Hypoxia in the pathogenesis of preeclampsia

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Oxidative stress is required for the development of hypoxic injury and has been investigated as a key factor in the pathogenesis of preeclampsia. In preeclampsia, hypoxia at the implantation site can contribute to lesion formation, leading to poor placentation. Hypoxia-inducible factor-1α (HIF-1α) is a known transcription factor involved in placentation. Increased levels of HIF-1α can induce secretion of soluble vascular endothelial growth factor receptor-1 (sFlt-1), which is known to be a major factor influencing the pathogenesis of preeclampsia. Meanwhile, HIF-1α and HIF-1β mediate the maintenance and production of endothelial progenitor cells and bone marrow-derived stem cells, which play important roles in placental vascular development. Related dysfunction can result in preeclampsia. It is also known that glycolytic enzyme phosphoglycerate mutase (PGAM) is deacetylated and activated by reactive oxygen species (ROS), the former of which may regulate cell proliferation through the effects of ROS without the participation of HIF-1α. In this review, we characterize the roles of HIF and PGAM in the pathogenesis of preeclampsia.

Introduction

Preeclampsia is a pregnancy-specific disorder associated with hypertension and proteinuria. The condition manifests in 7–10% of pregnancies, causing high maternal and fetal morbidity and mortality. The pathophysiology is partly explained as poor placentation, which is caused by impaired trophoblast invasion. Recently, the “two-stage disorder theory” was proposed to explain the pathogenesis of preeclampsia. During the first stage of pathogenesis, extravillous trophoblasts (EVTs) invade the uterine decidua and myometrium, resulting in the remodeling of maternal spiral arteries 2 weeks after implantation. This remodeling carries maternal blood to the fetus. Shallow placentation results in unsuccessful vascular transformation, impairing fetal viability and increasing the risk for preeclampsia. According to the “two-stage disorder theory”, during the second stage of pathogenesis, maternal humoral factors (including reactive oxygen species [ROS]) are secreted from the placenta into the systemic circulation. In preeclampsia, ROS are produced in poorly perfused placentas, inducing vasoconstriction and resulting in endothelial dysfunction. Conversely, nitric oxide (NO) stimulates vasodilation, leading to increased uterine blood flow in normal pregnancy. Women who subsequently develop preeclampsia show increased ROS levels and decreased NO levels, even in early pregnancy. An imbalance between ROS and NO levels is thought to contribute to vasodilatory dysfunction in preeclampsia. The site of implantation is known to be hypoxic in early pregnancy. Soon after formation, the placenta exhibits oxygen concentrations as low as 3%. Hypoxia is necessary for the invasion of EVT into the uterine decidua and myometrium. Under hypoxic conditions, hypoxia-inducible factor (HIF)-1, a hypoxia-dependent transcription factor, plays several important roles, including that in the modulation of placental development. HIF-1 is stimulated by oxidative stress and growth factors to induce glycolytic activity.
hypoxia, glycolytic enzyme phosphoglycerate mutase (PGAM) activates glycolysis independently of HIF-1, leading to cellular senescence and proliferation.9) Under such conditions, the stabilized HIF-α subunit dimerizes with the HIF-1β subunit and activates the transcription of target genes involved in glucose metabolism, erythropoiesis, iron homeostasis, angiogenesis, and cell survival.10) HIF-1α is activated under hypoxic conditions and induces the transcription of numerous genes. HIF-1α is rapidly inactivated in normoxia, whereas HIF-1β is constitutively expressed and active. HIF-1α is abundantly expressed in the placenta, especially in early pregnancy, and is involved in placenta and placentation function.11) The abnormal protein reaction under hypoxic conditions could contribute to the pathogenesis of preeclampsia.12,13)

1. Hypoxia-related transcription factors in the physiology of pregnancy and the pathogenesis of preeclampsia

HIF is a heterodimeric transcription factor that consists of subunits α and β. Subunit-α consists of components 1α, 2α, and 3α. Under hypoxic conditions, HIF is transferred into the nucleus, where it regulates the expression of hypoxia-related genes, and HIF regulates cellular reactions under hypoxic conditions. Placenta occurs under hypoxia and the activity of subunit-α depends on the partial pressure of oxygen. Activated HIF-1α leads to poor placenta, which can lead to preeclampsia. In contrast, subunit-β is stable, its activity is independent of the partial pressure of oxygen, and HIF-1β induces hypoxic genes that are critical for normal placenta.14) Cowden et al. reported that a HIF-1β-deficiency in the placenta can lead to poor placenta.15) Hypoxia is thought to induce the production of vascular endothelial growth factor (VEGF), and enhances EVT invasion through the expression of adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) for placental vasculogenesis; this occurs through HIF-1β activation and HIF-1α reduction.

HIF is also critical for EVT invasion into the maternal uterine decidua and myometrium during placenta. For trophoblast invasion, EVTs should be differentiated from cytotrophoblasts; EVTs reconstitute maternal spiral arteries until 12 weeks of gestation. EVTs replace endothelial cells in the spiral arteries to supply sufficient maternal blood for placental perfusion. In preeclampsia, EVT invasion is disrupted and placenta is shalow. Disturbed placental angiogenesis impairs placental perfusion, leading to the production of abundant soluble vascular endothelial growth factor receptor-1 (sFlt-1) (an antagonist of VEGF) and soluble endoglin (sEng) (an antagonist of transforming growth factor [TGF]-β co-receptor), and reduces the production of placental growth factor (PIGF), which appears in the maternal circulation several weeks before the onset of preeclampsia. Placental hypoxia is thus thought to play an important role in the pathophysiology of preeclampsia (PE). Expression of placental HIF-1α and HIF-2α are increased in PE,16) which is characterized by placental hypoxia.17,18) HIF-1α and HIF-2α may regulate plasminogen activator inhibitor-1 (PAI-1) levels in cytotrophoblasts in a hypoxia-dependent manner during the 1st trimester of pregnancy.19) It is important that prolonged placental hypoxia and elevated level of placental PAI-1 in the placentation dysfunction in PE.

HIF-1α, -1β, and HIF-2α are also involved in hematopoiesis.20,21) The embryo encounters physiologic hypoxia in the uterine endometrium, and HIF is essential for the proliferation or survival of hematopoietic precursor cells during embryonic development. Furthermore, the levels of HIF-1α could modulate the mobilization of hematopoietic stem cells (HSCs) from or to the bone marrow.22) Hematopoiesis early in pregnancy is required for vasculogenesis. HIF-1α contributes to angiogenesis through VEGF production in an arylhydrocarbon receptor nuclear translocator (ARNT)-dependent manner.

Recently, it was suggested that placental trophoblast NAD(P)H oxidase plays an important role in the pathogenesis of preeclampsia through increased free radical generation.23,24) ROS are essential for the stability of HIF-1α; ROS scavengers may inhibit HIF-1 activity by neutralizing ROS and attenuating cellular proliferation leading to G1/S cell cycle arrest.25–27) HIF-1 is involved in this process during normal pregnancy. HIF-1 may influence the physiology of pregnancy through angiogenesis and embryonic development, as well as the pathogenesis of preeclampsia through ROS generation.

1-1. Hypoxia early in normal pregnancy

The expression and activity of HIF are reduced under normoxic conditions. Prior to remodeling of the spiral artery early in normal pregnancy, the implantation site is hypoxic; the resulting stimulation of HIF may play a critical role in normal pregnancy. It is thought that hypoxia is shorter in normal pregnancy than when preeclampsia is involved. Rajakumar et al. reported that physiological hypoxia leads to high expression of HIF-1α and -1β in the placenta early on.16) HIF-1α and -2α could be involved in the expression and function of many genes and proteins required to maintain normal pregnancy. TGF-β3 may inhibit cytotrophoblast differentiation, resulting in impaired EVT invasion early in the placenta.28) Furthermore, the levels of TGF-β3 and HIF-1α are positively correlated in the placenta. Lower levels of HIF-1α in hypoxic conditions inhibit the expression of TGF-β3, leading to decreased cellular proliferation and gelatinase A activity.29) HIF-2α modulates the expression of several molecules.
A HIF-2-specific cytoskeletal regulatory protein, LIM domain kinase 1 (LIMK1), is stimulated by HIF-2α and regulates the trophoblast cytoskeleton. Cytoskeletal integrity is an important component of EVT invasion. LIMK1 mediates EVT invasion by regulating the secretion of matrix metalloproteinase (MMP) from trophoblasts in the maintenance of normal pregnancy.30)

1-2. Hypoxia in preeclampsia

HIF-1α is expressed at high levels in the preeclamptic placenta and induces the production of sFlt-1 and sEng.31,32) Furthermore, HIF-1α overexpression reportedly induces a HELLP syndrome-like phenotype and fetal growth restriction.33) HIF-2α also regulates LIMK1, which modulates MMP expression and cytoskeletal integrity during EVT invasion. LIMK1 may also be involved in the differentiation of cytotrophoblasts into syncytiotrophoblasts through the cytoskeletal rearrangement of cytotrophoblasts, a mechanism critical for normal pregnancy. However, LIMK1 is reduced in the preeclamptic placenta, resulting in impairment of both EVT invasion and differentiation into syncytiotrophoblasts, leading to poor placentation.14) HIF is thus critical for the pathogenesis of preeclampsia.

Inflammation is integral to the pathogenesis of preeclampsia. In this context, inflammation is characterized by increased vasoconstriction and peripheral vascular resistance, which decreases uteroplacental blood flow, leading to placental dysfunction.34) In endothelial cells and trophoblasts, inflammation is associated with expression of ICAM-1, which impairs uteroplacental perfusion in preeclampsia.35) Inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNFα), and interferon-γ (IFNγ) induce the expression of inducible nitric oxide synthase (iNOS) in the vascular wall,36) causing excessive NO production, which in turn results in vascular collapse. Excess NO might lead to multiple organ failure in preeclampsia by accelerating inflammation and other immune reactions.

Antigen-presenting cells called macrophages also play an important role in inflammation. Macrophages display antigens on their surface via the major histocompatibility complex (MHC), which is recognized by T-cell receptors (TCRs). Macrophages that participate in inflammation can be divided into two types: M1 and M2 macrophages. M1 macrophages are induced by lipopolysaccharide (LPS) and IFNγ and secrete TNFα and IL-1β. Moreover, M1 can secrete NO through iNOS activation; this process is mediated by HIF-1α and yields active inflammation. M2 macrophages are activated by IL-4 and IL-13 and can reduce inflammation. M2 may activate arginase 1 and reduce the production of NO by HIF-2α.37)

In preeclampsia, erythropoietin (EPO) is increased in umbilical venous plasma.38) Hypoxia is known to stimulate the expression and activity of EPO.39) Severe placental hypoxia could induce the expression and activity of EPO in preeclampsia. Early in preeclampsia, disturbed remodeling of spiral arteries can render the uteroplacental circulation severely hypoxic. Previous studies have reported that the expression of EPO is regulated by HIF in hypoxia to stimulate bone marrow-derived hematopoiesis.10) Hypoxic induction of EPO in the kidney is known to be HIF-2-dependent,40) and HIF-2α, rather than HIF-1α, plays an important role in regulating the expression of endocrine EPO.41) EPO could stimulate hematopoiesis of erythroblasts via the EPO receptor in bone marrow. Increased EPO stimulates the proliferation of erythroblasts and erythrocyte progenitor cells from activated hematopoietic stem cells.

These trends affect fetal circulation. Fetal nucleated red blood cells (NRBCs) are reportedly increased in preeclampsia.38) Although increased levels of EPO are thought to stimulate the differentiation of endothelial progenitor cells (EPCs) from hematopoietic stem cells, the proliferation and differentiation of EPCs is reduced in the fetal circulation of preeclampsia. Furthermore, previous research from our laboratory indicates that EPO is an important contributor to the pathogenesis of preeclampsia.38) Previous research also suggests that preeclampsia involves severe hypoxia of the uteroplacental but not the systemic circulation. EPO could stimulate VEGF production from NRBCs, thereby stimulating EPC proliferation. In normal pregnancy, EPO induces placental vascularization through EPC proliferation. However, VEGF production in NRBCs derived from preeclampsia is not reactive to EPO, and increased NRBCs in fetal circulation disturb fetal EPC proliferation, resulting in placental hypo-vasculature in preeclampsia.

Preeclampsia involves disturbance of the EPC mobilization from bone marrow into maternal circulation. HIF-1 is thought to affect the pathogenesis of preeclampsia through several distinct mechanisms. One source of EPCs is hematopoietic stem cells. EPCs are critical for placental vasculogenesis, and thus impaired EPC mobilization could lead to preeclampsia. Therefore, HIF dysfunction may contribute to the pathogenesis of preeclampsia through EPC-induced vasculogenesis.42)

Another contributor to the pathogenesis of preeclampsia is decreased levels of 2-methoxyestradiol (2-ME), a natural metabolite of estradiol. Decreased levels of 2-ME result in elevated levels of sFlt-1.43) Preeclamptic symptoms induced by 2-ME are thought to be mediated by the inhibition of HIF-1α. Levels of 2-ME increase throughout gestation and inhibit HIF-1α function during normal pregnancy. Decreased levels of HIF-1α mediated by siRNA reduces EVT invasiveness.44) Under conditions of placental hypoxia, 2-ME may play a critical role...
role in EVT invasion leading to abundant placental vascularization.\(^{45}\) In the hypoxic conditions caused by preeclampsia, high HIF-1\(\alpha\) leading to increased sFlt-1 and sEng could decrease levels of 2-ME and thus inhibit EVT invasion.\(^{33}\)

Under hypoxic conditions, the balance between HIF-1\(\alpha\) and HIF-2\(\alpha\) is important for the process of inflammation in the pathogenesis of preeclampsia.

1-3. PGAM and hypoxia
PGAM appears to be another important factor mediating the pathogenesis of preeclampsia; however, the underlying mechanism remains to be elucidated. PGAM is a glycolytic enzyme that mediates the conversion of 3-phosphoglycerate to 2-phosphoglycerate. PGAM1 is expressed in brain and other many organs, while PGAM2 is mainly expressed in muscle. PGAM acts independently of HIF-1 to induce cellular proliferation through glycolysis, resulting in cancer progression.\(^{46}\) PGAM also reduces cellular senescence under hypoxic conditions, decreasing oxidative stress through the inactivation of NADPH. Conversely, oxidative stress activates PGAM by promoting binding between SIRT2 and PGAM.\(^{47,48}\) PGAM may also play an important role in hypoxic condition for the pathogenesis of preeclampsia.

**Conclusion (Figure 1)**

In early pregnancy, the implantation site is hypoxic, and these hypoxic conditions activate HIF and PGAM in the surrounding tissue. Activation of HIF and PGAM is critical for trophoblast proliferation and EVT invasion, which result in deep placentation through spiral artery reconstitution. In the pathogenesis of preeclampsia, the process of placentation early in pregnancy under hypoxic conditions is critical. In normal pregnancy, the uteroplacental circulation is normoxic after placentation is complete; however, hypoxia continues in preeclampsia due to shallow placentation. Spiral artery reconstitution is particularly important for pathogenesis, resulting in shallow placentation and poor placental vascularization. Under hypoxic conditions, the HIF-PGAM axis is thought to play an important role in the pathogenesis of preeclampsia.

**Author Contributions**

Keiichi Matsubara drafted the manuscript, performed the literature review, and prepared the figures.

**Abbreviations**

ARNT, arylhydrocarbon receptor nuclear translocator; EPC, endothelial progenitor cell; EPO, erythropoietin; EVT, endovascular trophoblast; HIF, hypoxia-inducible factor; HSC, hematopoietic stem cell; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; IFN\(\gamma\), interferon \(\gamma\); IL-1, interleukin-1; IL-6, interleukin-6; LIMK, LIM domain kinase; LPS, lipopolysaccharide; 2-ME, 2-methoxyestradiol; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NRBC, nucleated red blood cell; PGAM, glycolytic enzyme phosphoglycerate mutase; PlGF, placental growth factor; ROS, reactive oxygen species; sEng, soluble endoglin; sFlt-1, soluble vascular endothelial growth factor receptor-1; TCR, T-cell receptors; TGF\(\beta\), transforming growth factor \(\beta\); TNF\(\alpha\), tumor necrosis factor \(\alpha\); VEGF, vascular endothelial growth factor.

**Conflicts of Interest**

The authors declare no conflict of interest.

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