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DERLEME/ REVIEW

PREEKLAMPSİ PATOFİZYOLOJİSİNDE ROL OYNAYAN MOLEKÜLER YOLAKLAR

MOLECULAR PATHWAYS THAT PLAY A ROLE IN THE PREECLAMPSIA PATHOPHYSIOLOGY

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ÖZET

Preeklampsi (PE) gebeliklerin yaklaşık % 4-5'inde görülen, hipertansiyon ve üriner proteinüri ile seyreden obstetrik bir hastalıktır. Maternal ve fetal komplikasyonlara neden olabilmektedir. PE alanında çok sayıda yapılan araştırmalara rağmen altta yatan patogenez hala belirsizdir. Ancak ilgili bu araştırmalar ile birlikte PE'yi tetikleyen çok sayıda moleküler mekanizma olduğu sonucuna varılmıştır. Bu moleküler mekanizmalardan yola çıkarak PE iki evrede incelenebilir. İlk evre anormal plasentasyon nedeniyle oluşan plasental iskemidir. İkinci evrede ise iskemik plasentadan dolaşıma salınan nekrotik ve apoptotik faktörler, sistemik inflamasyon ve endotelyal disfonksiyona neden olur. Plasental hücrelerden salınan bu faktörlerden biri de antianjiyogenik faktörlerdir. Ayrıca PE'de antioksidan ve prooksidan mekanizmalarda rekürren iskemi reperfüzyon hasarından dolayı olduğu düşünülen dengesizlik mevcuttur. PE'deki sistemik inflamatuar yanıt maternal immün hücrelerin trofoblastlarla teması sonucu ortaya çıkan immün yanıtla ilişkilendirilmektedir. Bu derlemenin amacı PE'ye giden yolda rol oynayan mevcut moleküler mekanizmaları göstermektir. İlgili moleküler mekanizmaların daha iyi anlaşılması doğrutusunda gelişen PE patogenezine dair yeni görüşler, ilerideki çalışmalara ışık tutacaktır.

ANAHTAR KELİMELER: Preeklampsi, Anjiyogenik proteinler, İnflamasyon, Plasentasyon.

ABSTRACT

Preeclampsia (PE) is an obstetric disease seen in approximately 4-5% of pregnancies progressing with hypertension and urinary proteinuria. It may cause maternal and fetal complications. Despite numerous researches in the field of PE, the underlying pathogenesis remains unclear. However, with these related studies, it has been concluded that there are many molecular mechanisms that trigger PE. Based on these molecular mechanisms, PE can be examined in two stages. The first stage is placental ischemia caused by abnormal placentation. In the second stage, necrotic and apoptotic factors released from the ischemic placenta into the circulation cause systemic inflammation and endothelial dysfunction. One of these factors released from placental cells is the antiangiogenic factor. Also, there is an imbalance in the antioxidant and prooxidant mechanisms that are thought to be due to recurrent ischemia reperfusion injury in PE. The systemic inflammatory response in PE is associated with the immunological response resulting from the contact of the maternal immune cells with trophoblasts. The aim of this review is to present the current molecular mechanisms implicating the pathway leading to PE. The development of new insights into the pathogenesis of PE in conclusion of a better understanding of the relevant molecular mechanisms will guide further studies.

KEYWORDS: Preeclampsia, Angiogenic Proteins, Inflammation, Placentation.

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INTRODUCTION

Preeclampsia (PE) is a complication seen in approximately 4-5% of pregnancies (1). Despite promising therapies, it remains a leading cause of fetal and maternal morbidity and mortality (2, 3). PE criteria are ≥140 mmHg systolic blood pressure or ≥90 mmHg diastolic blood pressure after 20 weeks of pregnancy in a previously normotensive patient and ≥300mg proteinuria in 24-hour urine, 0.3 g/g protein: creatinine ratio or urine dipstick +1. In the updated classification, proteinuria criterion is not essential for diagnosis in the presence of other end organ damage, such as thrombocytopenia, impaired liver function, new renal failure, pulmonary edema or recent cerebral/visual disturbances. PE with severe features is any of the following: blood pressure ≥160/110 mmHg twice; platelet count <100,000 per microliter; impaired liver function as evidenced by two-fold elevated liver enzymes based on normal concentration or severe persistent right upper quadrant / epigastric pain; > 1.1 mg/dl (97.2 µmol/l) serum creatinine level with renal failure or doubling the serum creatinine level; pulmonary edema or new-onset cerebral, visual disorders (4).

Although significant progress has been made in the field of PE, the underlying pathogenesis remains unclear (4). The pathogenesis of PE can be examined in two stages. The first stage is placental ischemia caused by abnormal placentation. In the second stage, necrotic and apoptotic factors released from the ischemic placenta to circulation cause systemic inflammation and endothelial dysfunction. Abnormal placentation occurs in the early stage of PE without showing any clinical features. Placental ischemia/hypoxia, oxidative stress and immune mechanisms are involved. This is followed by maternal clinical syndrome with cardiovascular and renal findings. PE is defined as a multiorgan syndrome (5).

Abnormal Placentation

Transformation of the spiral arteries is assumed to be necessary to ensure the blood flow requirement in the placenta and to override the maternal vasomotor control (4). PE pathology begins with abnormal formation of maternal uterine spiral arteries (6). Spiral arteries that do not complete remodeling cause insufficient blood flow to the placenta at high pressure. The resulting placental ischemia/hypoxia causes the distortion of the placental villous structures, oxidative stress and following uteroplacental insufficiency (5).

Placental Ischemia and Hypoxia

Molecular mechanisms that mediate spiral artery remodeling are controversial. During normal pregnancy, cytotrophoblasts convert the adhesion molecules from the epithelial cell type to the vascular endothelial cell type. This transformation is necessary for the invasion of uterine spiral arterioles by cytotrophoblasts (7). Cytotrophoblasts that do not invade maternal spiral arterioles do not express endothelial adhesion markers such as vascular endothelial-cadherin (VE-cadherin) and alpha-V beta-3 (αVβ3) integrin, which are normally expressed by invading cytotrophoblasts (8). In human villus explants at 5-8 weeks of gestation, low oxygen tension triggers cytotrophoblast proliferation via hypoxia-inducible factor 1-alpha (HIF1α) (4). HIF1α and hypoxia-inducible factor 2-alpha (HIF2α) are products of oxygen sensing pathway. They regulate the expression of hypoxia-derived genes such as erythropoietin, vascular endothelial growth factor (VEGF) and nitric oxide (NO) synthase. The expression of HIF1α in human placentas increases in the first trimester. Permanently elevated levels of HIF1α may indicate placental stress and the development of PE (9). Studies have shown that preeclamptic placentas over-express HIF1α, HIF2α and do not reduce their expression on oxygenation. The reason for the consistently increased expression of HIF in preeclamptic placentas remains unclear, but it is associated with the pathway of 2-methoxy estradiol (2-ME) produced by catechol-O-methyltransferase (COMT) (4). 2-ME is an estradiol metabolite that increases during pregnancy and inhibits HIF1α (10).

Oxidative Stress

There is an imbalance between antioxidant and prooxidant mechanisms in PE. This imbalance is thought to be due to defective spiral artery remodeling which causes recurrent ischemia-reperfusion injuries (11).

The heme oxygenase (HO) pathway is an important mediator of oxidative stress. HO has three isoforms. HO1 and HO2 oxidize heme to produce biliverdin and carbon monoxide (CO). In the study, HO1 has been shown to be perivascular localized in human placental vessels and its induction has been shown to attenuate tumor necrosis factor (TNF) mediated cell damage. At the same time, the HO1 protein level decreased significantly in the preeclamptic placenta compared to the normotensive control placentas. In addition, adenoviral overexpression of HO1 in endothelial cells has been shown to inhibit placental release of antiangiogenic factors (4). In another study, induction of HO1 by cobalt protoporphyrin in PE animal model reduced sFlt-1 / VEGF (vascular endothelial growth factor) ratio and hypertension which is induced by placental ischemia (12).

Glrx (Glutaredoxin 1) is a cytosolic enzyme that reduces S-glutathionylation. It is an antioxidant enzyme whose localization is shown in the endometrium (13). Glrx activates the S-glutathionylation of nuclear factor kappa B (NFκB) components. With an increase of Glrx, the nuclear binding proteins of NFκB p65 / p50 increase. NFκB induces an increase in sFlt-1 with the Wnt5a pathway and inhibits angiogenesis in ischemia studies (14). Glrx, NFκB increase in PE has also been shown in various studies (15, 16).

Immune Mechanisms

The systemic inflammatory response in PE is associated with immunological response to the direct contact of the maternal immune cells with trophoblasts in the feto-maternal interface. This contact allows the tolerance of the maternal immune cells, resulting in trophoblast invasion or elimination of the feto-maternal interface. Also, this contact leads to the release of several factors, directly or indirectly. These are soluble factors (eg. cytokines), immunosuppressants (eg. progesterone and prostaglandins), specific suppressor molecules [eg. Human leukocyte antigen (HLA-G) and HLA-E], tolerogenic molecules [eg. TGF-β1 and interleukin (IL) -10] and immunomodulator products [eg. indoleamine 2,3-dioxygenase (IDO), Fas ligand (FasL) and TNF-associated apoptosis inducer ligand (TRAIL)] (17).

In the first trimester, 70% of the decidual lymphocytes are CD56bright CD16- NK (natural killer) cells. Other immune system cells in decidua are; 20% monocyte / macrophage, 10% T cells and 2% dendritic cells (18). These dNK cells are functionally different from the CD56dim, CD16+ NK cells in peripheral circulation. CD56bright CD16- dNK cells synthesize various chemokines, cytokines and growth factors and reduce cytotoxicity (17).

The recognition of HLA ligands expressed on trophoblasts by the maternal immune system induces immune response that controls trophoblast invasion and placentation via various factors (17). Extravillous cytotrophoblasts express an HLA class Ia molecule (HLA-C) and HLA class Ib molecules (HLA-E, HLA-F and HLA-G) (19). Fetal trophoblasts do not express HLA-A, HLA-B and MHC-II, which protect them from T cells (18). dNK and T cell subgroups express killer cell immunoglobulin-like receptors (KIRs) which interact with HLA ligands. Polymorphic KIRs are named according to their activator and inhibitory properties. While there are many activator receptors in maternal KIR haplotype B, there are only inhibitory receptors in KIR haplotype A (20). The interaction of KIR haplotype B and HLA-C stimulates the production of immunoregulatory cytokines and angiogenic factors from dNK cells (17). In particular, some of these factors serve as the major chemoattractants for trophoblasts [eg. CXCL10 / IP-10 (IFNγ induced protein), CXCL8 / IL-8, CXCL12 / SDF-1 (stromal cell derived factor) and CCL2 / MCP-1 (monocyte chemoattractant protein 1)] (18). These dNK cell-mediated factors provide sufficient trophoblast invasion and remodeling (17). HLA-G interacts with KIR2DL4, ILT2, ILT4 receptors in dNK cells and interacts with CD8 in T cells. This recognition causes apoptosis of CD8 + T cells via Fas / FasL pathway and protects trophoblasts from T cell-mediated cytotoxicity (21).

Interaction that can lead to a strong inhibition of KIRs, inhibits NK cell activation. This event is thought to play a role in PE. Inadequate activation of dNK cells leads to lysis of trophoblasts without HLA-G. The loss of trophoblasts that should invade the spiral arteries prevents placental development and spiral artery remode-

ling. For adequate activation of dNK cells, the haplotype B KIR receptor-ligand interaction is more important than the inhibitor haplotype A. Binding of KIR-AA haplotype without activator receptor to fetal HLA-C2 increases the sensitivity of PE. In PE, the interaction of KIR-AA and HLA-C causes defective angiogenic factors and increased antiangiogenic factor [sFlt-1, sEng (soluble endoglin)] release from dNK cells. At the same time, immunomodulators (IDO, TRAIL), CD30 (TNF receptor family, Th2 polarization marker) and HLA-G expression are also reduced (17).

Decidual macrophages existed throughout pregnancy and tissue repair, are associated with angiogenesis factors [eg. metalloproteinases (MMPs), vascular endothelial growth factor (VEGF)]. M2-type macrophages induce the expression of immunosuppressive cytokines (IL-10, IL-35), regulatory T cells (Treg) and phagocytose apoptotic trophoblast cells to prevent the release of proinflammatory cytokines. It also inhibits the cytotoxic function of dNK cells. Thus, it provides an immuntolerogenic environment. The polarization of M2 macrophages depends on Th2 immunosuppressive cytokines, which are present in low concentrations in PE (17). Studies have shown that decidua-specific VEGF stimulates the transition of macrophages into immunomodulatory M2-type macrophages. In PE, increased levels of sFlt1 prevent VEGF signal and M2 type macrophage population (22).

Normal placentation is also characterized by a profile of T cells and their cytokines. Decidual T cells are predominantly CD8 + phenotypes. While they regulate trophoblast invasion, CD4 + Treg cells increase the tolerance to the fetus. Decidual cells (DCs) are also thought to play a role in the differentiation of CD4 + T cells to the Th2 phenotype and in the regulation of dNK cell proliferation. Type 2 T helper (Th2) cytokines are predominant in the second trimester (eg. anti-inflammatory IL-4, IL-10, IL-13). Progesterone, estradiol, prostaglandin D2 and leukemic inhibiting factor promote the development of Th2 profile. In contrast, PE is characterized by an imbalance of Th1 cells and their associated cytokines, such as IFNγ. Upregulation of T helper 1 (Th1) cytokines containing IL-2, IL-6, IL-8, IL-12, TNF-α, IFN-γ and IL-17, and downregulation in IL-4, IL-10 production are observed in PE (17). This imbalance probably affects poor placentation and resulting maternal inflammation and endothelial dysfunction (4). The effective mediators of Th1 / Th2 transformation are not well understood (17).

IL-33 is a cytokine from the IL-1 family and induces Th2 response by binding to its receptor ST2 in normal pregnancy. sST2, in soluble form, triggers a predominant Th1 response with IL-33 inhibition. IL-33 and sST2 are thought to play a role in the pathogenesis of PE. In studies, IL-33 inhibition adversely affects trophoblast migration and invasion (23, 24).

Th1 cytokines (TNF-α, IL-2, IL-12, IL-18, and IFNγ) induce trophoblast apoptosis. Also, IFNγ and IL-12 inhibit angiogenesis. TNF-α from Th1 cytokines inhibits NO release and induces endothelial dysfunction (17). The chronic increase of proinflammatory cytokine TNF-α stimulates sFlt-1 secretion (25).

Th17 cells are the subgroup of CD4 + lymphocytes that produce proinflammatory IL-17. Some of the IL-17-producing cells have also been shown to produce Th1 cytokines (eg. IFNγ) (17). These are called Th17 / Th1. A small number of cells produce IL-4 together with IL-17, which is referred to as Th17 / Th2 (26). Pathogenic decidual Th17 / Th1 cells exist in unexplained recurrent abortions while Th17 / Th2 cells are present in healthy pregnancy. Treg and Th17 pass through similar stages of development. The increase at the ratio of Th17 to Treg cells in peripheral blood in PE is responsible for the increased maternal inflammatory response to the fetus (27). The proinflammatory cytokines and the predominant Th1 environment in the PE may be associated with Th17 differentiation. IL-1β and IL-6 inflammatory environment may contribute to the transformation of Treg cells into Th17. Also, dNK cells play a role in Th17 transformation and inflammatory response suppression by IL-10 and TGFβ1 (17). Another aspect of impaired immune tolerance in PE is reduction of CD4 + / CD25 + / FoxP3 + regulatory T cells (Treg) in peripheral blood and decidua (28). The proinflammatory environment in PE is thought to affect the Treg population (29). There are also studies on the effect of IL-33 on Treg function (30).

Complement activation from immunological mechanisms stimulates monocytes, leading to

the release of antiangiogenic factors. Recurrent pregnancy losses, preterm birth and PE are associated with complement activation, especially C5a, which increases the anti-angiogenic factor of sFlt-1 (17). It is also found that the possibility of developing PE was higher in women with higher levels of complement Bb (alternative pathway marker) (31). In another study, C4a deficiency and C4bp (classical pathway inhibitor) deposits are shown in preeclamptic placenta (17).

Maternal Syndrome

The symptoms of PE are not limited to the placenta. It can cause widespread effects that can be seen as maternal syndrome (4). In the second stage of PE, placental ischemia and increased placental oxidative stress result in severe systemic inflammation and endothelial dysfunction manifested by new-onset hypertension and proteinuria. Oxidative stress results in placental necrosis and apoptosis. The trophoblast microparticles shedding into maternal circulation indicate ischemia and apoptosis in placental cells. These microparticles create an inflammatory load and indirectly affect endothelial function (17).

Biochemical Factors

There are several possibilities for stimulating inflammation in PE. Some of these possibilities are factors released by endothelial injury. These are proinflammatory cytokines, oxidative stress markers, thrombomodulin, fibronectin, endothelin-1 and Von Willebrand factor. Some other factors release from placental cells such as antiangiogenic factors (17). Protein-toxic aggregates such as transthyretin also increase in PE. Transthyretin is released from the trophoblasts through vesicles and is transported to outside of the cell. Transthyretin in these vesicles can lead to cellular stress response by providing targeted delivery of toxic proteins to other maternal organs. Therefore, it is thought to play a role in the response of inflammation in PE (32).

Studies support the pathological role of imbalance in circulating angiogenic factors in the etiology of the maternal syndrome (4). VEGF is an endothelial mitogen factor and proangiogenic stimulating vasculogenesis. It also affects vascular permeability and vasodilatation. VEGF is mostly produced from the placenta, also from the monocyte and endothelium. Specific receptors are the vascular endothelial growth factor receptor (VEGFR1 / Flt-1) in the placenta and the VEGFR2 / kinase insert domain receptor (KDR) in the vascular endothelial cell (33). VEGF activates eNOS (endothelial NO synthase) by increasing intracellular calcium through PI3K (phosphatidylinositol 3 kinase) / Akt signaling pathway. Another pathway also activates MAPKs (mitogen-activated protein kinases) and PLA2 (phospholipase A2) via PKC (protein kinase C). As a result, PGI2 (prostacyclin) increases. Thus, vasodilatation and permeability are increased by PGI2 and NO (34). TGF-β1 also plays a role in angiogenesis by regulating VEGF expression (35). PlGF is a member of the VEGF family produced by trophoblasts. It is also released by the endothelium (36). PlGF is involved in vasculogenesis and vasodilatation via binding Flt-1 (33). In normal pregnancy, PlGF circulation begins at the 8th week and reaches its maximum concentration towards the end of the 2nd trimester and decreases until delivery (36). PlGF concentration decreases in PE (33).

Antiangiogenic sFlt-1 / sVEGFR-1 is produced by placenta and passed into maternal circulation. sFlt-1 increases in the third trimester of normal pregnancy. sFlt-1, overexpressed from endothelial cells and trophoblasts of ischemic placenta in PE, induces maternal endothelial dysfunction leading to preeclamptic symptoms (33). sFlt-1 is a soluble variant of membrane bound receptor VEGFR1 that binds to proangiogenic proteins VEGF and PlGF; therefore, sFlt-1 acts as a ligand trap, reducing free VEGF and PlGF. Nonfunctional VEGF which could not bind to its receptor leads to increased VEGF in preeclamptic placenta. High levels of sFlt-1 binding VEGF and PlGF cause endothelial cell dysfunction in various organs (4). It has also been shown that sFlt-1 indirectly inhibits VEGF mediated NO synthesis, thus leading to increased reactive oxygen products and vasoconstriction (2). Increased sFlt-1 causes placental insufficiency via inhibiting cytotrophoblast differentiation and invasi-

on (17). Syncytial fragments shedding into the maternal circulation have been described as an important source of placental sFlt-1 in PE (4).

sEng is an antiangiogenic protein that inhibits the TGFβ signaling pathway (2). ENG (endoglin) is a membrane glycoprotein involved in the TGF beta receptor complex (TGF-β1 and TGFβ3). It is produced by endothelium and monocytes. Trophoblasts in the placenta are also an important source of ENG. The primary roles of ENG are angiogenesis, endothelial cell differentiation and vascular tone regulation via eNOS (37). The proteolysis of the extracellular part of the ENG creates the sEng that limits eNOS due to the TGF-β function (2). TGF-β is an anti-inflammatory and vasodilatory factor and its elimination with sEng leads to vasoconstriction and endothelial dysfunction (33). sEng is highly expressed in PE and eclampsia (4). sEng regulators are not known exactly. However, similar to sFlt-1, angiotensin II receptor (AT-1) autoantibodies stimulate the release, while HO-1 inhibits the release (2). sEng, as in sFlt-1, is expressed in hypoxia and oxidative stress conditions but is also stimulated by inflammatory TNF-α and IFNγ released from endothelial and placental cells (38). Carbon monoxide (CO), the HO-1 metabolite, inhibits sFlt-1 and sEng expression. Due to HO-1 role in the pathogenesis of PE, women with PE have less CO exhalation than normal pregnants (39).

Hypertension

Hypertension occurring in PE does not appear to be mediated by the renin-angiotensin-aldosterone system (RAAS), because renin, aldosterone and angiotensin II levels decrease in PE compared to physiological increase in normal pregnancy. This hypertension may develop with antiangiogenic factors and angiotensin II type 1 receptor agonistic autoantibodies (AT1-AA) (4). Increased production of various mediators such as sFlt-1, sEng, STBMs(syncytiotrophoblast microparticles), inflammatory factors, AT1-AA and reactive oxygen species (ROS) released by the hypoxic placenta causes vascular endothelial dysfunction. In addition, in PE, NO, PGI2 levels which are endothelium-derived vasodilators in the plasma decrease and vasoconstrictors such as endothelin-1 (ET-1), thromboxane A2 (TXA2), Ang II and AT1R increase (33). Upregulation of the bradykinin (B2) receptor and the heterodimerization of B2 with AT1s are thought to contribute to hypertension and increased angiotensin II response in PE. However, there is no human experimental study of the pathway yet (40). The hydrogen sulfide (H2S) system is another important pathway in vasodilatation and angiogenesis. H2S decreases in PE. Because placental expression of cystathionine lyase, the enzyme responsible for the production of H2S, has been reduced (4).

The mechanisms that are effective in the development of PE are not fully known. However, ischemic environment, oxidative stress, released immunological and biochemical factors, inflammation and endothelial dysfunction are factors triggering PE. This review summarizes our current understanding of the molecular mechanism of PE. The development of new insights into the pathogenesis of PE in conclusion of a better understanding of the relevant molecular mechanisms will guide further studies.

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