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Molecular mechanisms of preeclampsia

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ABSTRACT

Preeclampsia (PE) is one of the major obstetric syndromes, manifested by a persistent increase in blood pressure and associated complications, and in severe cases — by systemic damage to the organs of mother and fetus. Due to complexity of the etiology of this disease, key and reliable molecular markers that could be used as predictors for early diagnostics of PE or as therapeutic targets for its treatment have not been found yet. This review analyzes the data accumulated to date on the most important molecular processes underlying the development of PE — an imbalance between the synthesis of proangiogenic and antiangiogenic factors (soluble fms-like tyrosine kinase sFlt-1, endoglin Eng, placental growth factor PlGF and vascular endothelial growth factor VEGF), fetoplacental molecules (PAPP-A and PP-13), disturbances of immunological reactions (T-helper lymphocytes TH, killer cells uNK, TLRs receptors), genetic and epigenetic mechanisms (abnormal expression of miRNA, circRNA, lncRNA), activation of the effectors of the profibrotic signaling pathway of the cardiotonic steroid marinobufagenin and transcription factor Fli1. Current data highlights the complex profile of the etiology and pathogenesis of PE. Alteration in the balance of pro- and anti-angiogenic factors may be one of the earliest molecular mechanisms underlying abnormal placentation and placental ischemia. Disruption of epigenetic mechanisms regulating placentation and vascular growth, particularly abnormal alterations in the expression of several types of microRNAs, also play an important role in the development of PE. Further development of pathophysiological events associated with adverse pregnancy outcomes in PE includes oxidative stress and immune responses, as well as the development of vascular fibrosis.

Keywords: preeclampsia, antiangiogenic factors, fetoplacental molecules, immunological reactions, epigenetic mechanisms, profibrotic factors

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Молекулярные механизмы преэклампсии

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АННОТАЦИЯ

Преэклампсия (ПЭ) — один из больших акушерских синдромов, проявляющийся стойким повышением артериального давления и сопутствующими осложнениями, а в тяжелых случаях — системным поражением органов матери и плода. Из-за сложности этиологии этого заболевания до сих пор не найдены ключевые и достоверные молекулярные маркеры, которые можно было бы использовать как предикторы для ранней диагностики ПЭ или как терапевтические мишени для ее лечения. В обзоре анализируются накопленные к настоящему времени данные о важнейших молекулярных процессах, лежащих в основе развития ПЭ, — дисбалансе между синтезом проангиогенных и антиангиогенных факторов (растворимой fms-подобной тирозинкиназы sFlt-1, эндоглина Eng, фактора роста плаценты PlGF и фактора роста эндотелия сосудов VEGF), фетоплацентарных молекул (PAPP-A и PP-13), нарушении иммунологических реакций (Т-хелперов лимфоцитов TH, клеток-киллеров uNK, рецепторов TLRs), эпигенетических механизмах (аномальной экспрессии miRNA, circRNA, lncRNA), активации эффекторов профибротического сигнального пути кардиотонического стероида маринобуфагенина и транскрипционного фактора Fli1. Современные данные подчеркивают сложный профиль этиологии и патогенеза ПЭ. Изменение соотношения уровней проангиогенных и антиангиогенных факторов может быть одним из наиболее ранних молекулярных механизмов, лежащих в основе аномальной плацентации и ишемии плаценты. Нарушения эпигенетических механизмов регуляции плацентации и роста сосудов, в частности аномальные изменения экспрессии нескольких типов микро-РНК, также играют важную роль в развитии ПЭ. Дальнейшее развитие патофизиологических событий, связанное с неблагоприятными исходами беременности при ПЭ, включает оксидативный стресс и иммунные реакции, а также развития фиброза сосудов.

Ключевые слова: преэклампсия, антиангиогенные факторы, фетоплацентарные молекулы, иммунологические реакции, эпигенетические механизмы, профибротические факторы

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INTRODUCTION

Preeclampsia (PE) is one of the major obstetric syndromes of complex etiology, manifested by a persistent increase in blood pressure and a number of concomitant complications [17, 46, 52]. Despite significant progress in the development of medical technologies, effective prevention and treatment of PE remain limited, and in the case of severe course of this disease, first of all, preterm delivery is necessary to prevent systemic damage to the organs of the mother and fetus. This is largely due to the lack of reliable data on the molecular mechanisms underlying the development of PE and key markers that could be used for its early diagnosis or therapy.

However, several decades of scientific research have shown that placentation processes are disrupted in the early form of PE, and genetically determined pathologies of the maternal cardiovascular system play an important role in the development of the late type of PE [17, 46, 52]. Placentation, including differentiation and invasion of the extravillous trophoblast, is controlled by a variety of factors, including cytokines, growth factors, chemokines, and cell adhesion molecules [6, 14, 48]. Invasion of a defective trophoblast and inadequate transformation of the uterine vascular network leads to excessive production of reactive oxygen species and a change in the balance of activity of antioxidant defense enzymes. In a hypoxic environment, placental tissue is affected, and placental endothelial cells acquire increased susceptibility to apoptosis [6].

In addition, the study of the molecular mechanisms of PE has led to the understanding that the development of this condition is based on the same phenotypic and genotypic factors as in other pathologies that increase the risk of hypertension and heart disease. For example, in recent years, several circulating biochemical factors have been discovered, the imbalance between the synthesis of which in the body is associated with the occurrence of PE [9, 34, 46, 48]. These biomarkers include pro-angiogenic and anti-angiogenic factors such as soluble fms-like tyrosine kinase sFlt-1, endoglin, placental growth factor PlGF and vascular endothelial growth factor VEGF (vascular endothelial growth factor). Similar changes in the ratio of PlGF/sFlt-1 are also observed in heart failure, coronary heart disease, and chronic kidney disease [49, 57]. Therefore, it is proposed to use the determination of the levels of these molecules for the early diagnosis of PE. In addition, the development of PE is accompanied by impaired immune responses and abnormal activity of genetic factors [5, 28]. This review classifies the current understanding of the role of angiogenic dysfunction, impaired synthesis of molecular placental factors, inflammatory reactions, and genetic factors in the development of PE (Fig. 1).

PRO-ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS

For normal blood supply to the fetus, a full-fledged vascular network of the placenta is necessary [10, 14, 36], the formation and functioning of which, in turn, depends on factors regulating the growth of blood vessels — proangiogenic (vascular endothelial growth factor — VEGF, placental growth factor — PlGF, transforming growth factor-β — TGF-β), and antiangiogenic (soluble sEng endoglin and soluble fms-like tyrosine kinase sFlt-1). Throughout pregnancy, these factors are released into the mother's bloodstream, helping to adapt her cardiovascular system to a new state. However, if placental cells experience hypoxia and prolonged nutrient deficiency, an imbalance occurs between

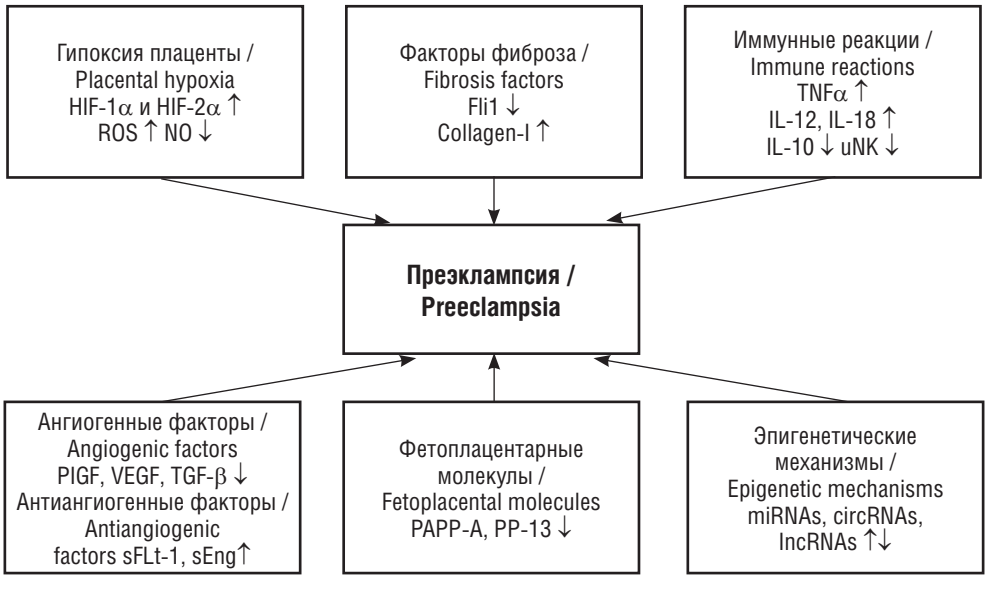

Fig. 1. A simplified scheme of molecular changes underlying the development of preeclampsia

Рис. 1. Упрощенная схема молекулярных изменений, лежащих в основе развития преэклампсии

the synthesis of proangiogenic factors VEGF, PlGF and TGF-β and antiangiogenic factors sFlt-1 and sEng, which contributes to the development of pathophysiological effects observed in PE [9, 18, 31, 46, 48]. Disproportionately high levels of antiangiogenic factors (sFlt-1 and sEng) compared with proangiogenic ones (PlGF, VEGF, and TGF-β) cause the generation of oxidative stress, endothelial dysfunction, extensive immune response, and activation of the maternal blood clotting system, which further leads to the development of renal endotheliosis, hypertension, and proteinuria [14, 46].

Placental growth factor (PlGF)

Proangiogenic placental growth factor (PlGF) is a glycosylated dimeric protein mainly expressed by trophoblast cells in the placenta, although small amounts of it are also found in some other tissues, such as the heart and skeletal muscles [11, 15, 54]. The main function of PlGF is to regulate the development and maturation of the placental vasculature in the early stages of gestation, in particular, differentiation and invasion of the trophoblast into the decidual tissue. In the first trimester of pregnancy, the content of PlGF in the circulating blood is low, but it increases significantly in the second trimester and reaches a peak by the 30th week, which promotes proliferation and growth of the trophoblast, after which it decreases. Therefore, low levels of PlGF in the bloodstream, often observed in PE, are a sign of abnormal placentation [50, 52]. In pathological conditions, PlGF binds to the soluble antiangiogenic factor sFlt-1, which inhibits the interaction of PlGF with its membrane receptor and leads to a decrease in the level of its free form circulating in the mother's blood.

Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor VEGF also belongs to the family of glycoproteins. By binding and activating its VEGFR receptor, it regulates the differentiation, growth and apoptosis of vascular endothelial cells, which ensures the formation of blood vessels and the lymphatic network. These functions are extremely important for maintaining endothelial cell homeostasis, blood vessel permeability, and transport of small molecules [39]. During pregnancy, VEGF is secreted by trophoblast cells and is one of the most important factors in maturation and maintenance of a functionally complete vascular network of the placenta [8, 52, 54].

The levels of PlGF and VEGF factors circulating in the mother's bloodstream are regulated by partial oxygen pressure. With the development of hypoxia due to defective placentation, hypoxia-induced factor-1 (HIF-1), a transcription factor responsible for regulating the expression of genes encoding proteins involved in the process of angiogenesis, including PlGF, VEGF, and their Flt-1 receptor, is activated in placental cells. Under conditions of hypoxia typical for PE, the level of PlGF decreases, but the VEGF content increases [48].

TGF-beta

Transforming growth factor-β (TGF-β) is a representative of a superfamily of pleiotropic factors that control a wide range of physiological functions, including in the cardiovascular and hematopoietic systems [22, 26]. Prolonged exposure to TGF-β on endothelial cells stimulates the expression of the gene and protein endothelial nitric oxide synthase eNOS, an enzyme that synthesizes endogenous nitric oxide, a mediator of vasodilation. TGF-β signaling is mediated by type I and type II receptors and modulated by an additional endoglin receptor.

During pregnancy, TGF-β plays one of the key roles in the development of the placenta, especially in the regulation of trophoblast differentiation in the first trimester of pregnancy [26, 52]. Initially, TGF-β activity is necessary for trophoblast invasion and cell transition from cytotrophoblast to extravillous trophoblast, and at later stages of gestation, TGF-β signal transmission induces normal vascularization and angiogenesis in placental endothelial cells. In addition, TGF-β functions as an anti-inflammatory growth factor that regulates the activity of placental and decidual macrophages, which ensures maternal tolerance to the semi-allogeneic fetus. Since the development of PE is associated with placental disorders, it is assumed that TGF-β is involved in the pathogenesis of this disease and may be a potential target for its therapy.

Soluble fms-like tyrosine kinase 1 (Flt-1)

The protein Flt-1 (Fms-like tyrosine kinase 1), also called VEGFR-1 (vascular endothelial growth factor receptor 1), exists in two forms — as a transmembrane cellular receptor with a molecular weight of 180 kDa and as a circulating molecule sFlt-1 (soluble sFlt-1) with a mass of 100 kDa. PlGF and VEGF factors are ligands for both types of this protein, however, it is the insufficient or excessive content of sFlt-1 that is associated with the development of diseases based on aberrant angiogenesis [32, 52, 57]. The mechanism of action of sFlt-1 is mainly related to its ability to bind VEGF and PlGF, acting as their natural antagonist and limiting their bioavailability. Since the content of sFlt-1 in the blood increases in conditions associated with impaired angiogenesis, it has been proposed as a marker for early diagnosis and severity of kidney damage, diabetic nephropathy, hypertension, tumors, atherosclerosis and some other diseases.

During pregnancy, the main site of Flt-1 synthesis is the placenta, where it is expressed by trophoblast cells [37, 54]. On the one hand, it protects cells from excessive VEGF concentrations in tissues, on the other hand, by binding and inhibiting proangiogenic PlGF and VEGF in the maternal circulation, circulating sFlt-1 can disrupt

the integrity of endothelial cells, provoking dysfunction of the endothelium and the microcirculatory bed of target organs. Excess circulating sFlt-1 is one of the key factors in the development of clinical symptoms associated with PE, such as hypertension, proteinuria, perinatal cardiomyopathy, and other adverse maternal and fetal outcomes. However, an excessive content of sFlt-1 may exist even before the development of hypertension and proteinuria, which makes this protein one of the significant markers for the early diagnosis of PE [48, 54].

Endoglin

Endoglin (Eng), or CD105 differentiation cluster, is a transmembrane glycoprotein with a molecular weight of 65 kDa. Eng was initially detected in B lymphocytes, but it is also expressed in mature cells of both the innate (macrophages and mast cells) and adaptive (T cells) immune systems [40]. A change in Eng activity in myeloid cells leads to spontaneous inflammation, which makes it a factor regulating the maturation of immune cells and providing immune responses. Later, Eng attracted attention due to its abnormal activity in pathologies associated with impaired angiogenesis, including hereditary hemorrhagic telangiectasia type 1 (HHT-1) [18, 47]. In this case, it acts as a co-receptor for the TGF-β1 and TGF-β3 molecules. In primary hemostasis and inflammation, Eng also functions as an integrin counter-receptor in endothelial cell adhesion signaling pathways.

In addition, Eng can exist as a circulating soluble form of sEng, an extracellular domain of a membrane protein cleaved by metalloproteinases. sEng acts as an endogenous TGF-β inhibitor capable of suppressing TGF-β and activin receptor-like kinase 1 signaling, as well as eNOS activation in the vascular network. This disrupts angiogenesis and vascular hemostasis, contributing to vasoconstriction, altering vascular permeability, which ultimately leads to hypertension [35, 55]. At the same time, sEng is an antagonist of membrane-bound endoglin and competes with fibrinogen for binding to integrin, disrupting thrombosis.

With these properties, Eng is one of the main factors of placental impairment in PE. Indeed, the manifestation of clinical symptoms of PE, in particular the development of hypertension, correlates with the overexpression of Eng in the endothelial cells of the vessels of the placenta and trophoblast, which, in turn, leads to an increase in its soluble form in the maternal circulation [35]. A meta-analysis of 20 clinical trials showed that the level of sEng in the blood plasma of pregnant women with PE was significantly higher than that of women with uncomplicated pregnancy almost throughout pregnancy, although it did not reach statistical significance in the first trimester [35]. Moreover, the sEng content increased both in early-onset PE and in its late form. These data allowed us to propose Eng and soluble sEng as prognostic markers of PE, as well as as therapeutic targets.

FETOPLACENTAL MOLECULES

Pregnancy-associated plasma protein A (PAPP-A)

PAPP-A (Pregnancy-Associated Plasma Protein-A, also called pappalizin-1) is a fetoplacental-specific Zn^{2+}-binding metalloproteinase with a molecular weight of 200 kDa, synthesized by trophoblast cells and secreted into the maternal bloodstream. By participating in the proteolytic cleavage of the insulin-like growth factor binding protein (IGFBP), PAPP-A regulates the action of local insulin-like growth factor (IGF), an enzyme that stimulates the development of the placenta and fetus [50]. In addition, this protein participates in bone remodeling processes, controlling the maximum increase in bone mass during puberty, folliculogenesis, wound healing, and atherosclerosis [30].

The level of PAPP-A in blood plasma gradually increases throughout the entire period of pregnancy, exceeding its content in non-pregnant women by 100 times during the first trimester and by 10,000 times during the third trimester. After childbirth, the PAPP-A content rapidly drops to basal values [30, 48]. However, with abnormal placentation or placental dysfunction, the concentration of PAPP-A decreases. It has been shown that a drop in PAPP-A levels in the first trimester of pregnancy may be associated with an increased risk of developing early PE. Thus, at the beginning of the second trimester of pregnancy, in women who subsequently developed PE, the PAPP-A content decreased to one-third compared with the values observed in women without PE. That is why PAPP-A has been proposed as a marker for predicting PE [50].

Placental protein 13 (PP-13)

PP13 is a homodimeric carbohydrate — binding protein of 139 amino acid residues with a molecular weight of 32 kDa, belonging to the galectin family and synthesized in the syncytiotrophoblast [53, 58]. The structural and functional properties of PP-13 are vital for the development of the placenta and embryogenesis due to the specificity of its conservative carbohydrate domain for recognition of glycoconjugates containing β-galactosides. Having the ability to initiate apoptosis in maternal T cells, PP-13 regulates trophoblast invasion and, ultimately, effective placentation and implantation of the embryo. By binding to β-actin in trophoblast cells, PP-13 ensures their migration to the placental bed, along with increased secretion of prostacyclines necessary for remodeling spiral arteries during early placentation. PP-13 also plays an important role in trophoblast differentiation and syncytialization, which promotes the secretion of immune proteins and pla-

cental hormones necessary for embryo development and maternal immune tolerance to the fetus.

Being a fetoplacental-specific molecule, PP-13 has also been proposed as a biomarker for predicting PE [58]. Concentrations of PP-13 in serum or plasma decrease during the first trimester, but then gradually increase as pregnancy progresses. However, the level of PP-13 in the blood serum during the first trimester in patients who developed PE in the early stages was significantly lower than in women with uncomplicated pregnancy [53]. Moreover, it has been shown that low levels of PP-13 in the blood during the first trimester of pregnancy increase the risk of PE.

IMMUNOLOGICAL FACTORS

The results of research in recent decades have confirmed the most important link between the pathogenesis of PE and disorders of the maternal immune system. Good regulation of immunological reactions is necessary to ensure a normal pregnancy, while in PE, incomplete remodeling of spiral arteries, placental hypoxia and oxidative tissue damage induce excessive inflammatory processes followed by apoptosis or necrosis and the release of pro-inflammatory molecules [5, 20, 48]. Cytokines, metalloproteases (MMPs), and angiogenic factors are necessary for placental maturation; therefore, decidual natural killer cells (NK) are present in large numbers in tissues at the beginning of gestation to regulate their levels [60]. A similar role is played by decidual macrophages, which also ensure the immune tolerance of the maternal organism to the fetus by immunosuppression of cytokines and phagocytosis of dead trophoblast cells. In addition, trophoblasts regulate vascular growth and apoptosis processes by synthesizing tumor necrosis factor (TNFa) and other growth factors [43].

In PE, the most critical changes in the functioning of the immune system include an abnormal proinflammatory shift in the population profile of T helper lymphocytes (TH) and a decrease in the level of natural killer uterine cells (uNK) [43, 48]. The PE phenotype is closely related to the abnormal reprogramming of TH cells from the Th2 subpopulation to Th1, which supports inflammation, since Th1 cells secrete numerous pro-inflammatory cytokines, including IL-12 and IL-18. Another immune anomaly observed in PE is an increase in the level of CD19+CD5+ B lymphocytes, which is the main cause of the formation of polyreactive antibodies, in particular autoantibodies to the angiotensin II type 1 receptor (AT1R) [12, 27, 48].

Natural uNK killer cells are one of the subpopulations of uterine cells localized at the mother–fetus interface and are involved in the early development of the placenta, for example, they regulate trophoblast invasion and remodeling of spiral arteries [33, 56]. uNKs express NK immunoglobulin-like receptors (KIR), which bind to HLA-C molecules (human leukocyte antigen) extravillous trophoblast. However, the number of uNKs and their association with placental cells differ between normotensive pregnancy and PE. Thus, a distinctive feature of PE is a deficiency of the maternal cell fractions CD56+/NKp46+ and CD56+bright/NKp46+, which occurs three to four months before the onset of the disease [56]. Moreover, some studies have shown that disruption of the interaction between the KIR of UNK cells and the HLA-C of the trophoblast is an important risk factor for PE due to polymorphism of the genes encoding maternal KIR and fetal HLA-C [56].

Uterine uNKs also secrete the anti-inflammatory cytokine interleukin 10 (IL-10), which is essential for maintaining a normal pregnancy due to its ability to prevent maternal immune responses to a semi-allogeneic fetus, reducing endoplasmic reticulum stress and antiangiogenic factor activity. However, with PE, IL-10 levels decrease and TNFα expression increases [7, 43].

Processes induced by oxidative stress play an equally important role in the development of PE. Excessive production of reactive oxygen species by mitochondria stimulates apoptotic caspases and the release of cf-mtDNA (cell-free mitochondrial DNA) [6, 44]. CpG dinucleotides within cf-mtDNA are recognized by TLR9 (toll-like receptor 9) endosome receptors, which triggers pro-inflammatory reactions, including cascades of interferon (IFN), AP-1 protein (MAPK/activator protein-1) and NF-kB (nuclear factor kappa B). CF-mtDNA and TLR9 activation play a major role in the development of PE, however, other TLRs (TLR4, TLR3) may also be involved in pathological processes in this disease. Abnormal expression of TLR3, TLR4, and TLR9 is associated with increased blood pressure, decreased vascular vasodilation, impaired spiral artery structure due to impaired trophoblast invasion, decreased VEGF levels, and increased sFlt-1 levels, leading to abnormal placentation and placental dysfunction [23, 25].

EPIGENETIC FACTORS

In recent decades, evidence has emerged that the development of PE is closely related to disorders of genetic and epigenetic mechanisms, in particular, changes in the expression of microRNAs (miRNAs), circulating RNAs (circRNAs), and long non-coding RNAs (lncRNAs) [12, 21].

Micro-RNA

Several microRNAs belonging to the C19MC cluster (chromosome 19 microRNA cluster) and expressed almost exclusively in the placenta play an important role in the regulation of placentation processes, including trophoblast differentiation and migration and angiogenesis [24, 45]. These micro-RNAs are secreted by the primary trophoblast and released into the maternal circulation as exosomes. The content of C19MC in the trophoblast increases as early as the 5th week of pregnancy and

further increases until the third trimester. However, in PE, the synthesis of these microRNAs is disrupted. Thus, overexpression of miR-515-5p, often observed in PE, is associated with suppression of syncytiotrophoblast differentiation. An abnormally high level of miR-517/a/b/c in the extravillous trophoblast in the first trimester of pregnancy leads to the release of excess antiangiogenic protein sFlt-1 and a decrease in the invasive abilities of the trophoblast, while miR-519d inhibits trophoblast invasion and migration. Abnormal activation of miR-518b in the placenta in PE contributes to excessive trophoblast proliferation. Increased expression of miR-517-5p reduces the proliferative and invasive abilities of human chorio-carcinoma cells. In addition, once in the maternal circulation, these microRNAs can cause immune cell dysfunction, contributing to a systemic inflammatory response, the development and progression of PE, as well as affect maternal immune tolerance during pregnancy and protection against infections [24, 45]. With the development of early PE, the level of miR-124 in the placenta also increases, which is considered as a negative regulator of angiogenesis, although the exact role of this miRNA remains unknown [59].

Circular RNAs

Circular RNAs (circRNAs) are non-coding RNAs with circular covalently closed structures formed by reverse splicing [12, 28, 63]. Being more stable than linear RNAs, circRNAs compete directly with miRNAs in the processes of cell migration and invasion. Recent studies have shown that impaired circRNAs expression may be the cause of pathophysiological processes in pregnancy complications, including underlying the development of PE. For example, changes in the expression profile of circRNA hsa_circ_0004904 and hsa_circ_0001855 in combination with RARP-A have been proposed to be used as a biomarker for early diagnosis of PE before the onset of obvious symptoms [29]. Overexpression of circRNA_06354 can provoke early-onset PE by altering the expression of molecules of the hsa-miR-92a-3p/VEGF-A signaling cascade, which leads to dysregulation of invasion and migration of trophoblast cells into spiral arteries [62]. Another representative of this type of RNA, circNIRK3, has several miRNAs as targets, including miR-124 and miR-558, and a decrease in its level is a potential cause of PE progression due to deregulation of miRNAs expression [59, 61].

Long non-coding RNAs

Recently, some placental pathologies and pregnancy complications, including PE, have been associated with abnormal expression of long non-coding RNAs (lncRNAs), positioning them as potential regulators of multiple molecular pathways involved in the pathogenesis of placental diseases [16, 38, 42, 51]. In addition, different types of lncRNAs were identified at different stages of the disease, which once again confirms the difference between the pathophysiological mechanisms of early and late PE. Increased or decreased expression of specific lncRNAs can lead to changes in trophoblast proliferation, invasion, migration, and apoptosis. Thus, in PE, the expression of lncRNA Linc00261 increases, which leads to a decrease in the level of miR-558 and disruption of trophoblast invasion and migration [13]. Therefore lncRNAs have also been proposed to be used as PE markers. However, despite the description of several circulating lncRNAs (AF085938, AK002210, BC030099, and G36948), their potential as diagnostic markers of PE is low due to their low content and difficulties in quantification.

FACTORS OF FIBROSIS DEVELOPMENT

The most well-known mechanism of fibrosis development and fibroblast activation is the activity of factor TGF-β [22]. However, fibrogenesis may also be associated with hypoxia and stimulation of hypoxia-inducible factor alpha (HIFa), lysophosphatidic acid, sphingosine-1-phosphate, plasma coagulation cascade, and matrix metalloproteinases capable of stimulating fibroblasts [26].

Another profibrotic mechanism described in the tissues of the cardiovascular system in hypertensive diseases is associated with abnormal production of the cardiotonic steroid marinobufagenin (MBH) [4, 19]. Binding of MBH to the Na/K-ATPase of cell membranes triggers a cascade involving the interaction of Src kinase with the epidermal growth factor EGFR receptor, followed by translocation of PKC-δ into the nucleus and inhibition of the transcription factor Fli1, which functions as a negative regulator of the collagen gene promoter [19, 41]. As a result, excessive synthesis and accumulation of collagen-1 in tissues is induced.

The development of PE is closely related to an increase in MBH synthesis and fibrosis of the tissues of the cardiovascular system, involving a Fli1-dependent mechanism. Thus, in umbilical vessels and placentas obtained from patients with PE, Fli1 expression decreased by 4-9 times, while the levels of pro-collagen-1 and collagen-1 increased by 2.5–3 times [3]. Similar results were obtained in pregnant Sprague-Dawley rats, in which a PE-like condition was modeled by excessive salt intake (1.8%) with water [1]. The development of experimental PE in animals was accompanied by a 7-fold decrease in Fli1 levels and a 4-fold increase in collagen-1 synthesis in the thoracic aorta. However, administration of antibodies to MBH to rats returned the level of Fli1 to almost normal, although it did not affect the content of collagen-1 [1]. At the same time, induction of a PE-like state did not lead to activation of TGF-β.

A direct link between MBH and Fli1-dependent fibrosis processes has been confirmed in *in vitro* expe-

riments. Thus, treatment of umbilical artery fragments obtained from healthy women in labor with nanomolar concentrations of MBH (1–10 nM) for 48 hours resulted in a 4-5-fold decrease in Fli1 expression and a 2-3-fold increase in the synthesis of pro-collagen-1 and collagen-1 [3]. Moreover, silencing of the FLI1 gene in umbilical artery explants obtained from healthy women in labor after treatment with Fli1 siRNA not only suppressed Fli1 expression at the protein level, but also induced a significant increase in the levels of pro-collagen-1 and collagen-1 [2]. The relationship between MBH, fibrotic processes, and Na/K-ATPase activity was confirmed after treatment of fragments of healthy umbilical arteries with canrenone, an active metabolite of spironolactone used in antihypertensive therapy, which completely restored Fli1 expression and partially inhibited MBH-induced collagen-1 synthesis [3].

CONCLUSION

Thus, current data highlight the complex profile of the etiology and pathogenesis of PE. A change in the ratio of pro-angiogenic and anti-angiogenic factors may be one of the earliest molecular mechanisms underlying abnormal placentation and placental ischemia. Disorders of the epigenetic mechanisms of regulation of placentation and vascular growth, in particular, abnormal changes in the expression of several types of microRNAs, also play an important role in the development of PE. Further development of pathophysiological events associated with adverse pregnancy outcomes in PE includes oxidative stress and immune reactions, as well as the develop.

ADDITIONAL INFORMATION

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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