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Molecular Mechanisms Underpinning the Pathophysiological, Genetic and Hormonal Alterations in Preeclampsia

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Introduction

Preeclampsia, a disorder characterized by hypertension and proteinuria after 20 weeks of gestation, remains a leading cause of maternal and perinatal morbidity and mortality worldwide. Despite decades of research, the precise etiology of preeclampsia remains elusive. However, emerging evidence suggests that a complex interplay of molecular mechanisms involving genetic, hormonal, and pathophysiological factors underpins its development and progression. This review aims to delve into the intricate molecular pathways involved in preeclampsia, shedding light on the genetic, hormonal, and pathophysiological alterations that contribute to its pathogenesis. Genetic predisposition plays a crucial role in the development of preeclampsia, as evidenced by familial clustering and heritability studies. Genome-Wide Association Studies (GWAS) have identified several genetic loci associated with preeclampsia susceptibility, implicating genes involved in vascular function, immune regulation, and placental development. Notably, variants in genes encoding proteins such as the Angiotensinogen (AGT), Endothelial Nitric Oxide Synthase (eNOS) and Vascular Endothelial Growth Factor (VEGF) have been linked to an increased risk of preeclampsia. Moreover, epigenetic modifications, including DNA methylation and histone acetylation, contribute to the dysregulation of gene expression patterns observed in preeclamptic placentas. Understanding the genetic architecture of preeclampsia is essential for elucidating its underlying pathophysiology and developing targeted therapeutic interventions [1].

Description

Endocrine factors play a pivotal role in the pathogenesis of preeclampsia, with aberrant levels of hormones contributing to vascular dysfunction, endothelial damage, and placental insufficiency. Dysregulation of the renin-angiotensin-aldosterone system (RAAS) is a hallmark feature of preeclampsia, leading to vasoconstriction, sodium retention, and hypertension. Additionally, imbalances in circulating levels of hormones such as estrogen, progesterone, and relaxin have been implicated in the pathophysiology of preeclampsia. Estrogen, for instance, exerts vasodilatory effects and promotes angiogenesis, whereas progesterone maintains uteroplacental circulation and immune tolerance during pregnancy. Dysfunctional interactions between these hormones contribute to endothelial dysfunction, oxidative stress, and inflammation observed in preeclampsia. Unraveling the intricate hormonal network underlying preeclampsia may offer novel therapeutic targets for intervention and management. [2]. Compensatory gene expression cells may alter the expression of genes to compensate for the increased load of defective proteins. This includes upregulating proteasome components and molecular chaperones to enhance protein quality control. Alternative splicing can be modulated in response to NMD deficiency, potentially bypassing PTCs or reducing the production of aberrant mRNAs. Impaired NMD can trigger cellular stress responses, such as the Unfolded Protein Response (UPR) and oxidative stress pathways, aiming to restore homeostasis. Chronic NMD impairment may lead to sustained inflammatory signaling, as misfolded or aberrant proteins accumulate, potentially contributing to inflammation-related diseases [3,4].

Preeclampsia is characterized by systemic endothelial dysfunction and impaired placental development, leading to maternal multiorgan complications and fetal growth restriction. Endothelial dysfunction, marked by reduced nitric oxide bioavailability and increased oxidative stress, contributes to vasoconstriction, platelet aggregation, and microvascular thrombosis in preeclampsia. Moreover, defective placentation, characterized by shallow trophoblast invasion and inadequate spiral artery remodeling, results in placental ischemia and the release of antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). These circulating factors disrupt vascular homeostasis, exacerbate hypertension, and contribute to the systemic inflammatory response observed in preeclampsia. Furthermore, maternal endothelial activation and immune maladaptation contribute to the pathogenesis of preeclampsia-associated complications, including eclampsia, HELLP syndrome and placental abruption. Understanding the pathophysiological alterations underlying preeclampsia is crucial for developing targeted therapeutic strategies aimed at mitigating its maternal and perinatal sequelae [5].

Conclusion

In conclusion, preeclampsia represents a multifactorial disorder characterized by intricate molecular mechanisms involving genetic, hormonal, and pathophysiological alterations. Genetic predisposition, hormonal dysregulation, and endothelial dysfunction contribute to the development and progression of preeclampsia, culminating in maternal multiorgan complications and adverse perinatal outcomes. Elucidating the molecular pathways implicated in preeclampsia pathogenesis holds promise for identifying novel biomarkers for early detection, risk stratification, and targeted therapeutic interventions. Collaborative efforts integrating clinical research, molecular biology, and systems biology approaches are essential for unraveling the complexities of preeclampsia and improving maternal and perinatal health outcomes globally.

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Conflict of Interest

There are no conflicts of interest by author.

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