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Corresponding Author
Archana Sahu,
Department of Obstetrics and Gynaecology, Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India
nscbmc.@gmail.com

Author Designation
[1]Professor
[2]Third Year PG Resident
[3]Senior Resident

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Understanding Epigenetics Mechanisms in Human Placental Development and Pathogenesis of Preeclampsia

[1]Pooja Jain, [2]Archana Sahu and [3]Anjali Patil
[1-3]Department of Obstetrics and Gynaecology, Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India

Abstract
This review thoroughly examines the role of epigenetic regulations in both normal placental development and preeclampsia (PE), a significant placental disorder. We discuss the latest advancements in understanding the effects of DNA methylation, non-coding RNA (particularly long non-coding RNA (lncRNA) and microRNA (miRNA) and, to a lesser extent, histone post-translational modifications on normal and aberrant placental function. Additionally, we investigate the potential of using circulating epigenetic marks in maternal blood as biomarkers for predicting PE onset and assessing its severity. The relationship between epigenetic marks and their impact on gene expression is systematically analyzed for each type of epigenetic modification studied.

INTRODUCTION

Preeclampsia (PE) affects approximately 2-5% of pregnancies. Traditionally defined by the onset of hypertension and proteinuria, this condition typically emerges in mid-gestation or later. It is often conceptualized as a two-stage disease: initially characterized by asymptomatic placental dysfunction, followed by a symptomatic phase that begins no earlier than the 20th week of gestation. The placenta is pivotal in the pathogenesis of PE. During pregnancy, cytotrophoblasts (CTs) infiltrate and remodel the spiral arteries within the myometrium, leading to a substantial increase in blood flow to the placenta. Classical etiology posits that this deep invasion is inadequate in preeclampsia[1-3]. It is widely accepted that preeclamptic pregnancies are marked by disrupted placentation due to insufficient CT invasion and spiral artery transformation. This results in reduced blood flow and impaired placental oxygenation, causing episodes of hypoxia and hyperoxia, which in turn induce oxidative stress, necrosis and inflammation[4,5].

In a thought-provoking paper, B. Huppertz challenges the conventional understanding of PE etiology by decoupling the lack of deep trophoblast invasion from preeclampsia and instead associating it with the phenotype of fetal growth restriction (FGR)[6]. According to this perspective, PE is primarily caused by defects in villous trophoblasts (which do not participate in invasion, unlike extravillous trophoblasts) combined with maternal susceptibility. Huppertz's argument is based on the observation that invasion defects are not histologically apparent in many preeclampsia cases. This idea is further supported by mouse models of preeclampsia that exhibit no significant fetal growth restriction, aligning with the observation that trophoblast invasion is less critical in rodents[7]. More broadly accepted is the notion, also reinforced by Huppertz, that hyperoxia, rather than hypoxia, plays a central role in the disease's progression[6-8].

The preeclamptic placenta releases vasoactive molecules, pro-inflammatory cytokines, microparticles, and syncytial fragments into the maternal circulation, ultimately leading to systemic endothelial dysfunction[9]. Epigenetic mechanisms are crucial in regulating placental development and physiology[10]. Significant epigenetic modifications have been identified in the preeclamptic placenta and other affected tissues, suggesting a substantial role in the disease's progression[11-15].

Epigenetics Mechanisms in Human Placental Development: Epigenetic processes are pivotal in governing gene expression throughout development and in specialized tissues[16,17]. These mechanisms encompass DNA methylation, histone modifications, and the biogenesis and function of noncoding RNAs (ncRNAs). They exert control over gene expression by influencing the accessibility of DNA to transcription factors and other regulatory proteins. Moreover, ncRNAs contribute to post-transcriptional regulation of gene expression. Epigenetic mechanisms play a critical role in cellular differentiation and consequently in developmental processes, as outlined in Table 1.

Epigenetic Alterations in Preeclampsia: The variations in DNA methylation associated with preeclampsia have been investigated across various cellular origins. In addition to examining placental cells, researchers have explored circulating maternal blood cells or cell-free DNA, alongside maternal endothelial cells (although these are less accessible) and cord-blood white blood cells of fetal origin. A comprehensive inventory of genes exhibiting altered methylation is detailed in Table 2.

CONCLUSION

In recent years, there has been a surge in studies investigating the role of epigenetics in regulating placental development and its potential involvement in placental pathologies. However, a precise understanding of how these epigenetic modifications correlate with gene expression remains elusive. Specifically, our understanding of how DNA methylation or histone modifications influence gene expression during normal and pathological placental development is limited. Furthermore, our knowledge regarding the mechanisms governing the establishment of different epigenetic marks throughout development is quite limited.

Nonetheless, recent research has begun to unveil the role of epigenetics in regulating crucial processes in placental development, such as cell fate determination, syncytialization and extravillous trophoblast (EVT) migration and invasion. The advent of new technologies enabling the study of epigenetic and transcriptomic profiles of various cell types within the placenta is expected to significantly enhance our understanding of epigenetics in placental function.

Moreover, in the context of preeclampsia (PE), although studies examining epigenetic modifications have mainly focused on the placenta, it is important to note that the antiangiogenic and cytotoxic factors released by the PE placenta have the potential to induce epigenetic changes in maternal target tissues, including blood cells and endothelial cells. This could have implications for maternal and fetal health in the future and warrants detailed investigation.

Understanding the epigenetic regulation in preeclampsia at both placental and systemic levels could offer new insights into biomarkers and therapeutic targets for managing this condition. However, the application of epigenetic markers as

Table 1:Epigenetics Mechanisms for Development of Human Placenta

Epigenetics Mechanism	Target	Cell Type	Biological Importance
Genome-wide methylation[16]	PMDs (Partially Methylated Domains)	Human placenta: Chorionic Villi	Involvement in immune response, Epithelial-mesenchymal transition and inflammation
H3K27me3[17]	Genome Wide	vCT	High representation of H3K27me3 in vCT
H3K4Me2; H4K20me3[18]	Genome Wide	SCTs	Co-localization of H3K4Me2 with active RNAP II in STB nuclei
H3K9/27me3[19]	MMP-2, MMP-9	Human placenta	Relationship with trophoblasts motility and invasion
Hypomethylated promoter[20]	MASPIN	Human placenta	Inhibition of EVTs migration and invasion
lncRNA H19[21]	Binds small RNAs and proteins	vCT, JAR	Regulation of cell proliferation and apoptosis
lncRNA RPAIN[22]	C1q	HTR8/SVneo	Suppression of cell proliferation and invasion., inhibition of C1q expression
lncRNA SPRY4-IT1[23]	HuR	HTR8/SVneo	Control of cell migration and apoptosis., interference with ß-catenin Wnt signaling
lncRNA TUG1[24]	RND3 epigenetic	HTR-8/SVneo, JEG-3	Silencing of RND3 transcription through means involving EZH2., regulation of cellular proliferation, migration and invasion in trophoblasts
miR-141-3p and miR-200a-3p[25]	Transthyretin (TTR) binding	syncytialized BeWo	Suppression of TTR expression via direct to its 3'UTR., regulation of thyroxin uptake by SCT
miR-155[26]	Cyclin D1	HTR-8/SVneo	Reduction of trophoblast proliferation
miR-17-92, miR-106a-363, miR-106b-25[27]	GCM1		Inhibition of trophoblast differentiation
miR-34[28]	Plasminogen activator inhibitor-1 (PAI-1), SERPINA3	JAR	Regulation of cell invasion
miR-675[29]	NOMO1, Igf1R	JEG3 cells	Restriction of trophoblast proliferation

Table 2: Epigenetics Mechanisms for Development of Preeclampsia

Cell Type	Gene	Methylation State in PE	Possible Target
Placenta and maternal plasma[30]	SERPINB5	Hypomethylated	Facilitates Trophoblast Invasion
First-trimester maternal white blood cell and placenta samples[31,32]	ABCA1	Hypomethylated	Plays a role in Cholesterol Transport in Macrophages
First-trimester maternal white blood cell, placenta samples, umbilical cord blood[31,32]	GNAS	Hypomethylated	Implicated in Diabetes, Hypertension, and Metabolic Diseases
Placenta[33]	TIMP3	Hypomethylated	Acts as a Metalloprotease Inhibitor
Umbilical cord blood, placenta samples[34]	IGF2	Hypomethylated	Contributes to Embryonic Development and Fetal Growth
Placenta[35]	WNT2	Hypermethylated	Influences Placentation and Cell Signaling
Placenta[36]	SPESP1	Hypermethylated	Involved in Fertilization
Placenta[37]	SOX7	Hypermethylated	Affects Embryonic Development and Cell Fate
Placenta[37]	CDX1	Hypermethylated	Contributes to Trophoblast Invasion Restriction
Placenta[37]	ADORA2B	Hypermethylated	Linked to Placenta Impairment and Fetal Growth Restriction
Placenta[38]	PTPRN2	Hypermethylated	Participates in Phosphate Metabolic Processing
Placenta[39]	HLA-G	Hypermethylated	Essential for Maternal Immune Tolerance and Immune

diagnostic or prognostic tools for preeclampsia has not yet been successful. One possible explanation for this could be the technological immaturity in extracting circulating RNAs from plasma, leading to discrepancies in results among different laboratories and a lack of consensus in defining a diagnostic miRNA panel. This situation may evolve over time, potentially leading to significant utilization of these markers in complex diseases like preeclampsia.

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