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Role of molecular signaling pathways in the pathogenesis of adenomyosis

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The prevalence of genital endometriosis and adenomyosis, in particular, is tending to increase. The lack of a complete understanding of the pathogenetic mechanisms and multifactorial causes of adenomyosis, the low effectiveness of existing drug therapy, and the importance of preserving reproductive function make it necessary to further study the pathogenesis of the disease, search for new non-invasive highly informative diagnostic methods and develop a new strategy for pathogenically based drug therapy. The review presents current data on the role of signaling pathways in the pathogenesis of the development of adenomyosis based on domestic and foreign literature sources retrieved from the electronic databases PubMed, CyberLeninka, and Google Scholar in the period from 1999 to 2020. Considerable emphasis is placed on the discussion of the research results in recent years. Based on the analysis, the role of transforming growth factor β (TGFβ), vascular endothelial growth factor (VEGF), dual-specificity protein phosphatase (PTEN), Notch receptors, and eukaryotic translation initiation factors (eIFs) in the signaling of adenomyosis is presented. Further advanced study of signaling pathways in the pathogenesis of adenomyosis will allow developing highly specific and highly sensitive markers for non-invasive diagnostics, as well as new directions for drug treatment of the disease.

Keywords: adenomyosis; genital endometriosis; adenomyosis signaling pathways; Notch1/Numb/Snail signaling; Snail; Slug; VEGF; PTEN; E_2/Slug/VEGF; TGF-β1/Smad3.

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Роль молекулярных сигнальных путей в патогенезе аденомиоза

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Наблюдается тенденция к увеличению распространенности и генитального эндометриоза, и аденомиоза. Отсутствие достаточного понимания патогенетических механизмов и многофакторных причин развития аденомиоза, низкая эффективность медикаментозной терапии, важность сохранения репродуктивной функции обусловливают необходимость дальнейшего изучения патогенеза заболевания, поиска новых неинвазивных высокоинформативных методов диагностики и разработки новой стратегии патогенетически обоснованной медикаментозной терапии. В обзоре представлены современные данные о роли сигнальных путей в патогенезе развития аденомиоза на основании отечественных и зарубежных литературных источников, размещенных в электронных базах данных PubMed, CyberLeninka, Google Scholar в период с 1999 по 2020 г. Сделан акцент на обсуждении результатов исследований последних лет. На основании анализа представлена роль трансформирующего фактора роста β (TGFβ), фактора роста эндотелия сосудов (VEGF), фосфатазы с двойной субстратной специфичностью (PTEN), трансмембранных рецепторных белков Notch, эукариотических факторов инициации трансляции (eIFs) в сигнальных путях развития аденомиоза. Дальнейшее углубленное изучение сигнальных путей в патогенезе аденомиоза позволит разработать высокоспецифические и высокочувствительные маркеры неинвазивной диагностики и новые направления медикаментозного лечения заболевания.

Ключевые слова: аденомиоз; генитальный эндометриоз; сигнальные пути аденомиоза; Notch1/Numb/Snail signaling; Snail; Slug; VEGF; PTEN; E_2/Slug/VEGF; TGF-β1/Smad3.

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Adenomyosis is one of the common gynecological diseases. The frequent combination of external genital endometriosis (EGE) and adenomyosis indicates the commonality of their pathological processes [1]. However, various theories of occurrence and the discovery of new pathogenetic mechanisms have made adenomyosis a separate nosological form of endometrioid disease [2–4]. Adenomyosis is characterized by invasion of functional or ectopic endometrial and stromal glands into the myometrium with or without local hyperplasia [5]. Based on the current understanding of wound healing, a new hypothesis was proposed to explain the pathogenesis of adenomyosis, i.e., endometrial–myometrial rupture caused by iatrogenic trauma. According to this hypothesis, not only hypoxia at the injury site is important in the development of adenomyosis but also the epithelial–mesenchymal transition (EMT), improved survival, and proliferation of endometrial cells that are scattered and displaced by iatrogenic procedures [6]. Although adenomyosis is benign, it has several properties similar to those of malignant tumors, including adhesion, invasion, and implantation [7].

EMT is crucial in the pathogenesis of various proliferative diseases, such as adenomyosis, EGE, uterine fibroids, and oncological processes, particularly the invasion and metastasis of breast cancer [8, 9]. EMT is a fundamental component of embryonic cell development, physiological processes of stem cell maturation, and wound healing [10, 11]. In the EMT process, the apical–basal polarity of epithelial cells and intercellular contacts disappear, the expression of epithelial markers is significantly reduced, and the expression of mesenchymal markers increases; as a result, the cells transition into mobile mesenchymal ones [5, 10]. By acquiring the ability to migrate and invade, cells become resistant to apoptosis and increased the secretion of degradation enzymes that lyse the surrounding extracellular matrix [12]. During embryonic development, these characteristic changes are called "EMT type 1," which nearly mesenchymal cellular phenotype and changes are short-term. Changes during inflammation and fibrosis are called "EMT type 2," are long term, and often lead to pathological consequences. As regards oncogenesis, "EMT type 3" is distinguished as an aggressive, uncontrolled phenomenon characterized by abnormal expression of oncogenes and absence of tumor suppressor genes, which leads to an increase in the invasive and migratory properties of cells and further EMT activation [13]. After the loss of intercellular contacts, the mesenchymal tumor cell can penetrate the intercellular matrix and basement membrane into the blood capillaries and metastasize to other organs and tissues. Many enzymes are involved in the EMT process, including matrix metalloproteinases (MMP-1, MMP-2, and MMP-9), which activate heterotopic invasion in endometriosis and adenomyosis [12, 14] and the penetration of tumor cells into the bloodstream in the case of oncological diseases [13, 15]. More than 20 types of MMPs are known and play key roles in various stages of collagen and elastin degradation [16].

An increase in the production of MMP-2 and MMP-9 in endometriosis leads to an increase in the ability of endometrioid cells to invade and is an important element in disease pathogenesis [16].

The molecular process in EMT is plastic and can undergo regression to reverse back to the epithelial phenotype. The reverse process is called the mesenchymal–epithelial transition [16].

Among the molecular factors involved in EMT, inducers, regulators, and effectors can conditionally be distinguished [15, 17, 18]. Inducers are growth factors and receptors that initially signal mesenchymal changes, namely, hepatocyte growth factor (HGF) and fibroblast growth factor (FGF), transforming growth factor-β (TGFβ), and platelet-derived growth factor (PDGF), supporting their constant proliferation and cell differentiation. Growth factors induce EMT with subsequent invasion and migration. Regulators are represented by transcription factors, and effectors are responsible for the final shape of the cell and its ability to invade [17].

Adhesion contacts between cells are homodimeric intercellular junctions linked by classical E- and N-cadherins. EMT is mainly triggered by a decrease in the expression level of the epithelial marker E-cadherin [19, 20]. The process, called cadherin switch, involves a progressive loss of E-cadherin expression and its replacement by mesenchymal-type cadherins such as N-cadherin and cadherin-11 [20]. The decrease in the level of E-cadherin is directly or indirectly affected by several transcription factors, consisting of three families, namely, Snail, ZEB, and Twist. N-cadherin, as a member of the superfamily of integral membrane glycoproteins that regulate cell adhesion and motility, plays an important role in EMT. The transition from the expression of E-cadherin to the expression of N-cadherin is often noted in many aggressive cancers [21]. N-cadherin stimulates the activation of the mesenchymal transcription factors Snail and Slug, causing the modulation of the fibroblast growth factor receptor (FGFR), leading to increased invasion, proliferation, and metastasis of tumor cells.

EMT induction depends on numerous signaling pathways, such as Notch1/Numb/Snail [5], TGFβ/Smad [8, 9, 22], eIF3 [9], and E_2/Slug/vascular endothelial growth factor (VEGF) [23]. These cascades regulate the inflammatory response, fibrosis, angiogenesis, and proliferative processes in diseases and, thus, may be promising pharmacodynamic treatment targets.

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Mesenchymal transcription factors Snail and Slug

The Snail transcription factor, first discovered in Drosophila as a Zinc finger transcription factor, is a key regulator of EMT [43]. Snail and Slug are associated with tumor cell migration, invasion, and metastasis. Snail is involved in the regulation of EMT during the development of various oncological processes, including breast and ovarian cancer [14, 25]. Unlike Snail, Slug is also involved in EMT-associated wound healing, belongs to the Zinc finger family of transcription factors, and plays an important role in EMT during embryonic development and metastasis of various cancers by inhibiting E-cadherin [26]. Another mechanism of tumor development is the activation of inflammatory mediators, which in chronic inflammation increases the expression of Snail and ZEB proteins, which in turn contributes to the development of fibrosis, "tumor" EMT, and subsequent metastasis [24].

In adenomyosis, the expressions of Snail and Slug in the endometrium are increased ($p < 0.01$) both in the proliferative and secretory phases of the menstrual cycle, compared with indicators in the endometrium of healthy women [5, 9].

Slug and Snail are involved in the EMT of cancer cells; in particular, their high expression was revealed during the development of mammary tumors [27, 28]. In addition, the susceptibility to tumor treatment depends on the activities of Snail and Slug. Thus, Haslehurst et al. revealed that in ovarian carcinoma cells, high expressions of Snail and Slug caused resistance to cisplatin [29]. Inhibition of their expression led to a significant decrease in tumor activity and metastatic behavior of squamous cell carcinoma cells, which can be used in developing methods for treating oncological processes [30].

TGFβ and other transcription factors of the EMT

TGFβ is a cytokine protein that controls proliferation and cell differentiation in cells. TGFβ is a well-studied and potent EMT inducer [9, 15, 22]. It has three isoforms, namely, TGFβ1, TGFβ2, and TGFβ3. The TGFβ1 family represents a part of the superfamily of proteins known as the TGF superfamily, which includes inhibins, activins, anti-Müllerian hormone, bone morphogenetic protein, and decapentaplegic protein factor. In normal epithelial cells and early stages of oncogenesis, TGFβ can be induced by external signals and acts as an antiproliferative factor. In adenomyosis and EGE, platelet TGFβ1 activates the TGFβ1/Smad3 signaling pathway, which triggers EMT, smooth muscle metaplasia, transformation of fibroblast to myofibroblast, and development of fibrosis [9]. In the analysis of the expression levels of TGFβ1 and p-Smad3 proteins in stromal cells, these parameters were significantly increased in the endometrium with adenomyosis compared with the endometrium of healthy women [31]. Cai et al. [9] revealed a significant increase in the expression of TGFβ1 in the endometrium of women with adenomyosis compared with its expression level in healthy women.

For other hyperplastic processes, increased levels of Smad3 and Co-Smad and numbers of TGFβ-R1 and TGFβ-R2 receptors were also detected in uterine fibroids cells, which partly determine the tendency toward aggressive growth [32]. TGFβ isoforms are released into the extracellular matrix of myoma, after which they are activated by tissue proteases. Thus, TGFβ becomes an active ligand, binds to one of its receptors (TGFβ-R1, TGFβ-R2, or TGFβ-R3), and triggers the EMT cascade mechanism. TGFβ1 and TGFβ2 are equally found in the cells of both myoma and intact myometrium. Lee and Nowak revealed that the concentration of TGFβ3 mRNA is five times higher in leiomyoma cells than in healthy myometrium cells [33]. Moreover, a study demonstrated the refractoriness of myoma to the potential antiproliferative effects of TGFβ1 and TGFβ3 and concluded that the TGFβ signaling pathways in leiomyoma cells are disrupted. In addition, TGFβ3 induces the secretion of fibronectin by tumor cells and thus enhances fibrotic processes in myomatous nodules. The profibrotic effect of TGFβ3 was confirmed by an increase in the expression of type I and III collagens in myoma cells as a result of the action of this growth factor [34]. The validity of considering TGFβ3 as a potential subject for pharmacological action is confirmed in a series of experimental works. Lee and Nowak [32] showed that the use of antibodies that neutralize TGFβ led to a decrease in the amount of type I and III collagen mRNA in myoma cells, which reduced their potential for tumor growth and fibrosis. Another study noted that in vivo blockade of TGFβ signal transmission by the type I ALK5/TGFβR kinase inhibitor (SB525334) in Eker rats is associated with a decrease in the size and number of myomatous nodules. However, SB-525334 appeared to be a mitogenic and antiapoptotic factor for renal epithelial cells and enhanced the growth of renal cell carcinoma in rats [35].

TGFβ-dependent signal transmission is a prototype EMT inducer in various oncological diseases [36]. Subsequently, cancer cells can increase the amount of secreted TGFβ, affecting the surrounding cells. Thus, the induction of mesenchymal changes in cells triggers "tumor" EMT. As the tumor grows, angiogenic mediators are released, including VEGF, IGF, TGFβ, HGF, and FGF [37]. Tumor-induced inflammation leads to the emergence of immune cells that secrete cytokines (such as tumor necrosis factor-α, interferon-γ, interleukin-6, and interleukin-1β).

Transcription factor VEGF

VEGF is considered a signaling protein, a mitogen, which is the main promoter of angiogenesis and vasculogenesis in pathological and physiological conditions and a highly

specific mitogen for endothelial cells [38]. Several different members of this family are known, with VEGFA as the most important member. Placental growth factors, which are the proteins VEGFB, VEGFC, and VEGFD, discovered later also belong to the VEGF family. VEGF induces angiogenesis, protects tumor and endothelial cells from apoptosis, and plays an important role in the neovascularization of the resulting endometrioid implants [39].

VEGF has three types of receptors, namely, VEGFR1, VEGFR2, and VEGFR3. In women with adenomyosis, the levels of VEGF mRNA and the corresponding protein in the eutopic endometrium are increased, which confirms the assumption about the key role of this growth factor in the pathological angiogenesis of adenomyosis [40]. In patients with adenomyosis, an inadequate increase in the VEGF level concerning its inhibitor was detected. An imbalance between an increase in the activity of pro-angiogenic and anti-angiogenic growth factors contributes to an increase in the proliferative activity of blood vessels and the growth of ectopic endometrium.

Orazov et al. [41] revealed that higher VEGF expression is characteristic of patients with adenomyosis-associated pelvic pain compared with women with adenomyosis and abnormal uterine bleeding. A high expression was revealed in epithelial cells of the ectopic endometrium, smooth myometrial myocytes, and stromal cells of the myometrium. High expression of VEGF in the endometrium and myometrium and the intensity of neovascularization are one of the important mechanisms of angiogenesis in adenomyosis and pathogenetic mechanisms of the formation of chronic pelvic pain caused by this disease [41].

A high VEGF activity is associated with the onset of oncological processes. The role of VEGF in the development of endometrial hyperplasia and cancer in obesity has been established [42].

Role of TWIST proteins in EMT

Twist and ZEB proteins can suppress apoptosis and oncogenic aging. An increase in Twist expression leads to a decrease in the level of E-cadherin expression, which in turn causes activation of EMT. Twist also promotes the activity of mesenchymal markers such as fibronectin, vimentin, alpha-smooth muscle actin (alpha-SMA), and N-cadherin.

Li [43] examined the expression of mRNA and the level of proteins Twist, N-cadherin, and E-cadherin in a group of patients with EGE in comparison with a control group and revealed that Twist and N-cadherin were expressed in both stromal cells and glandular epithelium. As expected, the highest and lowest expressions of these parameters were recorded in the ectopic endometrium in ovarian endometriosis and in the endometrium of women in the control group, respectively. By contrast, E-cadherin expression was the highest in the endometrium of women without endometriosis. Thus, a positive correlation between N-cadherin and Twist and a negative correlation between E-cadherin and Twist indicate the key role of the protein in EMT induction in endometriosis, namely, an increase in the migratory and invasive capacity of endometrial stromal cells [43].

The discovery of the pathogenic role of Twist in the development of endometriosis may be a promising therapeutic target for the treatment of the disease. Its inhibition can slow down the progression and reduce the frequency of disease relapses.

Furuya et al. studied the factors ZEB (ZEB1/ZEB2) in endometriosis and noted an increase in ZEB1 expression in endometrioid foci [44]. In addition, ZEB1 expression was most frequently detected in epithelial cells of infiltrative endometriosis, which identifies ZEB1 as a potential indicator of endometriosis invasiveness or severity.

Role of N-cadherin in the pathogenesis of adenomyosis

N-cadherin is a member of the superfamily of integral membrane glycoproteins that regulate cell adhesion and cell motility. The transition from E-cadherin expression to N-cadherin expression often occurs in many aggressive forms of cancer [45]. N-cadherin stimulates the activation of Snail and Slug, causing modulation of the FGFR, leading to an increase in the invasion, proliferation, and metastasis of carcinoma cells [45]. N-cadherin-mediated cell adhesion accelerates the migration of cells in a three-dimensional matrix; as a result, the transformed cells form elongated multicellular chains and migrate faster than individual cells. In adenomyosis, N-cadherin is activated in ectopic epithelial cells and is actively involved in the disease pathogenesis. The expression of N-cadherin in both the proliferative and secretory phases of the menstrual cycle was significantly higher in the endometrium of women with adenomyosis than in women without adenomyosis.

Role of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) in adenomyosis development

Among factors of the receptor status of the ectopic endometrium and genetic abnormalities of these cells in adenomyosis, the expression of the *PTEN* gene is interesting, as its product catalyzes the cleavage of the phosphate group at the position of the 3D inositol ring of phosphatidylinositol-3-phosphates, thus participating in signal transduction in the cell. The PTEN protein is a significant suppressor of the PI3K/AKT/mTOR signaling pathway, which enables us to

consider it as a tumor growth suppressor protein, and the loss of PTEN function is often observed in both hereditary and sporadic cancers.

PTEN controls various biological processes in cells, including maintenance of genome stability, survival, migration, proliferation, and metabolism. A slight decrease in the level and activity of PTEN contributes to tumor development and progression. PTEN regulation is the subject of intensive research in tumor biology. New modes of PTEN functioning and regulation have recently been discovered, including the existence of its various isoforms and its ability to form dimers. Thus, new therapeutic possibilities were identified for the prevention and treatment of the oncological process by regulating the PTEN function [46].

The expressions of the *PTEN* anti-oncogene and a similar protein in endometrioid heterotopies and eutopic endometrium are known to decrease in adenomyosis [21, 47]. A decrease in the expression level of the PTEN protein may be associated with a mutation in the gene itself and its promoter region. When assessing the expression of PTEN in various forms of adenomyosis in patients with nodular adenomyosis, the expression of the *PTEN* anti-oncogene in the stroma of heterotopies correlated with the expression of the same gene in the epithelium, whereas in the diffuse form of adenomyosis, no correlation was registered between these parameters. The absence of a correlation among the immunohistochemical parameters of the eutopic and ectopic endometrium indicates the autonomy of the pathological processes of endometrioid heterotopias [48].

In 2017, Hu et al. [47] evaluated the expression of PTEN and proteins associated with the cell cycle and apoptosis in the endometrium of the adenomyosis group and control group. As a result, the expression of miR-17 was significantly increased in the endometrial tissues of the adenomyosis group ($p < 0.05$), which can affect cell apoptosis and PTEN regulation and contribute to the onset and development of adenomyosis. By contrast, the expression of PTEN protein was significantly lower in the endometrium of the adenomyosis group than in the control group ($p < 0.05$). When miR-17 expression was suppressed, PTEN expression increased ($p < 0.05$).

Notch1/Numb/Snail signaling pathway

The Notch family, which includes four members (Notch1–4), represents transmembrane receptor proteins [49]. Mature Notch receptors are heterologous dimers that consist of a large extracellular ligand-binding domain, a single-pass transmembrane structure, and a small cytoplasmic subunit (Notch intracellular domain, NICD) [50]. Transmembrane ligands Delta/Serrate and Lag2 family bind to Notch receptors, causing heterodimer cleavage and NICD release. The NICD is then transported into the nucleus and modulates the transcription of downstream target genes, including those associated with EMT, such as Snail and Slug, as described above. Snail and Slug subsequently bind to the E-cadherin promoter, suppressing its expression [51]. Despite the similarities, the four Notch receptors are structurally different, which probably determines their expression patterns and unique functions. The activation of the Notch signaling pathway is initiated by two sequential proteolytic cleavages of Notch, which are induced by ligand–receptor interaction between two adjacent cells.

The Notch signaling pathway regulates cell development, proliferation, survival, and differentiation of cells in various organs, while uncoupling of the cascade links results in the development of malignant tumors [52, 53]. The prototype of the signaling pathway associated with the Notch signaling pathway is human acute lymphoblastic leukemia/lymphoma (T-ALL). The *NOTCH1* gene has been found in a specific chromosome translocation found in some human T-ALL cases. After this discovery, mutations in the *NOTCH1* gene are found in most cases of T-ALL in humans, which leads to the aberrant activation of the Notch signaling pathway. These data reveal that the Notch signaling pathway plays an important role in the pathology of T-ALL, and the activation of mutations in the *NOTCH1* gene is the main cause of T-ALL development. In addition, overexpression of Notch1 is observed in breast and pancreatic cancer [53, 54]. However, the Notch cosignaling pathway acts as a tumor suppressor in neuroendocrine tumors such as carcinoid and medullary thyroid cancer [55]. These results suggest that the Notch signaling pathway can act as a tumor suppressor or an oncogenic factor in humans, depending on the cell type and context. Thus, the detection of a higher expression of Notch1 in women with endometrial cancer than in the endometrium of healthy women is significant [56].

The transcription factor Notch1 can be an EMT inducer, and the suppression of Notch1 expression promotes partial EMT reversal and a decrease in the expression of genes responsible for maintaining pluripotency. Notch signal transmission can also stimulate TGFβ1-induced EMT through induction of Snai1 [57]. In various human cancer models, the activation of Notch signal transmission mediated by Jagged1 can increase the expressions of Snail and Slug, which leads to E-cadherin suppression and triggers the aforementioned processes [58].

In EMT, Notch signals are transmitted with multiple transcription and growth factors such as Snail, Slug, TGFβ, FGF, and PDGF [59, 60]. A significant increase in the expression of Notch1 was found in the endometrium with adenomyosis in both the proliferative and secretory phases when compared with the values in the control group. A high expression of Notch1 in adenomyosis indicates its significant role in disease pathogenesis as well as in the differentiation and decidualization of endometrial stromal cells. In the human

endometrium, Notch1-3 is expressed not only in stromal cells but also in glandular epithelial cells, and the expressions of Jagged and DDL4 are mainly noted in glandular epithelial cells [61]. In some studies, the expression of Notch1 in the endometrium of women with adenomyosis was higher in the proliferative phase than in the secretory phase and is the lowest in the postmenopausal period [5]. By contrast, Cobellis et al. established that the expressions of Notch1 and Jagged1 increased from the proliferative to the secretory phase [56]. In endometrial carcinoma, the expressions of Notch, Jagged1, and DLL4 are significantly increased and are associated with disease stage and prognosis, and blocking the Notch signaling pathway inhibits the growth and invasion of endometrial adenocarcinoma cells [62]. Blocking the Notch signaling induces apoptosis in Ishikawa cells [63], while increased estrogen levels promote the growth of these cells by activating the Notch signaling pathway [64]. Blocking the Notch signal transmission pathway by c-secretase led to the suppression of cell proliferation by regulating the cell cycle and apoptosis in Ishikawa cells. Given the important role of the Notch signaling pathway in tumor development, these results suggest that c-secretase may be a potential target for new therapeutic strategies for the prevention of endometrial cancer.

In the Notch1/Numb/Snail signaling pathway, the Numb protein acts as an inhibitory regulator of Notch1 signaling, which acts by stimulating ubiquitination and degradation of the Notch1 intracellular domain. Its functions include the regulation of cell division, adhesion, and migration. The suppression or loss of Numb expression may correlate with the development and enhancement of invasion of multiple tumors [65]. Qi et al. [5] were the first to investigate the role of Numb in the development of adenomyosis. The expression of Numb did not change during the menstrual cycle either in the endometrium of healthy women or in the endometrium of women with adenomyosis, which indicates the hormonal independence of this protein expression. In adenomyosis, the expression of Numb in the ectopic endometrium was reduced compared with that in the endometrium of the control group. This suggests that aberrant negative regulation of Numb may be associated with the genesis and development of adenomyosis.

TGFβ1/Smad3 signaling pathway in adenomyosis

In adenomyosis and EGE, platelet TGFβ1 activates the TGFβ1/Smad3 signaling pathway, which leads to triggering of EMT, smooth muscle metaplasia, transformation of fibroblasts into myofibroblasts, and development of fibrosis [22]. The discovery and further study of this signaling pathway elucidate the importance of the platelet link in the pathogeneses of EGE [66] and adenomyosis [30]. Zhang et al. [22] examined the activation of the TGFβ1/Smad3 signaling pathway in endometrioid cells. They revealed that the expressions of TGFβ1 genes and proteins phosphorylated by Smad3 in endometrial samples from women with endometriosis after co-culturing with activated platelets were significantly increased compared with that in the endometrial samples from women without gynecological diseases.

Owing to the cyclic activation of endometrioid heterotopies, platelets enter the microenvironment from the damaged vasculature and are activated in the surrounding space, which results in the activation of thrombin, thromboxane A2 (TXA2) and, possibly, collagen produced by heterotopies of stromal cells. Through the release of TGFβ1 and induction of the TGFβ/Smad signaling pathway, activated platelets promote EMT triggering, transformation of fibroblast into myofibroblast, which leads to an increase in cell contractility, collagen synthesis, smooth muscle metaplasia, and increased fibrogenesis. Platelet TGFβ1 and the TGFβ/Smad signaling pathway co-promote EMT, myofibroblast development, and fibrous transformation, ultimately leading to fibrosis, which is characteristic of endometriosis and adenomyosis. The researchers leave open the possibility that myofibroblasts may also originate from other sources, such as in pathological tissue regeneration, and suggest the simultaneous participation of other signaling pathways or immune cells in EMT in endometriosis.

The development of fibrosis is influenced by various pathophysiological mechanisms resulting from chronic, recurrent, frequent inflammatory changes caused by various stimuli such as repeated injury. Fibrogenesis enhancement underlies wound healing, tissue neogenesis, remodeling, and development of fibrosis. The described processes, namely, the ability to fibrosis, are characteristic of endometriosis and adenomyosis. Thus, endometrioid heterotopies are not only separate proliferating endometrial stromal and epithelial cells, but they interact and are closely related to the microenvironment, contact with other cells (platelets and macrophages), and contain all the necessary molecular components to activate fibrogenesis. Moreover, endometrioid cells are not static but can evolve to fibrosis, acquiring new phenotypes. This provides further evidence that tissues affected by endometrioid heterotopies undergo repeated damage and healing, which ultimately leads to fibrous lesions resistant to hormonal treatment [67]. This dynamic process may explain some of the conflicting research findings and the lack of universal and specific biomarkers for diagnostics and prognosis of genital endometriosis. The TGFβ/Smad pathway is a therapeutic target for endometriosis and adenomyosis. Thus, the discovery of the role of platelets in disease pathogenesis helps determine the appropriate biomarkers and recommend anticoagulant drugs for use in non-hormonal therapy of endometriosis.

Signaling pathway of eIF3 in adenomyosis

Translational control plays a major role in the regulation of protein expression and occurs mainly at the initiation stage, which is controlled by multiple eukaryotic translation initiation factors (eIFs) [68]. According to a recent transcriptome analysis of eutopic endometrium in women with adenomyosis, the eukaryotic initiation factor (eIF2 2) and eukaryotic initiation factor 3 (eIF3) signaling pathways are involved in EMT. Suppression of eIF3e in endometriosis can increase the translations of Snail and Zeb2, which in turn triggers the EMT mechanism. In addition, stable eIF3e levels promote wound healing through enhanced angiogenesis. As indicated above, endometrioid lesions are partly wound surfaces that undergo repeated tissue damage and repair, and adenomyosis is characterized by the loss of epithelial properties of cells and acquisition of mesenchymal properties of cells. eIF3e can be also involved in EMT in EGE and adenomyosis [9, 69]. eIF3e is involved in EMT in endometriosis through TGFβ1 activation and promotes cell proliferation by enhancing angiogenesis in the ectopic endometrium. eIF3e immunoreactivity is significantly reduced in adenomyosis in comparison with that women without adenomyosis.

A study found an increase in the immunoreactivities of TGFβ1, Snail, and vimentin, as well as a significant decrease in the level of E-cadherin in the epithelial cells of endometrioid lesions, which determines the initiation and implementation of EMT [9]. In addition, the degree of eIF3e staining correlated positively with the levels of E-cadherin and negatively with the levels of the aforementioned mesenchymal factors.

Considering the important role of platelets in the development of endometriosis and adenomyosis, the coagulation properties of the patients' blood were studied. The activated partial thromboplastin time and thrombin time were significantly reduced and fibrinogen levels were increased in women with endometriosis when compared with women without endometriosis. Women also had a significant increase in the number of circulating degranulated platelets, and their proportion decreased significantly 1 month after surgical treatment of endometriosis. These data indicate a state of hypercoagulation in women with endometriosis and indicate a close relationship between the coagulation system and inflammatory process [70]. In coagulation assessment, changes in the myometrium in adenomyosis are quite similar to those in EGE and undergo platelet-induced EMT, which leads to hypercoagulation in adenomyosis. A decrease in eIF3e expression probably affects EMT in the development of adenomyosis because of the activation of the TGFβ1 signaling pathway [71]. A negative correlation was revealed between the platelet count and eIF3e expression level, which indicates a possible effect of platelets on the reduction of eIF3e level and development of adenomyosis.

E_2/Slug/VEGF signaling pathway

The E_2/Slug/VEGF signaling pathway represents the effect of estradiol on the Slug transcription factor, which subsequently leads to a decrease in the epithelial E-cadherin factor using the mechanisms described above and to the effect on VEGF, which is the key mediator of angiogenesis and neurogenesis. Huang et al. [23] studied the role of estradiol (E_2) in the pathogenesis of adenomyosis and revealed that an increase in estradiol levels triggers the E_2/Slug/VEGF signaling pathway. The stimulation of the signaling pathway increases the pro-angiogenic activity in vascular endothelial cells An animal experiment confirmed that suppression of E_2 or VEGF can reduce the severity of adenomyosis. These results emphasize the importance of estrogen-induced angiogenesis in the development of adenomyosis and provide a potential strategy for disease treatment by acting on the links of the E_2/Slug/VEGF signaling pathway [23].

Despite the intensive study of the molecular mechanisms of adenomyosis, many issues of the disease pathogenesis remain studied insufficiently or controversial; therefore, further investigation is required. The study of signaling pathways and the characteristics of signal transmission will make it possible to understand the pathogenetic mechanisms of adenomyosis development, which is fundamentally important for predicting the efficiency of therapy and thus ensuring the targeted therapeutic effect of drugs on the main components involved in the implementation of signaling pathways.

ADDITIONAL INFORMATION

The study was performed within the research and exploratory works of the research, development, and technological works AAAA-A20-120060990051-3.

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