REVIEW PAPER

The role of molecular factors in gestational hypertension and the pathogenesis of preeclampsia

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Highlights

• Preeclampsia is characterized by high blood pressure and protein excretion in pregnant women after 20 weeks.

• The sFlt-1 molecule is involved in the pathogenesis of preeclampsia by interfering with angiogenesis.

• Cell signaling associated with inflammation and oxidative stress might have main a role in preeclampsia.

• Molecules involved in microRNA biogenesis are involved in the preeclampsia pathogenesis.

Graphical Abstract
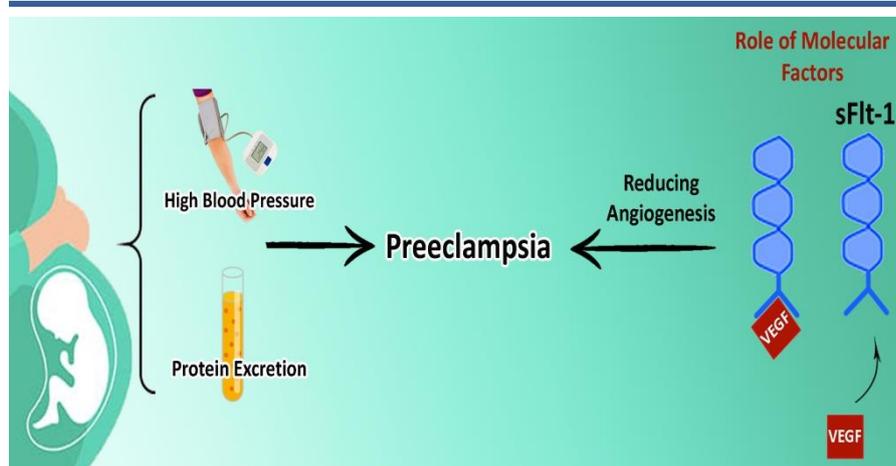
Abstract

Preeclampsia (PE) is classified as a systemic condition that generally develops with high blood pressure and protein excretion in pregnant women after 20 weeks. This condition is characterised by inadequate placental blood flow and damages several organs. The illness is a complicated ailment that starts with an aberrant trophoblast invasion of the uterine decidua, endothelial dysfunction, and platelet aggregation, finally leading to a faulty placenta. Defective placenta causes difficulties such as hypoxia, oxidative stress, stimulation of the mother's immune system, and some other situations. Although the specific origin of this illness has not yet been discovered, various cellular signalling pathways may be implicated in its development. One of the molecules that may be implicated in preeclampsia is the sFlt-1 molecule. This protein has an inhibitory influence on vascularization of the placenta by lowering signalling VEGF, which leads to apoptosis of foetal vascular and disrupted placenta and exchange of nutrients, which finally leads to foetal growth limitation and preeclampsia. The renin-angiotensin-aldosterone pathway, inflammatory cytokines, and the Nrf2/HO-1 pathway are also implicated in the pathophysiology of this condition. The biogenesis route of microRNAs involved in controlling gene expression might be regarded as extra variables implicated in preeclampsia. The goal of this work was to elucidate the molecular components involved in the pathophysiology of preeclampsia.

Introduction

Gestational hypertension is the most common medical problem during pregnancy. Pregnancy blood pressure disorders occur among 5-10% of women. Mothers who develop blood pressure disorders throughout pregnancy are at risk of intrauterine growth retardation, abruption of the placenta, preterm labor, and the disease has a variety of long-term complications for both fetus and mother. The risk of fetal death in this disease is 3.6 per 1000 pregnancies (1). The American College of Obstetricians and Gynecologists (ACOG) divides gestational hypertension into four categories to facilitate the diagnosis of gestational hypertension during pregnancy, including gestational hypertension, chronic hypertension, and chronic hypertension with preeclampsia (PE), and preeclampsia-eclampsia (2). Gestational hypertension is a blood pressure that suddenly appears after 20 weeks of pregnancy with no signs of dysfunction of the organ. Chronic hypertension is the blood pressure that a person has before pregnancy. Chronic hypertension with preeclampsia refers to organ dysfunction in women with chronic hypertension. This type of high blood pressure occurs when an individual suffering from high blood pressure before pregnancy and after pregnancy, high blood pressure intensifies and protein excretion in the urine and other complications of high blood pressure during pregnancy are observed in her. Preeclampsia-eclampsia occurs when a healthy person's blood pressure rises after 20 weeks of pregnancy and there is evidence of damage in organ with proteinuria, hepatic or renal dysfunction, and thrombocytopenia, and pulmonary edema, central neurological and visual disturbances (3).

However, preeclampsia is a major problem in pregnancy. It is a multifactorial disorder defined as a systemic syndrome that is usually correlated with high blood pressure (diastolic blood pressure BP≥ 90 mm Hg or systolic BP≥ 140 mm Hg) and protein excretion appears in pregnant women for the first time after 20 weeks. Approximately 5-7% of pregnant women are affected and it kills 70,000 mothers and 500,000 fetuses worldwide each year (4). To date, the exact cause of preeclampsia has not been determined, but the placenta is considered to be the main cause of this disease, and its treatment is currently delivery and removal of the fetus and placenta from the mother. This syndrome is characterized by poor placental blood flow and may affect several organs. Preeclampsia is a complex phenomenon that begins with an abnormal trophoblast invasion and endothelial dysfunction and has a variety of both short-term and long-term destructive effects on the fetus and mother, including seizures (eclampsia), elevated transaminases, and hemolytic anemia, thrombocytopenia, HELLP syndrome followed by kidney, heart, lung, and stroke disorders. Fetal problems of preeclampsia include fetal growth retardation, preterm delivery, hypoxia-related neurological damage, cardiovascular disease, and can ultimately lead to maternal and fetal death (5). The severity of preeclampsia depends on the symptom's onset time. Premature preeclampsia puts the fetus at a higher risk of mortality and preterm birth than preeclampsia which appears late in pregnancy (6).

The preeclampsia mechanism is not identified exactly, but according to research, abnormal placenta due to low invasion of cytotrophoblasts and incomplete reconstruction of spiral arteries in the first trimester of pregnancy and maternal syndrome due to imbalance between maternal hormones, immune cells, maternal genetics, miRNA involvement, etc. in the second and third trimesters of pregnancy that lead to organ damage and clinical manifestations have been identified as major contributors to the disease. The aim of this study was to investigate the role of molecular factors in gestational hypertension and the pathogenesis of preeclampsia (7).

The sFlt-1 as a key molecule in the preeclampsia disorder

Soluble fms-Like Tyrosine Kinase 1 (sFlt-1) is a 90 to 100 kDa glycosylated protein produced by the Flt-1 gene. This molecule acts as a deceptive receptor by bonding to PlGF and VEGF and reducing them in the mother's bloodstream, therefore, reducing the ability of these factors for angiogenesis. Although its levels in the mother's bloodstream increase dramatically during pregnancy, they increase more in preeclampsia than in normal pregnancies, leading to the assumption that excess sFlt-1 levels are a major cause of maternal vascular symptoms (8). Trophoblast cells are the main producer of sFlt-1. The sFlt-1 level in the serum of a healthy pregnant person is 20 to 50 times higher than that of a non-pregnant person, which indicates its importance in a regular pregnancy. This molecule works as a controller of trophoblast invasion of uterine decidua and

maintains the position of the placenta at the appropriate depth of the uterine wall (9). At 11 weeks of gestation, in preeclamptic placenta, production of sFlt-1 is significantly elevated. The elevated expression occurs 5 weeks before the start of clinical signs. According to research, preeclamptic placenta has indicated a 4-fold elevation in levels of sFlt-1 compared to people with normal pregnancies (10).

sFlt-1 play an inhibitory role on vascularization of placenta by reducing VEGF signaling, which leads to apoptosis of fetal vascular and disrupted placental and nutrient exchange, which ultimately leads to restriction of fetal growth and preeclampsia. PlGF and VEGF-A have an important role in fetal angiogenesis during pregnancy. Although expression of VEGF-A is crucial for angiogenesis/vasculogenesis in the fetus, a 2-3-fold elevation in it could stop fetal growth. Also, overexpression of VEGF-A causes vascular defects of the placenta and loss of the fetus. This suggests that limiting levels of VEGF is crucial for placental growth and survival of the fetal. VEGF is essential for angiogenesis, but high doses can cause vascular defects, fetal growth retardation, and miscarriage. sFlt-1 and VEGF must be in equilibrium, and an imbalance in the amount of production and inhibition of these two factors can lead to preeclampsia (11, 12).

Factors regulating sFlt-1 expression

The following are some of the factors that cause abnormal increases of sFlt-1 in preeclamptic women in the placenta tissue: a) high expression of VEGF-A causes regulation and production of sFlt-1 and reduces the ability of trophoblast cells to migrate and invade the uterine decidua and eventually cause incomplete placenta and preeclampsia. b) Retinoic acid (RA) negatively regulates the expression of sFlt-1 in decidua stromal cells. Because decidual cells preeclampsia show lower RA. c) Nitric oxide (NO) stops high blood pressure throughout pregnancy and reduces sFlt-1 and VEGF in plasma. Inactivation of NO leads to endothelial impairment and thus results in preeclampsia. d) Mitochondrial dysfunction leads to ROS production. ROS produces HIF, and HIF produces sFlt-1. Deficiencies in the proper functioning of maternal stromal cells can result in sFlt-1 overexpression (13).

Renin-angiotensin-aldosterone pathway in preeclampsia

The altered renin-angiotensin-aldosterone (RAAS) pathway was implicated in the etiology of preeclampsia. Numerous studies demonstrate that preeclampsia causes an increase in angiotensin II levels compared to normal pregnancies. Indeed, autoantibodies such as ATI-AA stimulate the activity of angiotensin II receptors, increasing their concentration in the mother's blood and thereby raising blood pressure. Indeed, physiological dysfunction in the endothelium results in the synthesis of endothelin-1 (ET-1). Endothelin itself is a cause of hypertension and proteinuria. Additionally, hypertension inhibits renin activity, which is connected with aldosterone suppression. This drop in the renin-angiotensin-aldosterone system activation occurs as a result of high blood pressure, and it also decreases the volume of blood circulation, resulting in an additional decrease in placental perfusion (14, 15).

Role of inflammatory cytokines in the preeclampsia pathogenesis

Immune cells have a critical role in the PE pathogenesis. Studies have shown the role of macrophages in the development of preeclampsia. Regarding different macrophage phenotypes, it has been found that phenotype M2 (anti-inflammatory) is predominant in normal pregnancy, while phenotype M1 (inflammatory) is predominant in preeclampsia. Natural killer (NK) cells make up 70 percent of the leukocytes in the endometrium early in pregnancy and have an important role in implantation and growth of placental. Interaction of KIRs receptors on NK cells with HLA ligands-C in trophoblasts stimulates NK cells to secrete angiogenic cytokines essential for invasion of trophoblast and vascular regeneration. Irregular peripheral NK cells (pNK) activation and decidual NK (dNK) cells result in preeclampsia. dNK cells have the main role in the invasion of trophoblast and the remodeling of the helical vessel (16). These cells potentiate trophoblast invasion by production of the CXCL8 and CXCL10 chemokines, which interact with some receptors including CXCR3 and CXCR1. In addition, dNK cells produce PlGF, angiopoietin-2, and VEGF, which cause placental growth and

angiogenesis in fetus. Disruption of interactions of dNK cells and trophoblasts leads to the weak placenta and an elevated PE risk (17). The number of CD4+ T cells increases with the level of inflammatory cytokines TNF-α and IL-17 in preeclampsia, while the regulatory T cells number and the level of anti-inflammatory cytokines decrease. The inflammatory markers levels including IL-6 and CRP increase in pregnancies with preeclamptic. This shows the IL-6 and CRP involvement in the PE pathogenesis and requires further research (18).

The role of HO1/ Nrf2 and mTOR signaling pathways in preeclampsia

It has been shown that many signaling pathways are involved in the PE pathogenesis. Oxidative stress in the placenta triggers the release of anti-angiogenic factors, including sEng and sFlt-1, while Nrf2 is one of the most vital molecules for the protection of cells versus oxidative stress. Nrf2 has a main role in the expression of genes encoding antioxidant proteins and balances anti- and pro-angiogenic factors, principally by targeting heme oxygenase-1 (HO-1). HO-1 mostly metabolizes heme to iron, biliverdin, and carbon monoxide (CO), and CO increases VEGF synthesis, ultimately dilating blood vessels and decreasing blood pressure. The Nrf-2/HO-1 pathway has a main protecting role in preeclampsia (19). The pathway of HO1/Nrf2 in antioxidant and anti-inflammatory reactions is shown in Figure 1. It has also been shown that silencing the GNG7 protein represses apoptosis in preeclamptic mice by activating the mTOR cellular pathway, thus hence, increasing the differentiation and proliferation of cytotrophoblasts. Suppression of the mTOR pathway reduces preeclampsia by reducing trophoblast cell invasion (20).
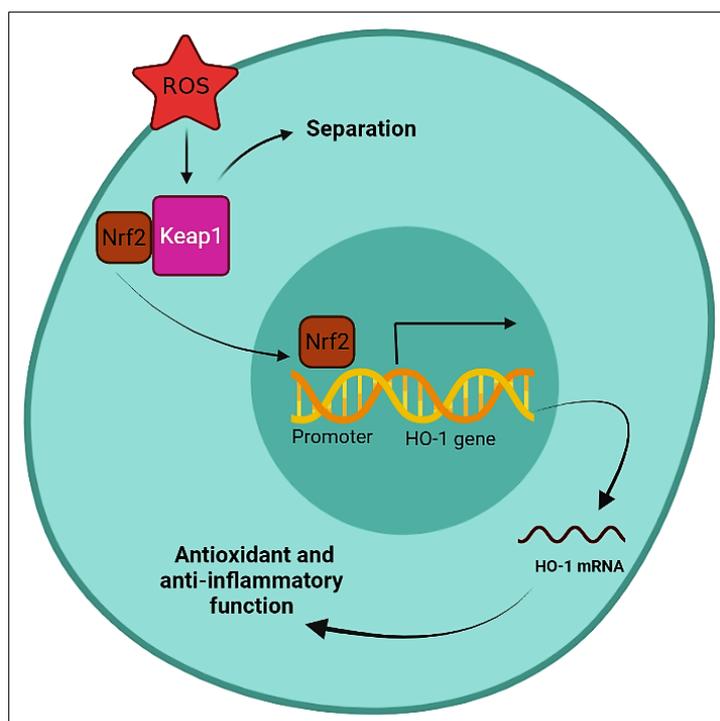

Figure 1. Role of Nfr2/HO-1 pathway in antioxidant and anti-inflammatory reactions. ROS could induce the separation of Nrf2 molecule from the Keap1. Then Nrf2 attaches to HO-1 promoter and induces its transcription. Finally, HO-1 contributes to antioxidant and anti-inflammatory reactions.

The miRNAs and pathogenesis of preeclampsia

MicroRNAs are small regulatory RNAs that have been poorly expressed and functioned in many diseases, including preeclampsia. The miRNAs importance in the preeclampsia development is a new event and the role of these molecules in the preeclampsia pathogenesis has been extensively studied since 2007 (21). The first published report revealed that two miRNAs expression in the preeclamptic placenta was significantly higher than in the normal placenta. Following this new finding, much research has been done on the association of miRNAs with preeclampsia, some of which are listed below. In a 2020 study, Matin et al., identified 91 miRNAs

that were altered in the placenta of pre-eclampsia individuals (22). For example, miR-26, miR-181a, miR-155, miR-195, miR-210, and miR-196 have increased expression, while miR-144 and miR-223 have been reported with a decreased expression. The miRNAs level present in the mother's plasma in severe preeclampsia was primarily evaluated by Levine et al., 2004. They identified seven miRNAs, including miR-574-5p, miR-181a, miR-342-3p, miR-103, miR-130b, miR-24, and miR-26a as possible markers for the diagnosis of preeclampsia (23). It has been well documented that changes in miRNA expression could lead to irregularity of various procedures, such as apoptosis prevention, migration, regulation of cell cycle, and trophoblast invasion. For example, increased expression of miR-155, miR-210, and miR-182 in pairs of preeclampsia is correlated with increased apoptosis, abnormal immune response, and angiogenic disorders. Some miRNA protein targets have been shown to increase in preeclampsia. Lin28 is an RNA-binding protein that plays a vital role in cell differentiation, invasion, and fetal growth. Some miRNA protein targets have been shown to increase in preeclampsia. Lin28 is an RNA-binding molecule that has a crucial role in cell invasion, differentiation, and fetal growth (24). Of the two Lin28 paralogs (that is Lin28A and Lin28B), Lin28B is 1,300 times more expressed in the human placenta than Lin28A, but its expression in preeclampsia is meaningfully lower. miR Let-7 controls expression of Lin28, and dysfunction of this miRNA and decreased Lin28B expression thus reducing trophoblast invasion, inflammation, and preeclampsia. Placental-specific miRNAs, located in chromosome 19 cluster (C19MC), could be correlated with the preeclampsia pathogenesis. One study found that 10 miRNAs (miR-518b, miR-516b, miR-1323, miR-515-5p, miR-516a-5p, miR-520a-5p, miR-526b, miR-525-5p, miR-520h, and miR-519d) in C19MC were found in higher amounts in the plasma of preeclampsia persons than in regular pregnant women. This indicates the C19MC involvement in the preeclampsia pathogenesis (25).

The role of miRNA in preeclampsia

Improper miRNA function causes many diseases such as cancer, neurological diseases, rheumatoid arthritis, ovarian cysts, diabetes, etc. Recently, dysregulation of miRNA expression has been found to be correlated with pregnancy complications, including post-implantation homeostasis and regulation of placental embryonic stem cells, fetal growth restriction, intrauterine growth retardation, and preeclampsia. If we want to mention role of the miRNAs in causing preeclampsia, miRNAs are involved in regulating trophoblast function, regulating both angiogenesis and regulating the function of mesenchymal stem cells, which have a main role in the preeclampsia pathogenesis. If miRNAs with a regulatory role in any of these stages increase or decrease in expression, they interfere with the function of these stages and can eventually lead to preeclampsia (26).

miRNAs and trophoblast proliferation, invasion, and apoptosis

It has been shown that the expression of the number of miRNAs in placental samples of patients with preeclampsia is significantly increased compared to normal pregnancies. For example, overexpression of miR-125b-1-3p decreases trophoblast invasion by suppressing the expression of S1PR1 protein, which has an essential role in inhibiting angiogenesis and maintaining vascular stability. miR-20a is readjusted in the placenta of samples with preeclampsia. This miRNA directly targets the FOXA1 protein, which is a member of the FOX transcription factor family. FOXA has a major role in cell migration and proliferation throughout growth. miR-210, by targeting the genes of several essential proteins, can suppress trophoblast proliferation, invasion, and migration. As a result, these effects lead to abnormal placental development, which is a major cause of preeclampsia. In addition to inhibiting trophoblast proliferation, differentiation, and migration, miRNAs can also interfere with placental development by causing trophoblast apoptosis. For example, overexpression of miR-29b by targeting MCL1 increases trophoblast apoptosis. In general, improper regulation of trophoblast differentiation, proliferation, and invasion in early pregnancy are some of the main pathogenesis during preeclampsia. Numerous miRNAs have been established to be involved in this process. Overexpression or reduced production of some of them can suppress the proliferation, differentiation, and invasion of trophoblast cells and also increase the apoptosis of trophoblast cells (27).

Regulation of angiogenesis

Numerous miRNAs are involved in regulating the several angiogenesis-related factors expression in preeclampsia. High levels of sFLT1 and decreased VEGF expression can impair angiogenesis and can be a cause of preeclampsia. Some miRNAs can affect the VEGF gene due to overexpression and reducing its amount, and eventually, angiogenesis may not be performed properly. For example, overexpression of miR-582-3p or miR-346 can meaningfully reduce VEGF levels in trophoblasts (28).

The role of miRNA biogenesis pathway molecules in preeclampsia

MicroRNAs have an essential role in the proper functioning of trophoblasts, angiogenesis, and ultimately placenta formation and growth, which are major contributors to the preeclampsia pathogenesis. Since the regulation of miRNA production and expression depends on the biogenesis pathway and the molecules that participate in it, changes in the expression and function of each molecule can increase the risk of preeclampsia. Several key molecules are involved in the miRNA processing pathway, including Drosha, DGCR8, Dicer, TRBP, Ran, and Exportin-5 (Figure 2). These molecules have the main role in the conversion of pri-miRNA to adult miRNA. If the genes of any of these molecules are mutated, the processing and production and finally the function of miRNA are disrupted (29). For example, the rs1640299 variety is positioned in the 3'UTR region of the DGCR8 gene, where the sequence containing this SNP binds miRNAs such as miR-583 and miR-1256 to the 3'UTR region of the DGCR8 gene, which controls the translation and production of DGCR8. Finally, this change can alter the maturation pathway of miRNAs and thus have a role in the preeclampsia development. In recent years, the association of some variants in the miRAN biogenesis pathway genes with the preeclampsia risk has been investigated. There was a true association between some of these varieties and the risk of preeclampsia. One of these variants is rs107019 of the Drosha gene, which increases the risk of preeclampsia more than 3 times (30).
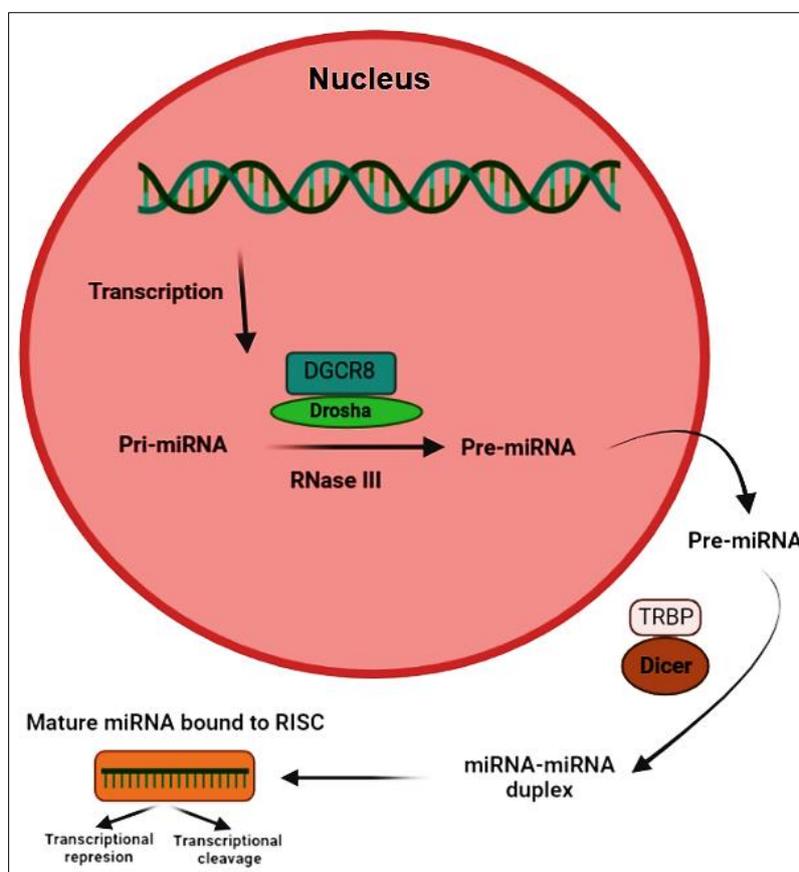

Figure 2. The miRNA biogenesis pathway. Some especial molecules such as DGCR8, Drosha, TRBP, and Dicer are involved in the miRNA pathway biogenesis.

Conclusion

Preeclampsia, characterised by elevated blood pressure and protein excretion, develops in pregnant women after 20 weeks. The condition causes a number of harmful, short- and long-term consequences on the foetus and mother, including pre-eclampsia, increased transaminases, thrombocytopenia, HELLP syndrome, and hemolytic anaemia, followed by kidney, heart, lung, and stroke diseases. Fetal growth retardation, premature birth, hypoxia-induced nerve damage, cardiovascular illness, and foetal mortality are all possible consequences of neonatal preeclampsia. The aetiology of this condition is unknown. Significant research has been conducted on the risk factors for preeclampsia. Chronic hypertension, the antiphospholipid syndrome, obesity, and pre-pregnancy diabetes mellitus are the most significant risk factors. Nulliparity, maternal age, use of assisted reproductive procedures, history of chronic renal disease, foetal trisomy 13, family history of preeclampsia, and genetic variables are all risk factors. There has been some research on the function of molecular factors in preeclampsia. By binding to PlGF and VEGF and lowering their levels in the mother's circulation, the sFlt-1 protein functions as a misleading receptor, impairing these factors' capacity to induce angiogenesis and so contributing to the pathophysiology of preeclampsia. Additionally, there is evidence that preeclampsia pathophysiology alters the renin-angiotensin-aldosterone system, inflammatory cytokines, HO1/Nrf2 signalling pathways, and microRNA biogenesis. Accurate characterization of the molecular signalling pathways implicated in preeclampsia development may aid in diagnosis and therapy of this condition.

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