetal development), placenta formation, and wound healing [4, 29, 30]. In addition to the main three subpopulations, an additional group of decidual cells with signs of mesenchymal–epithelial transition — transESCs — was found [4]. These cells are largely devoid of receptors and ligands that mediate the interaction with other decidual subpopulations. They are supposed to influence tissue repair and stimulate reepithelialization of the endometrium after menstruation and childbirth [31].

In cycles without conception, decreased progesterone levels lead to a disruption of the interaction between dESCs and uNKs, which involves a differentiation program toward senDESC and transESC phenotypes involved in tissue destruction and repair. Notably, senescent cells also attract neutrophils and macrophages, which, when activated and degranulated, enhance cellular senescence and degrade the intercellular matrix [32, 33]. The disruption of uNK and dESC interaction in the first trimester of pregnancy may cause early pregnancy loss. By the end of pregnancy, the number of sendESCs expressing factors and causing degradation and remodeling of the extracellular matrix increases significantly, which contributes to the onset of labor [16].

DECIDUALIZATION OF THE PERI-IMPLANTATION PERIOD AND DURING PLACENTATION

In the receptive endometrium ready for implantation in the secretory phase of the cycle, two superficial layers are distinguished, namely, the compact outer layer (stratum compactum) and the spongy layer (stratum spongiosum). Embryo implantation stimulates further decidualization of stromal fibroblasts of the secretory phase with differentiation into additional subgroups. Decidual cells can phenotypically differ depending on their location in the spongy or compact layer and the expression level of classical markers PRL and IGFBP1, and markers of mesenchymal origin, namely, alpha-smooth muscle actin and transgelin [34].

At implantation, the extravillous trophoblast first penetrates the compact layer, where a pool of cells synthesize galectin-9 and CLEC2D, which suppress the immune response and promote invasion [35]. In turn, IGFBP1 and PRL induce trophoblast invasion and proliferation through integrins and receptors to PRL. LIF and IL-11 production promotes blastocyst adhesion, invasion, and further placentation [1]. Thus, in the case of successful implantation, decidualizing ESCs are further segregated and differentiated from less specialized secretory phase populations.

DSCs play an important role throughout pregnancy by forming a tolerant microenvironment, the decidual membrane, to suppress the maternal immune response and prevent rejection of the allogeneic fetus. They have immunomodulatory properties against cells of innate and adaptive immunity [14]. The control of invasion is one of the important functions of the decidual membrane [36]. In addition to dESCs, the decidual tissue contains both cells of hematopoietic origin (macrophages, uNKs, and monocytes) and multicellular structures, namely, uterine glands and blood vessels, including spiral arteries that support the blood supply to the fetus [15]. B- and T-lymphocytes, mast cells, macrophages, dendritic cells, and neutrophils are involved in immunological tolerance, influencing embryo implantation (in addition to uNKs predominant in the decidual membrane) [37, 38]. To form a functionally complete placenta and ensure adequate fetal nutrition and growth, the decidual sheath must equally promote the development of invasive trophoblast and limit its over-invasion. During pregnancy, DSCs interact with immune cells of the uterine wall to form a special matrix for controlled trophoblast invasion and placenta formation [24].

ESC decidualization reduces uNK cytotoxicity through the wisp2/IGF1 signaling pathway [39] and the production of immunoregulatory factors, including PGE2 and indolamine-2,3-dioxygenase [40]. When IGF1 expression is reduced, uNK cytotoxicity becomes unregulated, resulting in increased secretory levels of proinflammatory cytokines. The decidual membrane may function as a biochemical and physical barrier that limits the penetration of invasive trophoblasts.

The decidual membrane also simultaneously produces both metalloproteinases (MMP) and their inhibitors, which counteract MMPs and limit cytotrophoblast invasion, protecting the endometrium [41]. DSCs also synthesize components of the extracellular matrix, including fibronectin, type IV collagen, laminin, and proteoglycans heparan sulfate and decorin [42, 43]. The synthesis of the EMILIN1 glycoprotein by dESCs provides an opportunity for invasive trophoblasts to migrate to EMILIN1 through haptotaxis-directed migration in which integrins are involved (in haptotaxis, the chemoattractant gradient is expressed or

bound at the surface compared with the classical chemotaxis model in which the gradient develops in the soluble fluid). Trophoblast signals, particularly PDGF-AA, trigger the chemotactic and invasive migration of ESCs [9].

REGULATION OF DECIDUALIZATION

Numerous factors regulate the decidualization of ESCs from initiation and control in the menstrual cycle, through the transition to gestational transformation, preparation for childbirth, and up to ensuring the detachment of the decidual membrane during labor. These include hormonal, paracrine, and autocrine substances; a regulatory signaling network including nuclear receptors; a plethora of transcription, transduction factors [44], epigenetic modifiers, various noncoding RNAs [45], and extracellular vesicles [46]; mechanical and cell–cell contact interactions; and the immune cellular environment. In this review, we did not describe in detail all known regulatory factors, citing references to review publications where possible. However, a failure in any link of the regulatory chain and an untimely shift in the balance of one or another factor or a deficiency of one or another component, will lead to implantation problems and pregnancy complications.

The role of extracellular vesicles and microRNAs in decidualization for embryo–maternal dESC interactions was demonstrated in embryo implantation [47]. Extracellular vesicles are membrane formations of cellular origin that deliver bioactive molecules from cells to cells [47]. The contents of the vesicles mediate intercellular communication and include numerous organic compounds such as DNA, microRNAs, proteins, and lipids [48].

Primary human ESCs secrete extracellular vesicles during decidualization. This process is controlled through the HIF2α–RAB27B signaling pathway. Decidual vesicles contain various proteins including cell signaling molecules, growth modulators, metabolic regulators, and factors that control endothelial cell expansion and remodeling. Extracellular vesicles secreted by decidual cells mediate functional connections between different cells in the uterus. The internalization of those cells that carry glucose transporter protein 1 (GLUT1) promotes glucose uptake by ESCs, supporting and promoting decidualization. In addition, the delivery of ESC-derived extracellular vesicles to endothelial cells stimulates endothelial proliferation, enhancing vascular network formation. Stromal extracellular vesicles also promote the transformation of cytotrophoblast cells into extravillous trophoblasts [46].

Thus, decreased activity of the noncoding RNA microRNA-138-5p, overexpression of G protein-coupled receptor 124 (GPR124), and over-activation of the NLRP3 inflammasome were associated with spontaneous miscarriage and were not observed in normal pregnancies. MicroRNA-138-5p and GPR124-related NLRP3 inflammasome were contained in DSC-derived extracellular vesicles, indicating their potential modulatory role in decidual programming and placentation [47, 49].

ROLE OF DECIDUAL CELLS IN EMBRYO RECOGNITION AND SELECTION

Blastocyst implantation is a critical event in human pregnancy and depends on both the physiological state of the blastocyst and the functional state of the uterine mucosa. Incomplete decidualization leads to a lack or absence of secretion of several hormonal and modulating factors and causes immune environment disorders, which is considered a critical factor in pregnancy failure. Habitual nonpregnancy includes more than two spontaneous abortions in the same couple. Evolution has endowed the endometrium with the ability to assess embryo quality: either no implantation of a poor-quality embryo occurs or the embryo is rejected soon after implantation.

The endometrium of patients with PNB has defects in embryo-quality recognition, which allows the implantation of low-quality embryos; thus, miscarriage occurs if subsequent embryonic development is impaired. The higher rate of embryo loss in patients with PUD strongly suggests endometrial dysfunction [15].

The property of the decidual membrane as a biosensor for embryo selection was described by co-culturing human embryos in vitro with dESCs [50, 51]. Embryo arrest induced a marked response characterized by the selective inhibition of key mediators of implantation and immunomodulators including IL-1b, IL-6, IL-10, IL-17, IL-18, HB-EGF, and eotaxin [50-52]. Changes in the conditioned medium obtained from the co-culture with embryos subsequently successfully implanted did not inhibit the ability of NKs in the decidual membrane to eliminate senescent and damaged DSCs in contrast to the medium taken from the co-culture with embryos that failed to implant. In human DSCs, embryos with developmental disorders induced endoplasmic reticulum stress. The above physiological mechanism is intended for the selection of low-viability embryos.

However, this response is specific only for decidual cells, and this effect was absent when co-cultured with endometrial mesenchymal stromal cells [53].

Age-related changes in the DSC secretome are associated with decreased endometrial plasticity and implantation failure [54].

In decidualization disorder leading to PNB, in addition to the aforementioned problems, the expressions of several factors such as transcription factor FOXO1A, transforming growth factor β2, prostaglandins and their receptors, IL-1, LIF, gp130 (glycoprotein 130), and Dickkopf1 are often impaired [54].

Negative effects on reproductive outcomes are most often caused by a significant increase in meiotic defects in the

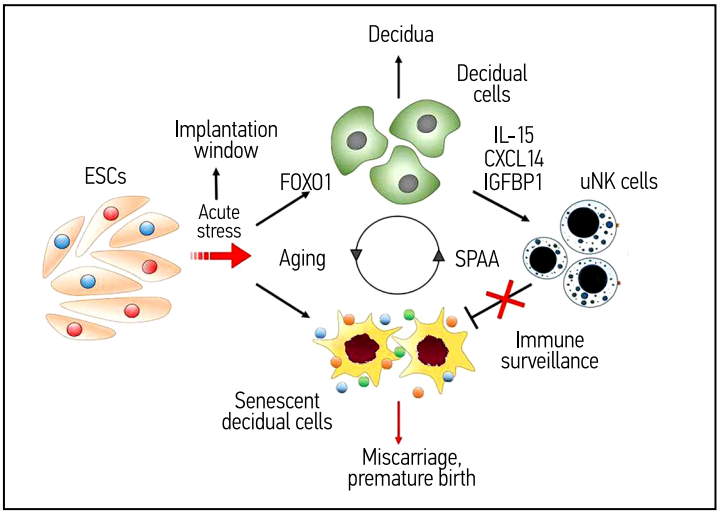

Fig. 2. The role of decidual cells in maintaining physiological pregnancy. Timely elimination of senescent decidual cells leads to the maintenance of pregnancy. SPAA — secretory phenotype associated with aging; ESCs — endometrial stromal cells; quoted from [62] with modifications.

oocyte, and most pregnancy complications, including fetal birth defects, are more common with increasing maternal age, as observed in both humans and laboratory animals. Pregnancy in old female mice is associated with impaired placental and fetal development. However, when embryos from old mothers are transferred to young recipients, the development of both the embryo and placenta largely returns to normal [55], which is consistent with the data on the presence of functionally distinct subpopulations of decidual cells [16].

Decidualization disorders can lead to morphofunctional changes in both endometrium, including endometrial mesenchymal stromal and stem cells [3, 56-58], and immune cells, including uNKs [59-61].

Decidualization can be accompanied by the appearance of a population of sendESCs [18]. High levels of sendESCs in the proliferative phase cause implantation failures [53]. Moreover, the IL-15 secreted by hESCs activates uNKs that can eliminate hESCs [18]. The above physiological mechanism is intended for the selection and choice of low-viability embryos.

Thus, progesterone-dependent anti-inflammatory decidual cells promote conception and maintenance of pregnancy, whereas proinflammatory, progesterone-independent, damaged or senescent ESCs control tissue remodeling. Accordingly, each decidual population engages innate immune cells: anti-inflammatory dESCs cooperate with uNKs to eliminate senescent ESCs, whereas senescent ESCs promote the recruitment of neutrophils and macrophages to assist with tissue destruction and repair. Meanwhile, the number of senescent ESCs that express factors responsible for the degradation and remodeling of the extracellular matrix increases toward the end of gestation, leading to the onset of labor [16]. The excess of proinflammatory sendESCs over anti-inflammatory dESCs favors the initiation of labor, and if this process occurs early, the pregnancy is terminated [16] (Fig. 2).

Notably, DSCs isolated from patients with reproductive disorders show aberrant decidualization in vitro, and they have lower PRL and/or IGFBP-1 levels than healthy women.

Clinical and experimental studies have demonstrated the role of the proinflammatory response in the genesis of miscarriage [57].

The decidual membrane plays an important role not only in the establishment and maintenance of pregnancy but also in the control of labor onset. Changes in the concentration of prostaglandins and increased proinflammatory response lead to the initiation of labor, both timely and preterm. During pregnancy, endogenous levels of prostaglandins in the decidual membrane are >150 times lower than that in the endometrium, and this is due to a decrease in prostaglandin synthesis.

Disorders of ESC differentiation are observed not only in PNB but also in preeclampsia, gestational diabetes mellitus, endometriosis, and antiphospholipid syndrome [9, 58].

Human ESCs and DSCs represent the same cells in different environments (nonpregnancy and pregnancy, respectively). Although some authors believe that DSCs arise exclusively as a result of ESC differentiation, this is debatable: decidualization does not end with the formation of the decidual sheath, as evidenced by the presence of stromal cells from the endometrium and decidual sheath in both undifferentiated (undecidualized) and decidualized states.

In addition, fibroblast-like cells derived from different tissues are accompanied by an increase in the expression of decidualization markers PRL and IGFBP1 during hormonal induction [62]. This fact confirms that cells from different organs can acquire the ability to decidualize.

Given that DSCs synthesize many growth factors and hormones, ectopic DSCs may be an important reserve

synthesizing various molecules to maintain the physiological course of pregnancy; however, this issue needs to be investigated.

CONCLUSION

In recent decades, much interest has been paid to molecular genetic mechanisms of decidualization, involving the transition from the initial stage of acute inflammation to the stage of anti-inflammatory secretion and finally to the stage of recession caused by cellular stress, which is caused by the presence of the embryo, reduced progesterone levels, aging, or a combination of all these factors. Endometrial decidualization is important not only in the establishment and maintenance of pregnancy but also in the prevention of early pregnancy losses, modulation of the immune response, control of the onset of labor, regulation of trophoblast invasion, and embryo selection. The maintenance of pregnancy requires the selective elimination of proinflammatory senescent decidual cells by activated uNKs. Therefore, preimplantation interventions or interventions will have a key effect on subsequent pregnancy outcomes. Decidualization markers may help stratify high-risk patients and increase the likelihood of successful pregnancy. Experimental animal models, the study of ESCs and DSCs in the culture combined with new technologies, and genome, transcriptome, and metabolome analyses all provide a new platform to study the mechanisms of decidualization. In-depth analysis of the information and practical application of this knowledge appear to be extremely important in predicting the course of pregnancy, treatment, and prevention of complications.

ADDITIONAL INFORMATION

Funding source. This article was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. T.A. Gusarova — the main idea and design of the article; N.V. Nizyaeva — text editing; S.A. Mikhalev — systematization of the material; N.B. Tikhonova — systematization of the material; D.A. Orgadeeva — design of the drawing; L.M. Mikhaleva, O.V. Sharapova — text editing.

REFERENCES

1. Habiba M, Heyn R, Bianchi P, et al. The development of the human uterus: morphogenesis to menarche. *Hum Reprod Update.* 2021;27(1):1–26. doi: 10.1093/humupd/dmaa036

2. Koos RD. Minireview: putting physiology back into estrogens' mechanism of action. *Endocrinology*. 2011;152(12):4481–4488. doi: 10.1210/en.2011-1449

3. Lucas ES, Vrljicak P, Muter J, et al. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window. *Commun Biol.* 2020;3(1):37. doi: 10.1038/s42003-020-0763-1

4. Rawlings TM, Makwana K, Taylor DM, et al. Modelling the impact of decidual senescence on embryo implantation in human endometrial assembloids. *Elife.* 2021;10:e69603. doi: 10.7554/eLife.69603

5. Wang W, Vilella F, Alama P, et al. Single-cell transcriptomic atlas of the human endometrium during the menstrual cycle. *Nat Med.* 2020;26(10):1644–1653. doi: 10.1038/s41591-020-1040-z

6. Wetendorf M, DeMayo FJ. The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network. *Mol Cell Endocrinol*. 2012;357(1-2): 108–118. doi: 10.1016/j.mce.2011.10.028

7. Maruyama T, Yoshimura Y. Molecular and cellular mechanisms for differentiation and regeneration of the uterine endometrium. *Endocr J*. 2008;55(5):795–810. doi: 10.1507/endocrj.k08e-067

8. Bhurke AS, Bagchi IC, Bagchi MK. Progesterone-regulated endometrial factors controlling implantation. *Am J Reprod Immunol*. 2016;75(3):237–245. doi: 10.1111/aji.12473

9. Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. *Endocr Rev.* 2014;35(6):851–905. doi: 10.1210/er.2014-1045

10. Erkenbrack EM, Maziarz JD, Griffith OW, et al. The mammalian decidual cell evolved from a cellular stress response. *PLoS Biol.* 2018;16(8):e2005594. doi: 10.1371/journal.pbio.2005594

11. Valdes CT, Schutt A, Simon C. Implantation failure of endometrial origin: it is not pathology, but our failure to synchronize the developing embryo with a receptive endometrium. *Fertil Steril.* 2017;108(1):15–18. doi: 10.1016/j.fertnstert.2017.05.033

12. Franasiak JM, Ruiz-Alonso M, Scott RT, Simón C. Both slowly developing embryos and a variable pace of luteal endometrial progression may conspire to prevent normal birth in spite of a capable embryo. *Fertil Steril*. 2016;105(4):861–866. doi: 10.1016/j.fertnstert.2016.02.030

13. Kajihara T, Tanaka K, Oguro T, et al. Androgens modulate the morphological characteristics of human endometrial stromal cells decidualized in vitro. *Reprod Sci*. 2014;21(3):372–380. doi: 10.1177/1933719113497280

14. Wu HM, Chen LH, Hsu LT, Lai CH. Immune tolerance of embryo implantation and pregnancy: the role of human decidual stromal cell- and embryonic-derived extracellular vesicles. *Int J Mol Sci*. 2022;23(21):13382. doi: 10.3390/ijms232113382

15. Vinketova K, Mourdjeva M, Oreshkova T. Human decidual stromal cells as a component of the implantation niche and a modulator of maternal immunity. *J Pregnancy*. 2016;2016:8689436. doi: 10.1155/2016/8689436

16. Muter J, Kong CS, Brosens JJ. The role of decidual subpopulations in implantation, menstruation and miscarriage. *Front Reprod Health*. 2021;3:804921. doi: 10.3389/frph.2021.804921

17. Christian M, Zhang X, Schneider-Merck T, et al. Cyclic AMP-induced forkhead transcription factor, FKHR, cooperates with CCAAT/

enhancer-binding protein beta in differentiating human endometrial stromal cells. *J Biol Chem*. 2002;277(23):20825–20832. doi: 10.1074/jbc.M201018200
18. Brighton PJ, Maruyama Y, Fishwick K, et al. Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium. *Elife*. 2017;6:e31274. doi: 10.7554/eLife.31274
19. Al-Sabbagh M, Fusi L, Higham J, et al. NADPH oxidase-derived reactive oxygen species mediate decidualization of human endometrial stromal cells in response to cyclic AMP signaling. *Endocrinology*. 2011;152(2):730–740. doi: 10.1210/en.2010-0899
20. Salker MS, Nautiyal J, Steel JH, et al. Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss. *PLoS One*. 2012;7(12):e52252. doi: 10.1371/journal.pone.0052252
21. Vrljicak P, Lucas ES, Lansdowne L, et al. Analysis of chromatin accessibility in decidualizing human endometrial stromal cells. *FASEB J*. 2018;32(5):2467–2477. doi: 10.1096/fj.201701098R
22. Grimaldi G, Christian M, Quenby S, Brosens JJ. Expression of epigenetic effectors in decidualizing human endometrial stromal cells. *Mol Hum Reprod*. 2012;18(9):451–438. doi: 10.1093/molehr/gas020
23. Leitao B, Jones MC, Fusi L, et al. Silencing of the JNK pathway maintains progesterone receptor activity in decidualizing human endometrial stromal cells exposed to oxidative stress signals. *FASEB J*. 2010; 24(5):1541–1551. doi: 10.1096/fj.09-149153
24. Aplin JD, Myers JE, Timms K, Westwood M. Tracking placental development in health and disease. *Nat Rev Endocrinol*. 2020;16(9):479–494. doi: 10.1038/s41574-020-0372-6
25. Marinić M, Mika K, Chigurupati S, Lynch VJ. Evolutionary transcriptomics implicates HAND2 in the origins of implantation and regulation of gestation length. *Elife*. 2021;10:e61257. doi: 10.7554/eLife.61257
26. Nancy P, Tagliani E, Tay CS, et al. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. *Science*. 2012;336(6086):1317–1321. doi: 10.1126/science.1220030
27. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular senescence: defining a path forward. *Cell*. 2019;179(4):813–827. doi: 10.1016/j.cell.2019.10.005
28. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. *Genes Dev*. 2020;34(23-24):1565–1576. doi: 10.1101/gad.343129.120
29. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol*. 2014;15(7):482–496. doi: 10.1038/nrm3823
30. Van Deursen JM. The role of senescent cells in ageing. *Nature*. 2014;509(7501):439–446. doi: 10.1038/nature13193
31. Owusu-Akyaw A, Krishnamoorthy K, Goldsmith LT, Morelli SS. The role of mesenchymal-epithelial transition in endometrial function. *Hum Reprod Update*. 2019;25(1):114–133. doi: 10.1093/humupd/dmy035
32. Salamonsen LA, Hutchison JC, Gargett CE. Cyclical endometrial repair and regeneration. *Development*. 2021;148(17):dev199577. doi: 10.1242/dev.199577
33. Lagnado A, Leslie J, Ruchaud-Sparagano MH, et al. Neutrophils induce paracrine telomere dysfunction and senescence in ROS-dependent manner. *EMBO J*. 2021;40(9):e106048. doi: 10.15252/embj.2020106048
34. Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal–fetal interface in humans. *Nature*. 2018;563(7731):347–353. doi: 10.1038/s41586-018-0698-6
35. Murata H, Tanaka S, Okada H. The regulators of human endometrial stromal cell decidualization. *Biomolecules*. 2022;12(9):1275. doi: 10.3390/biom12091275
36. Murata H, Tanaka S, Okada H. Immune tolerance of the human decidua. *J Clin Med*. 2021;10(2):351. doi: 10.3390/jcm10020351
37. Ticconi C, Pietropolli A, Di Simone N, et al. Endometrial immune dysfunction in recurrent pregnancy loss. *Int J Mol Sci*. 2019;20(21):5332. doi: 10.3390/ijms20215332
38. Lu H, Yang HL, Zhou WJ. Rapamycin prevents spontaneous abortion by triggering decidual stromal cell autophagy-mediated NK cell residence. *Autophagy*. 2021;17(9):2511–2527. doi: 10.1080/15548627.2020.1833515
39. Croxatto D, Vacca P, Canegallo F. Stromal cells from human decidua exert a strong inhibitory effect on NK cell function and dendritic cell differentiation. *PLoS One*. 2014;9(2):e89006. doi: 10.1371/journal.pone.0089006
40. Hisamatsu Y, Murata H, Tsubokura H, et al. Matrix metalloproteinases in human decidualized endometrial stromal cells. *Curr Issues Mol Biol*. 2021;43(3):2111–2123. doi: 10.3390/cimb43030146
41. Okada H, Tsuzuki T, Murata H. Decidualization of the human endometrium. *Reprod Med Biol*. 2018;17(3):220–227. doi: 10.1002/rmb2.12088
42. Halari CD, Nandi P, Jeyarajah MJ, et al. Decorin production by the human decidua: role in decidual cell maturation. *Mol Hum Reprod*. 2020;26(10):784–796. doi: 10.1093/molehr/gaaa058
43. Sharma S, Godbole G, Modi D. Decidual control of trophoblast invasion. *Am J Reprod Immunol*. 2016;75(3):341–350. doi: 10.1111/aji.12466
44. Liu H, Huang X, Mor G, Liao A. Epigenetic modifications working in the decidualization and endometrial receptivity. *Cell Mol Life Sci*. 2020;77:2091–2101. doi: 10.1007/s00018-019-03395-9
45. Ma Q, Beal JR, Bhurke A, et al. Extracellular vesicles secreted by human uterine stromal cells regulate decidualization, angiogenesis, and trophoblast differentiation. *Proc Natl Acad Sci U S A*. 2022;119(38):e2200252119. doi: 10.1073/pnas.2200252119
46. Wu HM, Lo TC, Tsai CL, et al. Extracellular vesicle-associated microRNA-138-5p regulates embryo implantation and early pregnancy by adjusting GPR124. *Pharmaceutics*. 2022;14(6):1172. doi: 10.3390/pharmaceutics14061172
47. Vyas N, Dhawan J. Exosomes: mobile platforms for targeted and synergistic signaling across cell boundaries. *Cell Mol Life Sci*. 2017;74(9):1567–1576. doi: 10.1007/s00018-016-2413-9
48. Tabeeva GI, Dumanovskaja MR, Asaturova AV, et al. Features of regulation and function of inflammasomes in inflammatory diseases of the female reproductive system. *Clinical and Experimental Morphology*. 2020;9(3):12–20. (In Russ). doi: 10.31088/CEM2020.9.3.12-20
49. Teklenburg G, Salker M, Molokhia M, et al. Natural selection of human embryos: decidualizing endometrial stromal cells serve as sensors of embryo quality upon implantation. *PLoS One*. 2010;5(4):e10258. doi: 10.1371/journal.pone.0010258
50. Bogdanova IM, Boltovskaja MN. Natural selection of human embryos: immune mechanisms of quality controi. *Immunologiya*. 2019;40(1):68–73. (In Russ). doi: 10.24411/0206-4952-2019-11008
51. Kong CS, Ordoñez AA, Turner S. Embryo biosensing by uterine natural killer cells determines endometrial fate decisions at implantation. *FASEB J*. 2021;35(4):e21336. doi: 10.1096/fj.202002217R

52. Deryabin PI, Borodkina AV. Stromal cell senescence contributes to impaired endometrial decidualization and defective interaction with trophoblast cells. *Hum Reprod*. 2022;37(7):1505–1524. doi: 10.1093/humrep/deac112
53. Tapia-Pizarro A, Figueroa P, Brito J, et al. Endometrial gene expression reveals compromised progesterone signaling in women refractory to embryo implantation. *Reprod Biol Endocrinol*. 2014;12:92. doi: 10.1186/1477-7827-12-92
54. Woods L, Perez-Garcia V, Kieckbusch J, et al. Decidualisation and placentation defects are a major cause of age-related reproductive decline. *Nat Commun*. 2017;8(1):352. doi: 10.1038/s41467-017-00308-x
55. Lucas ES, Dyer NP, Murakami K, et al. Loss of endometrial plasticity in recurrent pregnancy loss. *Stem Cells*. 2016;34(2):346–356. doi: 10.1002/stem.2222
56. Tabeeva GI, Dumanovskaja MR, Bogdanova IM, et al. Morphofunctional features of the uteroplacental unit and mouse embryo in the early stages of experimental miscarriage. *Clinical and Experimental Morphology*. 2020;9(3):50–60. (In Russ). doi: 10.31088/CEM2020.9.3.50-60
57. Garrido-Gomez T, Dominguez F, Quiñonero A, et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology. *Proc Natl Acad Sci U S A*. 2017;114(40):E8468–E8477. doi: 10.1073/pnas.1706546114
58. Bogdanova IM, Fokina TV, Stepanova II, et al. The role of the endometrial decidualization in the establishment and development of pregnancy. *Clinical and Experimental Morphology*. 2018;7(4):50–60. (In Russ). doi: 10.31088/2226-5988-2018-28-4-50-60.
59. Grebenkina PV, Mikhailova VA, Oshkolova AA, et al. Decidual natural killer cells and trophoblast cells: cellular, humoral and molecular mechanisms of interaction. *Medical Immunology (Russia)*. 2022;24(6):1085–1108. (In Russ). doi: 10.15789/1563-0625-DNK-2540
60. Milovanov AP, Ozhiganova IN. Embryochorionic insufficiency: anatomic and physiologic prerequisites, rationale, definitions and pathogenetic mechanisms. *Arkhiv Patologii*. 2014;76(3):4–8. (In Russ.)
61. Smits L, Bockstal MV, Frezin J. Deciduosis of the appendix: a rare cause of acute abdomen during pregnancy (a case report). *Pan Afr Med J*. 2020;37:316. doi: 10.11604/pamj.2020.37.316.26728
62. Kong C-S, Ordoñez AA, Turner S, et al. Involvement of uterine natural killer cells in the natural selection of human embryos at implantation. *BioRxiv*. 2020. doi: 10.1101/2020.08.14.251033

СПИСОК ЛИТЕРАТУРЫ

1. Habiba M., Heyn R., Bianchi P., et al. The development of the human uterus: morphogenesis to menarche // Hum Reprod Update. 2021. Vol. 27, N 1. P. 1–26. doi: 10.1093/humupd/dmaa036
2. Koos R.D. Minireview: putting physiology back into estrogens' mechanism of action // Endocrinology. 2011. Vol. 152, N 12. P. 4481–4488. doi: 10.1210/en.2011-1449
3. Lucas E.S., Vrljicak P., Muter J., et al. Recurrent pregnancy loss is associated with a pro-senescent decidual response during the peri-implantation window // Commun Biol. 2020. Vol. 3, N 1. P. 37. doi: 10.1038/s42003-020-0763-1
4. Rawlings T.M., Makwana K., Taylor D.M., et al. Modelling the impact of decidual senescence on embryo implantation in human endometrial assembloids // Elife. 2021. Vol. 10. P. e69603. doi: 10.7554/eLife.69603
5. Wang W., Vilella F., Alama P., et al. Single-cell transcriptomic atlas of the human endometrium during the menstrual cycle // Nat Med. 2020. Vol. 26, N 10. P. 1644–1653. doi: 10.1038/s41591-020-1040-z
6. Wetendorf M., DeMayo F.J. The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network // Mol Cell Endocrinol. 2012. Vol. 357, N 1-2. P. 108–118. doi: 10.1016/j.mce.2011.10.028
7. Maruyama T., Yoshimura Y. Molecular and cellular mechanisms for differentiation and regeneration of the uterine endometrium // Endocr J. 2008. Vol. 55, N 5. P. 795–810. doi: 10.1507/endocrj.k08e-067
8. Bhurke A.S., Bagchi I.C., Bagchi M.K. Progesterone-regulated endometrial factors controlling implantation // Am J Reprod Immunol. 2016. Vol. 75, N 3. P. 237–245. doi: 10.1111/aji.12473
9. Gellersen B., Brosens J.J. Cyclic decidualization of the human endometrium in reproductive health and failure // Endocr Rev. 2014. Vol. 35, N 6. P. 851–905. doi: 10.1210/er.2014-1045
10. Erkenbrack E.M., Maziarz J.D., Griffith O.W., et al. The mammalian decidual cell evolved from a cellular stress response // PLoS Biol. 2018. Vol. 16, N 8. P. e2005594. doi: 10.1371/journal.pbio.2005594
11. Valdes C.T., Schutt A., Simon C. Implantation failure of endometrial origin: it is not pathology, but our failure to synchronize the developing embryo with a receptive endometrium // Fertil Steril. 2017. Vol. 108, N 1. P. 15–18. doi: 10.1016/j.fertnstert.2017.05.033
12. Franasiak J.M., Ruiz-Alonso M., Scott R.T., Simón C. Both slowly developing embryos and a variable pace of luteal endometrial progression may conspire to prevent normal birth in spite of a capable embryo // Fertil Steril. 2016. Vol. 105, N 4. P. 861–866. doi: 10.1016/j.fertnstert.2016.02.030
13. Kajihara T., Tanaka K., Oguro T., et al. Androgens modulate the morphological characteristics of human endometrial stromal cells decidualized in vitro // Reprod Sci. 2014. Vol. 21, N 3. P. 372–380. doi: 10.1177/1933719113497280
14. Wu H.M., Chen L.H., Hsu L.T., Lai C.H. Immune tolerance of embryo implantation and pregnancy: the role of human decidual stromal cell- and embryonic-derived extracellular vesicles // Int J Mol Sci. 2022. Vol. 23, N 21. P. 13382. doi: 10.3390/ijms232113382
15. Vinketova K., Mourdjeva M., Oreshkova T. Human decidual stromal cells as a component of the implantation niche and a modulator of maternal immunity // J Pregnancy. 2016. Vol. 2016. P. 8689436. doi: 10.1155/2016/8689436
16. Muter J., Kong C.S., Brosens J.J. The role of decidual subpopulations in implantation, menstruation and miscarriage // Front Reprod Health. 2021. Vol. 3. P. 804921. doi: 10.3389/frph.2021.804921
17. Christian M., Zhang X., Schneider-Merck T., et al. Cyclic AMP-induced forkhead transcription factor, FKHR, cooperates with CCAAT/enhancer-binding protein beta in differentiating human endometrial stromal cells // J Biol Chem. 2002. Vol. 277, N 23. P. 20825–20832. doi: 10.1074/jbc.M201018200
18. Brighton P.J., Maruyama Y., Fishwick K., et al. Clearance of senescent decidual cells by uterine natural killer cells in cycling human endometrium // Elife. 2017. Vol. 6. P. e31274. doi: 10.7554/eLife.31274
19. Al-Sabbagh M., Fusi L., Higham J., et al. NADPH oxidase-derived reactive oxygen species mediate decidualization of human endome-

trial stromal cells in response to cyclic AMP signaling // Endocrinology. 2011. Vol. 152, N 2. P. 730–740. doi: 10.1210/en.2010-0899
20. Salker M.S., Nautiyal J., Steel J.H., et al. Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss // PLoS One. 2012. Vol. 7, N 12. P. e52252. doi: 10.1371/journal.pone.0052252
21. Vrljicak P., Lucas E.S., Lansdowne L., et al. Analysis of chromatin accessibility in decidualizing human endometrial stromal cells // FASEB J. 2018. Vol. 32, N 5. P. 2467–2477. doi: 10.1096/fj.201701098R
22. Grimaldi G., Christian M., Quenby S., Brosens J.J. Expression of epigenetic effectors in decidualizing human endometrial stromal cells // Mol Hum Reprod. 2012. Vol. 18, N 9. P. 451–458. doi: 10.1093/molehr/gas020
23. Leitao B., Jones M.C., Fusi L., et al. Silencing of the JNK pathway maintains progesterone receptor activity in decidualizing human endometrial stromal cells exposed to oxidative stress signals // FASEB J. 2010. Vol. 24, N 5. P. 1541–1551. doi: 10.1096/fj.09-149153
24. Aplin J.D., Myers J.E., Timms K., Westwood M. Tracking placental development in health and disease // Nat Rev Endocrinol. 2020. Vol. 16, N 9. P. 479–494. doi: 10.1038/s41574-020-0372-6
25. Marinić M., Mika K., Chigurupati S., Lynch V.J. Evolutionary transcriptomics implicates HAND2 in the origins of implantation and regulation of gestation length // Elife. 2021. Vol. 10. P. e61257. doi: 10.7554/eLife.61257
26. Nancy P., Tagliani E., Tay C.S., et al. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface // Science. 2012. Vol. 336, N 6086. P. 1317–1321. doi: 10.1126/science.1220030
27. Gorgoulis V., Adams P.D., Alimonti A., et al. Cellular senescence: defining a path forward // Cell. 2019. Vol. 179, N 4. P. 813–827. doi: 10.1016/j.cell.2019.10.005
28. Birch J., Gil J. Senescence and the SASP: many therapeutic avenues // Genes Dev. 2020. Vol. 34. N 23-24. P. 1565–1576. doi: 10.1101/gad.343129.120
29. Muñoz-Espín D., Serrano M. Cellular senescence: from physiology to pathology // Nat Rev Mol Cell Biol. 2014. Vol. 15, N 7. P. 482–496. doi: 10.1038/nrm3823
30. Van Deursen J.M. The role of senescent cells in ageing // Nature. 2014. Vol. 509, N 7501. P. 439–446. doi: 10.1038/nature13193
31. Owusu-Akyaw A., Krishnamoorthy K., Goldsmith L.T., Morelli S.S. The role of mesenchymal-epithelial transition in endometrial function // Hum Reprod Update. 2019. Vol. 25, N 1. P. 114–133. doi: 10.1093/humupd/dmy035
32. Salamonsen L.A., Hutchison J.C., Gargett C.E. Cyclical endometrial repair and regeneration // Development. 2021. Vol. 148, N 17. P. dev199577. doi: 10.1242/dev.199577
33. Lagnado A., Leslie J., Ruchaud-Sparagano M.H., et al. Neutrophils induce paracrine telomere dysfunction and senescence in ROS-dependent manner // EMBO J. 2021. Vol. 40, N 9. P. e106048. doi: 10.15252/embj.2020106048
34. Vento-Tormo R., Efremova M., Botting R.A., et al. Single-cell reconstruction of the early maternal–fetal interface in humans // Nature. 2018. Vol. 563, N 7731. P. 347–353. doi: 10.1038/s41586-018-0698-6
35. Murata H., Tanaka S., Okada H. The regulators of human endometrial stromal cell decidualization // Biomolecules. 2022. Vol. 12, N 9. P. 1275. doi: 10.3390/biom12091275
36. Murata H., Tanaka S., Okada H. Immune tolerance of the human decidua // J Clin Med. 2021. Vol. 10, N 2. P. 351. doi: 10.3390/jcm10020351
37. Ticconi C., Pietropolli A., Di Simone N., et al. Endometrial immune dysfunction in recurrent pregnancy loss // Int J Mol Sci. 2019. Vol. 20, N 21. P. 5332. doi: 10.3390/ijms20215332
38. Lu H., Yang H.L., Zhou W.J. Rapamycin prevents spontaneous abortion by triggering decidual stromal cell autophagy-mediated NK cell residence // Autophagy. 2021. Vol. 17, N 9. P. 2511–2527. doi: 10.1080/15548627.2020.1833515
39. Croxatto D., Vacca P., Canegallo F. Stromal cells from human decidua exert a strong inhibitory effect on NK cell function and dendritic cell differentiation // PLoS One. 2014. Vol. 9, N 2. P. e89006. doi: 10.1371/journal.pone.0089006
40. Hisamatsu Y., Murata H., Tsubokura H., et al. Metalloproteinases in human decidualized endometrial stromal cells // Curr Issues Mol Biol. 2021. Vol. 43, N 3. P. 2111–2123. doi: 10.3390/cimb43030146
41. Okada H., Tsuzuki T., Murata H. Decidualization of the human endometrium // Reprod Med Biol. 2018. Vol. 17, N 3. P. 220–227. doi: 10.1002/rmb2.12088
42. Halari C.D., Nandi P., Jeyarajah M.J., et al. Decorin production by the human decidua: role in decidual cell maturation // Mol Hum Reprod. 2020. Vol. 26, N 10. P. 784–796. doi: 10.1093/molehr/gaaa058
43. Sharma S., Godbole G., Modi D. Decidual control of trophoblast invasion // Am J Reprod Immunol. 2016. Vol. 75, N 3. P. 341–350. doi: 10.1111/aji.12466
44. Liu H., Huang X., Mor G., Liao A. Epigenetic modifications working in the decidualization and endometrial receptivity // Cell Mol Life Sci. 2020. Vol. 77. P. 2091–2101. doi: 10.1007/s00018-019-03395-9
45. Ma Q., Beal J.R., Bhurke A., et al. Extracellular vesicles secreted by human uterine stromal cells regulate decidualization, angiogenesis, and trophoblast differentiation // Proc Natl Acad Sci U S A. 2022. Vol. 119, N 38. P. e2200252119. doi: 10.1073/pnas.2200252119
46. Wu H.M., Lo T.C., Tsai C.L., et al. Extracellular vesicle-associated microRNA-138-5p regulates embryo implantation and early pregnancy by adjusting GPR124 // Pharmaceutics. 2022. Vol. 14, N 6. P. 1172. doi: 10.3390/pharmaceutics14061172
47. Vyas N., Dhawan J. Exosomes: mobile platforms for targeted and synergistic signaling across cell boundaries // Cell Mol Life Sci. 2017. Vol. 74, N 9. P. 1567–1576. doi: 10.1007/s00018-016-2413-9
48. Табеева Г.И., Думановская М.Р., Асатурова А.В., и др. Особенности регуляции и функции инфламмасом при воспалительных заболеваниях органов женской репродуктивной системы // Клиническая и экспериментальная морфология. 2020. Т. 9, № 3. С. 12–20. doi: 10.31088/CEM2020.9.3.12-20
49. Teklenburg G., Salker M., Molokhia M., et al. Natural selection of human embryos: decidualizing endometrial stromal cells serve as sensors of embryo quality upon implantation // PLoS One. 2010. Vol. 5, N 4. P. e10258. doi: 10.1371/journal.pone.0010258
50. Богданова И.М., Болтовская М.Н. Естественная селекция эмбрионов человека: иммунные механизмы контроля качества // Иммунология. 2019. Т. 40, № 1. С. 68–73. doi: 10.24411/0206-4952-2019-11008

51. Kong C.S., Ordoñez A.A., Turner S. Embryo biosensing by uterine natural killer cells determines endometrial fate decisions at implantation // FASEB J. 2021. Vol. 35, N 4. P. e21336. doi: 10.1096/fj.202002217R
52. Deryabin P.I., Borodkina A.V. Stromal cell senescence contributes to impaired endometrial decidualization and defective interaction with trophoblast cells // Hum Reprod. 2022. Vol. 37, N 7. P. 1505–1524. doi: 10.1093/humrep/deac112
53. Tapia-Pizarro A., Figueroa P., Brito J., et al. Endometrial gene expression reveals compromised progesterone signaling in women refractory to embryo implantation // Reprod Biol Endocrinol. 2014. Vol. 12. P. 92. doi: 10.1186/1477-7827-12-92
54. Woods L., Perez-Garcia V., Kieckbusch J., et al. Decidualisation and placentation defects are a major cause of age-related reproductive decline // Nat Commun. 2017. Vol. 8, N 1. P. 352. doi: 10.1038/s41467-017-00308-x
55. Lucas E.S., Dyer N.P., Murakami K., et al. Loss of endometrial plasticity in recurrent pregnancy loss // Stem Cells. 2016. Vol. 34, N 2. P. 346–356. doi: 10.1002/stem.2222
56. Табеева Г.И., Думановская М.Р., Богданова И.М. Особенности морфофункционального состояния маточно-плацентарной единицы и эмбриона мыши на ранних сроках экспериментального невынашивания беременности // Клиническая и экспериментальная морфология. 2020. Т. 9, № 3. С. 50–60. doi: 10.31088/CEM2020.9.3.50-60
57. Garrido-Gomez T., Dominguez F., Quiñonero A., et al. Defective decidualization during and after severe preeclampsia reveals a possible maternal contribution to the etiology // Proc Natl Acad Sci U S A. 2017. Vol. 114, N 40. P. E8468–E8477. doi: 10.1073/pnas.1706546114
58. Богданова И.М., Фокина Т.В., Степанова И.И. Роль децидуализации эндометрия в наступлении и развитии беременности // Клиническая и экспериментальная морфология. 2018. Т. 28, № 4. С. 50–60. doi: 10.31088/2226-5988-2018-28-4-50-60
59. Гребенкина П.В., Михайлова В.А., Ошколова А.А., и др. Децидуальные естественные киллеры и клетки трофобласта: клеточные, гуморальные и молекулярные механизмы взаимодействия // Медицинская иммунология. 2022. Т. 24, № 6. С. 1085–1108. doi: 10.15789/1563-0625-DNK-2540
60. Милованов А.П., Ожиганова И.Н. Эмбриохориальная недостаточность: анатомофизиологические предпосылки, обоснование, дефиниции и патогенетические механизмы // Архив патологии. 2014. Т. 76, № 3. С. 4–8.
61. Smits L., Bockstal M.V., Frezin J. Deciduosis of the appendix: a rare cause of acute abdomen during pregnancy (a case report) // Pan Afr Med J. 2020. Vol. 37. P. 316. doi: 10.11604/pamj.2020.37.316.26728
62. Kong C.-S., Orbonez A.A., Turner S., et al. Involvement of uterine natural killer cells in the natural selection of human embryos at implantation // BioRxiv. 2020. doi: 10.1101/2020.08.14.251033

AUTHORS' INFO

*** Natalia V. Nizyaeva,** MD, Dr. Sci. (Med.);
address: 61 Vavilova street, 117292 Moscow, Russian Federation;
ORCID: 0000-0001-5592-5690;
eLibrary SPIN: 9893-2630;
e-mail: niziaeva@gmail.com

Tatiana A. Gusarova, MD;
ORCID: 0000-0003-1827-2197;
eLibrary SPIN: 7743-0296;
e-mail: tatianagusarova73@mail.ru

Sergej A. Mikhalev, MD, Cand. Sci. (Med.);
ORCID: 0000-0002-4822-0956;
eLibrary SPIN: 8105-7908;
e-mail: mikhalev@me.com

Natalia B. Tikhonova, Cand. Sci. (Biol.)
ORCID: 0000-0001-5437-6933;
eLibrary SPIN: 1758-0245;
e-mail: nb-ti@hotmail.com

Darya A. Orgadeeva;
ORCID: 0009-0006-7715-0113;
eLibrary SPIN: 2057-7745;
e-mail: orgadeevada@gmail.com

Liudmila M. Mikhaleva, MD, Dr. Sci. (Med.), Associate Member of Russian Academy of Sciences;
ORCID: 0000-0003-2052-914X;
eLibrary SPIN: 2086-7513;
e-mail: mikhalevalm@yandex.ru

ОБ АВТОРАХ

*** Низяева Наталья Викторовна,** д.м.н.;
адрес: Российская Федерация, 117292, Москва, ул. Вавилова, д. 61;
ORCID: 0000-0001-5592-5690;
eLibrary SPIN: 9893-2630;
e-mail: niziaeva@gmail.com

Гусарова Татьяна Анатольевна;
ORCID: 0000-0003-1827-2197;
eLibrary SPIN: 7743-0296;
e-mail: tatianagusarova73@mail.ru

Михалёв Сергей Александрович, к.м.н.;
ORCID: 0000-0002-4822-0956;
eLibrary SPIN: 8105-7908;
e-mail: mikhalev@me.com

Тихонова Наталия Борисовна, к.б.н.;
ORCID: 0000-0001-5437-6933;
eLibrary SPIN: 1758-0245;
e-mail: nb-ti@hotmail.com

Оргадеева Дарья Александровна;
ORCID: 0009-0006-7715-0113;
eLibrary SPIN: 2057-7745;
e-mail: orgadeevada@gmail.com

Михалёва Людмила Михайловна, д.м.н.,
член-корреспондент РАН;
ORCID: 0000-0003-2052-914X;
eLibrary SPIN: 2086-7513;
e-mail: mikhalevalm@yandex.ru

Olga V. Sharapova, MD, Dr. Sci. (Med.), Professor;
ORCID: 0000-0003-0384-1705;
eLibrary SPIN: 5786-6566;
e-mail: sharapova-olga59@mail.ru

Шарапова Ольга Викторовна, д.м.н., профессор;
ORCID: 0000-0003-0384-1705;
eLibrary SPIN: 5786-6566;
e-mail: sharapova-olga59@mail.ru

* Автор, ответственный за переписку / Corresponding author