



Recent Advances of MicroRNAs, Long Non-coding RNAs, and Circular RNAs in Preeclampsia

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Preeclampsia is a clinical syndrome characterized by multiple-organ dysfunction, such as maternal hypertension and proteinuria, after 20 weeks of gestation. It is a common cause of fetal growth restriction, fetal malformation, and maternal death. At present, termination of pregnancy is the only way to prevent the development of the disease. Non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, are involved in important pathological and physiological functions in life cycle activities including ontogeny, reproduction, apoptosis, and cell reprogramming, and are closely associated with human diseases. Accumulating evidence suggests that non-coding RNAs are involved in the pathogenesis of preeclampsia through regulation of various physiological functions. In this review, we discuss the current evidence of the pathogenesis of preeclampsia, introduce the types and biological functions of non-coding RNA, and summarize the roles of non-coding RNA in the pathophysiological development of preeclampsia from the perspectives of oxidative stress, hypoxia, angiogenesis, decidualization, trophoblast invasion and proliferation, immune regulation, and inflammation. Finally, we briefly discuss the potential clinical application and future prospects of non-coding RNA as a biomarker for the diagnosis of preeclampsia.

Keywords: preeclampsia, microRNAs, long non-coding RNAs, circular RNAs, trophoblast, biological function

Abbreviations: 3', UTR 3' untranslated region; AT1-AA, agonistic autoantibodies against the angiotensin II type 1 receptor; BHLHE40, basic helix-loop-helix family member e40; CCAT1, Colon cancer-related transcription factor 1; CDK, cyclin D-dependent kinases; ceRNA, competitive endogenous RNA; circRNA, circular RNA; dMSCs, decidual-derived mesenchymal stem cells; EMT, epithelial-mesenchymal transition; FOXO1, forkhead box protein O1; HDAC4, histone deacetylase 4; HIF, hypoxia inducible factors; KCNQ1OT1, potassium voltage-gated channel subfamily Q member 1 overlapping transcript 1; LncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript1; miRNA, microRNA; MMP, matrix metallo protein; MSCs, mesenchymal stem cells; ncRNA, non-coding RNA; PE, preeclampsia; PGK1, phosphoglycerate kinase 1; PGK1P2, phosphoglycerate kinase 1, pseudogene 2; PI3K, phosphatidylinositol 3-kinase; PIK3R2, phosphoinositide-3-Kinase Regulatory Subunit 2; ROCK1, Rho-associated coiled-coil kinase 1; sEng, soluble endothelin; sFlt-1, soluble fms-like tyrosine kinase 1; siRNA, interfering RNA; SPRY4-IT1, sprouty homolog 4 intronic transcript 1; THSD7A, thrombospondin type-1 domain-containing 7A; TUG1, taurine upregulated gene 1; VEGF, vascular endothelial growth factor.

INTRODUCTION

Preeclampsia (PE) clinically manifests as new hypertension, proteinuria, or other clinical symptoms and signs of impaired end-organ function after 20 weeks of pregnancy (Duhig et al., 2018), and has an incidence of about 5–8% (Souza et al., 2013). PE is divided into early-onset PE and late-onset PE by 34 weeks. Early-onset PE is widely acknowledged to have defective placentation in the early stages of pregnancy, while late-onset PE appears to be driven by oxidative changes in the placenta induced by a mismatch between normal maternal perfusion and fetoplacental demands, coupled with a maternal genetic predisposition to cardiovascular and metabolic disease (Burton et al., 2019) and/or a high BMI (McLaughlin et al., 2018). Compared with late-onset PE, early-onset PE usually has more severe complications (Lisonkova et al., 2014) and smaller placental perfusion fraction (Sohlberg et al., 2014). The pathophysiological characteristics of early-onset PE are due to shallow trophoblast invasion, which affects the remodeling of spiral arteries, resulting in decreased uterine placental blood flow and oxygenation, leading to increased placental oxidative stress. Late-onset PE is manifested as a result of villous overcrowding at term. Due to limited gas exchange and nutrient supply, cellular growth is competitively inhibited, which ultimately leads to placental oxidative stress (Salomon et al., 2017). Abnormal remodeling of the uterine spiral artery and damage to the systemic vascular endothelial system are key to the onset of PE. Insufficient reconstruction of the uterine spiral artery may be related to the following factors. First, in the maternal inflammatory response, a significant increase in the level of hypoxia-inducible factor (HIF) protein in the placenta of patients with PE indicates that hypoxia is a major risk factor for PE (Ali et al., 2019). Decreased placental perfusion and oxidative stress are key to stimulating the release of cytokines, anti-angiogenic factors, and related downstream products. Eventually, inflammation and endothelial dysfunction of numerous organs and systems (including the vasculature, kidney, liver, and brain) have been observed in PE, especially early-onset PE (Kim et al., 2017). Second, vascular endothelial dysfunction is a possible factor, as the expression levels of soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sEng) are elevated in the circulating blood and placenta tissue of patients with PE (Steeegers et al., 2010). sFlt-1 and sEng are anti-angiogenic proteins that antagonize pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and placental growth factor (PLGF), leading to placental vascular dysplasia (Steeegers et al., 2010). Third, specific human leukocyte antigens on trophoblast cells in blood vessels may interact with natural killer cells and T cells of the maternal immune system, thereby altering the normal maternal–fetal immune tolerance (Wang X.Q. et al., 2018).

Non-coding RNA (ncRNA) can be transcribed from the genome but does not produce a functional protein, and can be divided into housekeeping and regulatory types. Housekeeping ncRNA includes ribosomal RNA, transfer RNA, and small nucleolar RNA, whereas regulatory ncRNA generally includes microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) (Gomes et al., 2013). lncRNA and

circRNA can share the miRNA response elements of linear messenger RNA (mRNA). They competitively bind to miRNA, thereby affecting the regulatory function and gene expression of miRNA (Lukiw, 2013). The competitive endogenous RNA (ceRNA) hypothesis indicates that an interaction network exists among miRNA, lncRNA, circRNA, and mRNA. ncRNA is not a so-called junk product but rather plays important biological roles in cell physiology, development, and metabolism. It can regulate transcription and post-transcriptional gene expression levels in various diseases (Yoon et al., 2013). Whether all transcripts are functional remains controversial, but it is clear that a large number of ncRNAs have functions. These functional ncRNAs are of great significance for the maintenance of normal cell functions as well as the occurrence and development of abnormal biological functions, and can regulate epigenetic inheritance, transcription, and post-transcriptional biological processes, in addition to participating in the regulation of multiple signaling pathways underlying cellular processes.

Whole-genome analysis of placenta-derived miRNA, lncRNA, and circRNA led to the identification of abnormally expressed ncRNAs associated with PE. Studies have confirmed that ncRNAs play important roles in regulating the development and function of the placenta and the pathogenesis of PE. The abnormal placental transcriptome of PE is affected by both genetic and epigenetic pathways. However, how differentially expressed genes and transcripts regulate the occurrence and development of PE has not been fully elucidated. In this review, we summarize recent advances of research into ncRNAs (including miRNAs, lncRNAs, and circRNAs) in the pathogenesis of PE.

MiRNAs IN PE

MiRNAs

MicroRNA is single-stranded RNA with a length of 22–28 nt, and is formed from a miRNA precursor with a hairpin ring structure through the sequential activities of the Drosha and Dicer ribonuclease III endonucleases. miRNA is conserved evolutionarily, and its expression shows tissue and stage specificity. It is an important element in physiological and pathological processes in various cells. miRNA affects the stability of target genes and inhibits the expression of target proteins. Mature miRNA binds to an RNA-induced silencing complex (RISC), and then specifically binds to the target RNA, causing its degradation. In animal cells, most miRNAs are not completely complementary to their target genes. The seed region of miRNA is complementary to the 3' untranslated region (3' UTR) of the target gene to prevent transcription (Djuranovic et al., 2011). miRNA is involved in a broad range of life processes including cell proliferation, differentiation, apoptosis, and migration (Sun and Lai, 2013). It has been speculated that miRNA regulates one third of human genes. During pregnancy, miRNA is involved in regulating the initiation of pregnancy and ensuring stability throughout pregnancy through the regulation of inflammation, immune tolerance, angiogenesis, apoptosis, and other processes (Schjenken et al., 2016).

MiRNAs in the Pathogenesis of PE

Abnormally expressed miRNAs in the placenta participate in the occurrence and development of PE in terms of maternal-fetal hypoxia, angiogenesis, immunity, and inflammation through different cellular pathways and modes of action. Chim et al. (2008) first reported the presence of miRNA in the circulating blood of pregnant women. In a panel of TaqMan microRNA Analyses for 157 well-established miRNAs, they found that 17 occurred at concentrations >10-fold higher in the placentas than in maternal plasma and were undetectable at the end of pregnancy. The expression levels of multiple miRNAs such as miR-517-5p and miR-520a-5p in the circulating blood of patients with PE in early pregnancy are elevated, which consistent with those in the placenta of pregnant women with PE (Hromadnikova et al., 2013). **Table 1** shows differential expression of miRNA involved in PE pathophysiology.

Oxidative Stress and Hypoxia Damage

During pregnancy, the production of reactive oxygen species (ROS) in the serum of pregnant women increases due to the normal systemic inflammatory response (Yang et al., 2012). Vascular remodeling disorders in PE lead to decreased placental perfusion and oxygenation, intensifying oxidative stress associated with the production of ROS and toxic lipid peroxides (Myatt, 2010). In pregnant women with PE, miR-335-5p is significantly up-regulated. ROS can increase the expression level of miR-335-5p in trophoblasts in a p53-dependent manner, leading to down-regulation of Sp1 and subsequent inhibition of the epithelial-mesenchymal transition (EMT) and cell migration (Lu et al., 2020). Compared with gestational week-matched controls, the circulating level of miR-195 was reduced in pregnant women with PE, and the expression levels of FAD-dependent oxidoreductase domain containing 1 (FOXRED1) and pyruvate dehydrogenase phosphatase regulatory subunit (PDPR) in the placenta were significantly elevated. Under chronic hydrogen peroxide stimulus, miR-195 expression decreased. miR-195 could suppress mitochondrial energy production via targeting of FOXRED1 and PDPR, which led to trophoblast cell apoptosis under oxidative stress (Wang H. et al., 2018). Perfluorooctanesulfonic acid, which induces oxidative stress, significantly increases miR29-b during the pathogenesis of PE (Sonkar et al., 2019).

The initial stage of placenta formation occurs in a relatively hypoxic environment. This environment can promote trophoblast cell invasion and blood vessel formation. However, continuous hypoxia leads to abnormal trophoblast differentiation and insufficient invasion, resulting in uterine spiral artery recasting disorders and decreased placental blood perfusion. Eventually, the angiogenic function of the placenta becomes abnormal (Berkane et al., 2007). miR-210 is an important hypoxia sensor regulated by Hipper-Lindau tumor suppressor genes, HIF-1 α , HIF-2 α , and the inducible factor prolyl hydroxylase (Seyom et al., 2015). miR-210 is significantly elevated in PE plasma and placenta, which is associated with cell migration, vascular remodeling, and growth during embryo formation (Zhao et al., 2016). Patients with mild or severe PE have about four or ten times the level of miR-210 in the plasma relative to

healthy people, respectively (Wu et al., 2015). Under hypoxic conditions, miR-210 expression in trophoblasts is significantly up-regulated. Histopathological results show that high expression of miR-210 can lead to down-regulation of HSD17B1 and E2 levels (Song et al., 2015), while low expression of miR-210 can lead to down-regulation of PTPN2 in the PDGFR-Akt pathway and thus promote cell proliferation, migration, and invasion (Li J. et al., 2019). 17- β hydroxylase is the receptor of miR-210, and is mainly expressed in placental syncytiotrophoblasts. Its level falls significantly before PE occurrence. Sorting nexin 16 (SNX16) plays a negative regulatory role in cell migration and tumorigenesis. The expression of miR-196a-5p is reduced in the PE placenta, while the expression of SNX16 is increased (Zhang L. et al., 2013). Up-regulation of miR-196a-5p can inhibit SNX16 expression. Luciferase reporter gene analysis has shown that miR-196a-5p binds to the 3' UTR of SNX16 mRNA. An increase of miR-196a-5p or knockdown of SNX16 can restore cell viability, migration, invasion, and expression of matrix metalloprotein 2 (MMP-2) and MMP-9 under hypoxic conditions. Furthermore, BHLHE40 binds to the promoter of the miR-196a-5p gene. BHLHE40 knockdown alleviated PE symptoms in pregnant C57/BL6N mice, suggesting that the BHLHE40/miR-196a-5p/SNX16 axis is involved in the pathogenesis of PE (Zhang L. et al., 2013).

Among hypoxia-related miRNAs, miR-141 (Wu D. et al., 2019), miR-517 (Anton et al., 2015), miR-218, and their host genes slit guidance ligand 2 (SLIT2) and SLIT3 have elevated expression levels in placental tissues of patients with PE (Fang et al., 2017). miR-141 down-regulates the expression of MMP-2, p62, and microtubule-associated protein 1A/1B-light chain 3 (LC3B) in HTR-8/SVneo cells by targeting the C-X-C motif chemokine ligand 12 β (CXCL12 β) gene, while also up-regulating Rho-associated coiled-coil containing protein kinase 1 (ROCK1) and Ras homolog family member A (RhoA) expression, promoting the apoptosis of HTR-8/SVneo cells and inhibiting their invasion and vascularization abilities (Wu D. et al., 2019). In vitro cell experiments indicate that hypoxia can induce high expression of miR-218, which is down-regulated after HIF-1 α gene knockout. Chromatin immunoprecipitation results suggest that HIF-1 α can directly bind to the promoters of SLIT2 and SLIT3. Further studies have shown that miR-218 targets LIM and SH3 protein 1 (LASP1), thereby inhibiting the infiltration of trophoblast cells, which may eventually induce the onset of PE (Fang et al., 2017). Hypoxia affects the expression of miR-145-5p, which is down-regulated in the PE placenta. Low expression of miR-145-5p inhibits the activity and invasiveness of HTR-8/SVneo cells, whereas overexpression of miR-145-5p promotes these effects. Furthermore, research suggests that FLT1 is the target gene of miR-145-5p (Lv et al., 2019).

Regulation of Angiogenesis Factors and Promotion of Vascular Endothelial Damage

Angiogenesis plays a key role in tissue repair and organ growth, and an imbalance of angiogenesis can easily lead to the occurrence and development of PE (Zhang M. et al., 2016). The dynamic balance between vasodilator and contractile factors, such as VEGF and its receptor sFlt-1 (Zhu et al., 2009), PLGF

TABLE 1 | miRNAs in the pathogenesis of Preeclampsia.

miRNAs	Source	Expression	Target	Function	References
miR-106b	Placental tissues and peripheral blood mononuclear cells	upregulated	MMP-2	invasion and proliferation	Li et al., 2017c; Eghbal-Fard et al., 2019
miR-126	Placental tissues and endothelial progenitor cells	downregulated	PIK3R2	proliferation, differentiation, migration and vascular sprouting	Yan et al., 2013
miR-128a	Placental tissues	upregulated	Bax	apoptosis	Ding et al., 2016
miR-133	Placental tissues	upregulated	Rho/ROCK signaling pathway	apoptosis	Zhang W.M. et al., 2019
miR-136	MSCs, exosomes of peripheral blood and umbilical cord mesenchymal stem cells	upregulated	BCL2, VEGF	suppress proliferation and promote apoptosis of MSCs	Ji et al., 2017; Motawi et al., 2018
miR-141	Placental tissues, peripheral blood	upregulated	CXCL12 β , MMP-2, p62, LC3B, ROCK1, RhoA, EG-VEGF	apoptosis, invasion and vascularization	Wang C.Y. et al., 2019; Wu J.L. et al., 2019
miR-141-3p	HUVECs	upregulated	Notch2	tube formation, migration, invasion and apoptosis	Ling et al., 2021
miR-145-5p	Placental tissues and umbilical cord blood	downregulated	FLT1, Cyr61	trophoblast viability and invasion	Hromadnikova et al., 2017; Wen et al., 2018; Lv et al., 2019; Wang Y. et al., 2019
miR-155	Placental tissues and maternal plasma	upregulated	eNOS	invasion and migration	Li et al., 2014; Gan et al., 2017
miR-16	Placental tissues	upregulated	Notch2	proliferation, migration and invasion	Yuan et al., 2020
miR-17	Placental tissues	upregulated	ephrin-B2/Eph-B4 receptor	angiogenesis	Wang et al., 2012
miR-181a-5p	Placental tissues and maternal plasma	upregulated	IGF2BP2	Invasion, proliferation, apoptosis and migration	Wu et al., 2018; Huang et al., 2019; Gusar et al., 2020
miR-196a-5p	Placental tissues	downregulated	SNX16, BHLHE40	trophoblast viability, migration, and invasion	Zhang L. et al., 2013
miR-203	Placental tissues and maternal vessel	upregulated	VEGFA	proliferation, migration and invasion	Wang Y. et al., 2016; Liu et al., 2018
miR-205	Placental tissues and maternal plasma	upregulated	MED1	cell differentiation	Mouillet et al., 2010; Yang et al., 2015
miR-20a	Placental tissues	upregulated	FOXA1	proliferation, migration and invasion	Wang Y. et al., 2014; Yuan et al., 2020
miR-20b	Placental tissues	upregulated	MMP-2, MCL-1	proliferation, migration and invasion	Jin et al., 2017; Zhang S.S. et al., 2020
miR-210	Placental tissues and maternal plasma	upregulated	HIF-1a, HIF-2 α , HSD17B1, E2, PTPN2, KCMF1, THSD7A, NOTCH1	proliferation, migration apoptosis and invasion, vascular remodeling and growth, tube-like formation capabilities	Ishibashi et al., 2012; Zhang et al., 2012; Luo et al., 2014; Seyom et al., 2015; Song et al., 2015; Wu et al., 2015; Luo et al., 2016; Zhao et al., 2016; Li J. et al., 2019; Wang R. et al., 2019
miR-214-5p	Placental tissues	upregulated	Jagged 1/Notch	proliferation, migration and invasion	Gong et al., 2020a
miR-218	Placental tissues	upregulated	LASP1	invasion	Fang et al., 2017
miR-218-5p	Placental tissues	downregulated	TGFB2	invasion and differentiation	Brkic et al., 2018
miR-299	Placental tissues	upregulated	HDAC2	invasion and migration	Gao et al., 2018
miR-29b	Placental tissues and dMSCs	upregulated	MCL1, MMP-2, VEGFA, ITGB1,HDAC4,	apoptosis, invasion, angiogenesis, proliferation, migratory and tubule formation	Li et al., 2013; Xin et al., 2017
miR-30a-3p	Placental tissues	upregulated	IGF-1	invasion and apoptosis	Lu et al., 2020
miR-335-5p	Placental tissues	upregulated	ROS/p53, Sp1	migration and EMT	Jiang et al., 2015; Lu et al., 2020
miR-342-3p	Placental tissues and maternal plasma	upregulated	ID4, PDGFRA	cell viability, apoptosis and invasion, proliferation, migration, and G1/S phase transition	Wu et al., 2012; Yang and Guo, 2019; Han et al., 2020
miR-346	Placental tissues and maternal plasma	upregulated	LRP6	proliferation, migration and invasion	Tsai et al., 2017; Zhang L. et al., 2020
miR-376c	Placental tissues and maternal plasma	downregulated	ALK5, ALK7, TGF-b/Nodal	proliferation, migration and invasion	Fu et al., 2013

(Continued)

TABLE 1 | Continued

miRNAs	Source	Expression	Target	Function	References
miR-378a-5p	Placental tissues	downregulated	Nodal	cell growth, survival, migration and invasion	Luo et al., 2012
miR-454	Placental tissues	downregulated	Nodal/ALK7, EPHB4	proliferation and invasion	Shi et al., 2019
miR-494	dMSCs	upregulated	CDK6, CCND1, VE Wang R. et al., 2019 GF	arrests G1/S transition, migration and impairs HUVEC capillary formation	Chen S. et al., 2015
miR-495	Umbilical cord tissue and dMSCs	upregulated	-	cell cycle, apoptosis, migration, invasion and tube formation	Li et al., 2017b
miR-517	Placental tissues and maternal plasma	upregulated	sFLT1, ERK/MMP-2 pathway	proliferative and invasive	Anton et al., 2015; Fu et al., 2018; Hromadnikova et al., 2019
miR-520g	Maternal serum	upregulated	MMP-2	migration and invasion	Jiang et al., 2017
miR-646	Human peripheral blood-derived endothelial progenitor cells	upregulated	VEGF-A, HIF-1 α	differentiation, migration, angiogenesis	Dong X. et al., 2020

(secreted by placental trophoblasts), and endothelin, can promote the growth, differentiation, migration, and infiltration of blood vessels in the placenta and decidua, and maintain vascular intima integrity and placental vascular permeability.

miR-126 is a powerful miRNA related to angiogenesis. miR-126 expression decreases in pregnant women with PE, which is positively correlated with the degree of placental ischemia in PE. Blood flow can activate zinc finger transcription factors to induce miR-126 expression (Yan et al., 2013). An imbalance of angiogenic factors in PE, including a decrease of pro-angiogenic factor VEGF-A and increase in hypoxia, lead to reductions of miR-126 expression and endothelial cell numbers (Yan et al., 2013). Hong et al. (2014) showed that miR-126 was under-expressed in the placenta tissues of patients with PE based on quantitative reverse transcription polymerase chain reaction (qRT-PCR), and was positively correlated with VEGF mRNA expression. In addition, miR-126 and miR-378 target tumor suppressor candidate 2 (TUSC2) to up-regulate pro-angiogenic factors; therefore, low expression levels of these two miRNAs in PE may lead to spiral artery remodeling disorder, placental ischemia, hypoxia, and hypoperfusion (Weber et al., 2016). Studies on the pathway of miR-126/PIK3R2/PI3K/AKT cells indicate that the 3' UTR of miR-126 targets and regulates phosphoinositide-3-kinase regulatory subunit 2 (PIK3R2), which is an important component of the VEGF pathway. After miR-126 activation, PIK3R2 expression decreases, while the mRNA and protein levels of phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT) increase (Zhu et al., 2009), which further illustrates the important role of miR-126 that promotes angiogenesis and anti-apoptotic mechanisms, suggesting its potential function in the pathogenesis of PE.

The survival of mesenchymal stem cells (MSCs) and angiogenesis at the maternal-fetal interface are essential factors for a successful pregnancy. miR-136 is highly expressed in MSCs derived from PE decidua. High levels of miR-136 can inhibit the proliferation of MSCs and promote the apoptosis of MSCs by targeting BCL2, and can impair human umbilical vein endothelial cell (HUVEC) capillary formation and trophoblast cell invasion

by inhibiting VEGF (Ji et al., 2017). In addition, the expression level of miR-29b increases in decidua-derived mesenchymal stem cells (dMSCs) of severe PE patients, and overexpression of miR-29b targets histone deacetylase 4 (HDAC4) to reduce the proliferation ability of dMSCs, as well as the migration and tubule-formation abilities of HUVECs (Xin et al., 2017). Expression of miR-495 increased in the umbilical cord tissue and MSCs of patients with pregnant women with severe PE (Li et al., 2017b). Further studies confirmed that miR-495 targets BMI-1 to promote cell apoptosis, inhibit the migration and invasion of trophoblasts, and hinder tubule formation by HUVECs.

Roles in Trophoblast Cell Invasion

Trophoblasts are the main cell type of the placenta and are involved in the formation of the placenta. miR-210 not only influences trophoblast invasion by adapting to oxidative stress but also directly affects cell invasion by targeting specific cell invasion markers. In PE placentas, the thrombospondin type 1 domain containing 7A (THSD7A) level is significantly down-regulated and inversely proportional to the level of miR-210. Hypoxia significantly increases miR-210 expression and inhibits THSD7A expression in a time-dependent manner, confirming that THSD7A inhibits the invasion of miR-210 into HTR8/SVneo cells (Luo et al., 2016). In another study, up-regulation of miR-210 reduced Notch1 expression; impaired HTR8/SVneo proliferation, migration, invasion, and tubule formation; and promoted apoptosis; down-regulation of miR-210 had the opposite effects. These findings suggest that miR-210 plays a role in trophoblast dysfunction by reducing Notch1 expression (Wang R. et al., 2019).

As shown by microarray analysis, miR-49 is highly expressed in dMSCs in PE. miR-494 prevents the G1/S transition of dMSCs by targeting cyclin dependent kinase 6 (CDK6) and cyclin D1 (CCND1). The supernatant of miR-494-overexpressing dMSCs reduces the migration of HTR-8/SVneo cells and impedes the formation of HUVEC capillaries by inhibiting VEGF (Chen S. et al., 2015). In situ hybridization demonstrated that the level of miR-20a was higher in PE than in normal placental tissue,

and showed that the up-regulation of miR-20a can inhibit the proliferation, migration, and invasion of trophoblast cells by inhibiting the expression of forkhead box A1 (FOXA1) (Wang Y. et al., 2014). In addition, miR-646 expression is elevated in endothelial progenitor cells isolated from the peripheral blood of pregnant women with PE (Dong D. et al., 2020). miR-646 reduces angiogenesis and inhibits the proliferation, differentiation, and migration of endothelial progenitor cells by down-regulating VEGF-A and HIF-1 α expression.

Roles in Immune Regulation and Inflammation

As a powerful tool for post-transcriptional regulation, microRNAs not only participate in the pathological process of PE through oxidative stress, hypoxia damage, vascular endothelial damage, and regulating the biological functions of trophoblast cells, but also regulate the immune response. In a healthy pregnancy, proper immune regulation prevents excessive systemic inflammation. In PE, abnormal activation of decidual T cells, uterine natural killer cells, macrophages (Faas and De Vos, 2018), and the imbalanced differentiation of helper T cell subsets destroy normal maternal-fetal immune tolerance. The activation of immune cells and subsequent secretion of cytokines affect angiogenesis, trophoblast invasion, and spiral artery remodeling, which is considered to be an indirect cause of insufficient reconstruction of the uterine spiral artery (Geldenhuis et al., 2018). MiR-223 was down-regulated in the placenta and circulating samples of pregnant women with PE (Sheikh et al., 2016). Shi et al. (2013) showed that after miR-223 knockout, the expression of immune and inflammation-related genes in mice changes significantly, with the number of immune T cells decreasing and the fetus-to-placenta mass ratio gradually decreasing as pregnancy progresses. After the female mouse reproductive tract comes into contact with semen, the expression of miR-223 is up-regulated. In contrast, down-regulation of miR-223 expression has an adverse effect on immune tolerance in female mice. Therefore, after maternal exposure to semen containing foreign antigens, miR-223 can increase maternal immune tolerance and foster pregnancy. In addition, studies of the IL-6/miR-223/STAT3 cell pathway suggest that down-regulation of miR-223 expression can lead to activation of signal transducer and activator of transcription 3 (STAT3), which is accompanied by pro-inflammatory production of the cytokine interleukin 6 (IL-6). Enhanced IL-6 expression can reduce miR-223 levels, leading to vascular dysfunction and promoting macrophage infiltration, with adverse effects on the invasion of cytotrophoblast cells into the decidua and myometrium (Lockwood et al., 2008). Immunohistochemistry has further demonstrated that the decidua and trophoblast cells of patients with PE exhibit high expression of IL-6 (Lockwood et al., 2008), which is the main factor inducing decreased miR-223 expression (Dong D. et al., 2020). Low expression of miR-223 in PE may be a compensatory mechanism that activates endothelial function and increases angiogenesis. Down-regulation of miR-223 increases the expression of β 1 integrin and promotes angiogenesis (Shi et al., 2013). Ischemia and hypoxic stress can target the upstream promoter of miR-223 CCAAT enhancer binding protein alpha

(C/EBP- α) through HIF protein, thereby reducing the miR-223 level (Seifeddine et al., 2008).

Inflammation-related miR-125b is up-regulated in placental tissues and serum of PE patients. Sphingosine-1-phosphate lyase-1 (SGPL1) is a target gene of miR-125b. miR-125b down-regulates SGPL1 expression and enhances IL-8 production, which can be reversed by abolishing the overexpression of SGPL1. Therefore, miR-125b can increase IL-8 expression in PE, which in turn induces maternal inflammation (Yang et al., 2016). Kopriva et al. (2013) suggested that high expression of miR-210 in the placenta of patients with PE is related to inflammatory factors, and that the appearance of inflammation is related to overactivation of toll-like receptor 3 (TLR3) (Bugge et al., 2017). TLR3 is activated in patients with PE (Chatterjee et al., 2012); by activating HIF-1 α and NF- κ Bp50, TLR3 induces the up-regulation of miR-210 and further down-regulates the target gene signal transducer and STAT6. miR-155 can enhance the AP-1/NF- κ B inflammatory response pathway by regulating cyclin D1, which targets interleukin 1 receptor associated kinase 3 (IRAKM), NF κ B inhibitor interacting Ras like 1 (NKIRAS1), and phosphatase and tensin homolog (PTEN), suggesting that miR-155 is related to superficial implantation in spiral arteries, a characteristic of PE (Xue et al., 2013).

In general, Each miRNA has multiple target genes, such as miR-210, which not only targets HSD17B1s (Song et al., 2015), but also targets PTPN2 (Li J. et al., 2019), KCMF1 (Luo et al., 2014), THSD7A (Tian et al., 2020), and Notch1 (Wang R. et al., 2019) to regulate the biological function of trophoblast and participate in vascular remodeling, growth and tube formation. Besides, several miRNAs also target the same gene. MMPs are important regulators of vascular and uterine remodeling. Decreased vascular MMP-2 may lead to the decrease of vasodilation, the enhancement of vasoconstriction, hypertensive pregnancy, and PE (Chen and Khalil, 2017). miR-141 (Wu D. et al., 2019) and miR-520g (Jiang et al., 2017) down-regulate the expression of MMP-2 and participate in the pathogenesis of PE by inhibiting angiogenesis and the migration, invasion, proliferation of trophoblast. This complex regulatory network not only regulates the expression of multiple genes through one miRNA, but also fine-tunes the expression of specific genes through cooperation of several miRNAs.

LncRNA IN PE

LncRNA

Long non-coding RNA is commonly present in eukaryotic cells. Defined by a length of more than 200 nucleotides and lack of open reading frames, lncRNA can regulate gene expression at the epigenetic, transcriptional, and post-transcriptional levels (Sun and Kraus, 2015), and its proportion exceeds 80% of total RNA (Guttman and Rinn, 2012). Most lncRNAs are produced through transcription by RNA polymerase II, and their sources are diverse. They can be produced due to the destruction of gene structures encoding proteins, or through rearrangement of two separate untranslated chromosomes to produce a lncRNA containing multiple exons. According to

the genomic location of lncRNAs, they can be roughly divided into five categories: sense lncRNA, antisense lncRNA, intragenic lncRNA, intergenic lncRNA, and bidirectional lncRNA. lncRNAs are important cis- and trans-regulators of gene activity, but their expression is primarily cis-acting, often reflecting the expression of neighboring genes. The expression and function of lncRNAs have tissue and spatiotemporal specificities, and play important roles in many life processes, such as chromatin modification, dose compensation effects, epigenetics, cell cycle, cell differentiation, transcription, and post-transcriptional regulation (Delas and Hannon, 2017). Their main regulation methods include acting as an activator or inhibitor of the transcript via coordinated interactions with the RNA-binding protein or regulation of the promoter of the targeted protein; forming an RNA-DNA complex to prevent the binding of transcripts; regulating DNA methylation or modifying histones; and forming complexes with proteins that affect the positioning of those proteins. lncRNA can also act as a miRNA sponge through base pairing and formation of the RISC, which reduces the activities of these small RNA molecules and inhibits the expression of miRNA-targeted genes (Guo et al., 2014).

lncRNAs in the Pathogenesis of PE

Long non-coding RNA have emerged as critical molecular regulators in biological processes and diseases, such as cancer, Alzheimer's disease, and cardiovascular disease. Recently, many groups have indicated that abnormally expressed lncRNAs in the placenta and circulating blood of pregnant women with PE participate in the pathophysiological process of PE by regulating the biological functions of trophoblasts, angiogenesis, decidualization, and inflammation. **Table 2** shows the differential expression of lncRNAs involved in PE pathophysiology.

Roles of lncRNAs in Regulating the Invasion and Migration of Trophoblast Cells

Trophoblast cells have invasion and migration characteristics like tumor cells. Insufficient infiltration of placental trophoblast cells and poor vascular remodeling are associated with pregnancy-related complications, including recurrent miscarriage, PE, eclampsia, and intrauterine growth retardation. lncRNA MALAT-1 was firstly identified in lung cancer (Ji et al., 2003). The expression level of MALAT1 lncRNA was reduced in the placentas of PE patients. After silencing of MALAT1 in the trophoblast cell line JEG-3, the cell cycle was arrested in the G0/G1 phase; caspase 3, caspase 9 and poly(ADP-ribose) polymerase 1 (PARP-1) levels increased significantly; and cell invasion and migration were inhibited (Chen S. et al., 2015). Similarly, Li et al. (2020) observed low MALAT1 expression in the placenta of early-onset eclampsia patients. Based on the RNA sequence, Fos was identified as a downstream functional gene of MALAT1. MALAT1 promotes the migration and invasion of trophoblast cells via Fos-induced EMT. Silencing the expression of MALAT1 (-/-) inhibits the invasion and migration of trophoblast cells. MALAT1-/- also leads to reduced expression of N-cadherin and vimentin, while the expression of E-cadherin is elevated, highlighting the role of MALAT1 in spiral artery remodeling damage during the placental pathogenesis

of early eclampsia. Another study demonstrated that MALAT1 expression decreased in the placenta of pregnant women with PE, whereas miR-206 expression increased. A dual-luciferase reporter experiment verified the interactions of MALAT1 and miR-206, as well as miR-206 and insulin-like growth factor-1 (IGF-1). MALAT1 inhibits trophoblast cell migration and invasion by regulating the IGF-1/PI3K/Akt signaling pathway via miR-206 (Wu et al., 2020). MALAT-1 plays a key role in regulating the angiogenesis, vascularization of the maternal decidua and fetal umbilical vasculature. Expression of MALAT1 in umbilical cord tissues and MSCs of patients with severe PE are also reduced (Li et al., 2017a). Transfection of a MALAT1 plasmid into MSCs causes the cell cycle to enter the G2/M phase and inhibits apoptosis. The supernatant of MALAT1-overexpressing MSCs promotes MSC migration, HTR-8/SVneo cell invasion, and HUVEC tube formation, whereas silencing of MALAT1 has the opposite effects. Hydrogen peroxide reduces MALAT1 expression in MSCs in a dose-dependent manner, indicating that peroxide may cause down-regulation of MALAT1 expression (Li et al., 2017a). In general, low expression of MALAT1 in the placenta of PE affects the cell cycle, apoptosis, invasion, migration, spiral artery remodeling, and tube formation through different target molecules.

Long non-coding RNA KCNQ1 is an imprinted gene that expresses only paternal alleles. KCNQ1OT1 mRNA expression was reduced in PE placental tissues, while miR-146a-3p expression was increased. A dual-luciferase reporter gene experiment confirmed the targeting relationship between KCNQ1OT1 and miR-146a-3p. Silencing KCNQ1OT1 expression up-regulates miR-146a-3p expression; inhibits HTR8/SVneo cell proliferation, invasion, and migration; and prevents CXCL12/CXCR4 signaling pathway activation. Thus, inhibiting miR-146a-3p expression can attenuate KCNQ1OT1, regulating cellular proliferation, invasion, and migration abilities and inhibiting the CXCL12/CXCR4 signaling pathway. The KCNQ1OT1/miR-146a-3p/CXCL12/CXCR4 molecular system may act as a regulatory network in the pathogenesis of PE by affecting the function of trophoblast cells (Chen F.R. et al., 2020). Yu et al. (2018) found that lncRNA TUG1 was significantly down-regulated in PE placental tissue, which inhibited the migration and invasion of trophoblast-like cells. Bioinformatics and functional analysis show that TUG1 interacts with miR-204-5p and negatively regulates the expression and function of miR-204-5p in trophoblast cells. TUG1 regulates the migration and invasion of trophoblasts through sponging of miR-204-5p; therefore, the TUG1/miR-204-5p axis may be a potential target for the intervention of PE. In another study, TUG1 was significantly reduced in the placentas of PE patients. Ectopic expression of TUG1 promotes cell proliferation, invasion, and angiogenesis, but has a negative regulatory effect on cell apoptosis. TUG1 can act as a molecular sponge of miR-29b, thereby regulating MCL1, VEGF-A, and MMP-2 during the development of PE (Li Q. et al., 2019). In addition, lncZBTB39 is up-regulated in the PE placenta, and its overexpression (downregulation) inhibits (enhances) invasion and migration of HTR8/SVneo cells and MMP-2 activity. lncZBTB39 negatively regulates the invasion and migration of trophoblast cells, and

TABLE 2 | LncRNAs in the pathogenesis of Preeclampsia.

lncRNAs	Source	Expression	Target	Function	References
AGAP2-AS1	Placental tissues	downregulated	miR-574-5p/JDP2	proliferation, invasion and apoptosis	Xu et al., 2020
ATB	Placental tissues	downregulated	-	migration, proliferation, and tube formation	Liu X. et al., 2017
CCAT1	Placental tissues	upregulated	D1-P16-CDK4	cell proliferation and cell cycle	Deng et al., 2015
DC	Dendritic cells	upregulated	p-STAT3	invasion	Zhang W. et al., 2017, 2020
EGFR-AS1	Placental tissues	downregulated	EGFR-JAK/STAT	proliferation	Zhao and Jiang, 2018
H19	Placental tissues	upregulated	PI3K/AKT/ mTOR	cell viability, invasion, autophagy	Xu J. et al., 2018
	Exosomes secreted by MSCs	upregulated	microRNA let-7b/FOXO1	invasion, migration and apoptosis	Chen Y. et al., 2020
HOTAIR	Placental tissues	upregulated	miR-106a/EZH2	proliferation, migration and invasion	Zhao et al., 2020
HOTTIP	Placental tissues	downregulated	RND3	cell proliferation and cell cycle	Li et al., 2018
KCNQ1OT1	Placental tissues	downregulated	miR-146a-3p/CXCL12/CXCR4	proliferation, invasion and migration	Chen Y. et al., 2020
Linc00261	Placental tissues	upregulated	miR-558/TIMP4	invasion, migration and apoptosis	Cheng et al., 2019b
LINC00511	Placental tissues	downregulated	miR-31-5p/HOXA7	proliferation, invasion and autophagy	Dong X. et al., 2020
lncRNA uc.187	Placental tissues	upregulated	-	proliferation, invasion and apoptosis	Cao et al., 2017
lncZBTB39	Placental tissues	upregulated	miR-210/THSD7A	invasion and migration	Tian et al., 2020
MALAT1	Placental tissues	downregulated	-	proliferation, migration invasion and apoptosis	Chen H. et al., 2015
	Placental tissues	downregulated	FOS	EMT, migration and invasion	Li et al., 2020
	Placental tissues	downregulated	miR-206/IGF-1	migration and invasion	Wu et al., 2020
	Umbilical cord tissues and MSCs	downregulated	VEGF/IDO	proliferation, angiogenesis, and Immunosuppressive	Li et al., 2017a
MEG3	Placental tissues	downregulated	NF- κ B, Caspase-3, and Bax	apoptosis and migration	Zhang et al., 2015; Liu W. et al., 2017
MIR503HG	Placental tissues	upregulated	NF- κ B, MMP-2/-9, the snail protein, and E-cadherin	proliferation, invasion, migration, apoptosis and cell cycle	Cheng et al., 2019a
NR_002794	Placental tissues	upregulated	-	proliferation, invasion and apoptosis	Ma et al., 2019
PGK1P2	Placental tissues	downregulated	miR-330-5p	angiogenesis, glycolysis metabolism and decidualization	Tong et al., 2018
PVT1	Placental tissues	downregulated	PI3K/AKT pathway	proliferation, migration and invasion	Xu Y. et al., 2018; Wang Q. et al., 2019
RP11-465L10.10	Placental tissues	downregulated	MMP-9	invasion	Fan et al., 2016; Long et al., 2016
RPAIN	Placental tissues	upregulated	C1q	proliferation, invasion and apoptosis	Song et al., 2017
SNHG5	Placental tissues	downregulated	miR-26a-5p/N-cadherin	proliferation, migration and invasion	Yang et al., 2019
SPRY4-IT1	Placental tissues	upregulated	Wnt/ β -catenin pathway	proliferation, migration and apoptosis	Zou et al., 2013, Zuo et al., 2016
Storkhead box 2	Placental tissues	upregulated	STOX2	differentiation and invasion	Oudejans et al., 2016
TCL6	Placental tissues	upregulated	PTEN	cell proliferation and cell cycle	Wu J.L. et al., 2019
TDRG1	Placental tissues	downregulated	miR-214-5p, Notch	proliferation, migration, and invasion	Gong et al., 2020b
TUG1	Placental tissues	downregulated	miR-204-5p, miR-29b/MCL1/VEGFA/MMP-2	migration, invasion, proliferation, apoptosis and angiogenesis	Yu et al., 2018; Li Q. et al., 2019
ZEB2-AS1	Placental tissues	downregulated	miR-149/PGF	proliferation, migration and invasion	Gao et al., 2019

likely maintains THSD7A mRNA expression through sponging of miR-210 (Tian et al., 2020).

The expression of lncRNA SPRY4-IT1 is elevated in PE placenta, which affects the EMT of vegetative cells via the Wnt/ β -catenin signaling pathway, thereby inhibiting trophoblast invasion and migration (Zuo et al., 2016). Similarly, lncRNA STOX2-IT3 regulates STOX2 gene expression to attenuate the differentiation and invasion of trophoblasts (Oudejans et al., 2016). Song et al. (2017) reported that lncRNA RPAIN is highly expressed in the placentas of patients with PE. When RPAIN is overexpressed, trophoblast proliferation and invasion is significantly inhibited, and trophoblast apoptosis increases significantly. Overexpression of RPAIN inhibits the expression of the complement protein C1q. C1q overexpression rescues the reduced cell invasion and enhanced apoptosis of trophoblast cells overexpressing RPAIN. Elevated RPAIN levels may play an important role in trophoblast invasion and spiral artery recasting via C1q regulation (Song et al., 2017).

lncRNAs Inhibit Trophoblast Proliferation and Cell Cycle

The colon cancer-related transcription factor 1 (CCAT1) gene is a lncRNA that is abnormally expressed in colon cancer tissues and is associated with proliferation activity and metastasis of colon cancer cells (Zhu et al., 2015). Higher expression of lncRNA CCAT1 was found in patients with PE. PE patients were divided into high-expression and low-expression groups according to CCAT1 expression. Compared with the low-expression group, the systolic blood pressure, diastolic blood pressure, and urine protein levels of CCAT1 high-expression group were elevated, while birth weight was significantly higher in the low-expression group than the high-expression group. In addition, overexpression of CCAT1 to observe the function of CCAT1 in the proliferation activity and cell cycle of Bew and JEG-3 cells showed that interference with CCAT1 led to significant trophoblast proliferation and cell cycle acceleration, whereas overexpression of CCAT1 had the opposite results. After overexpression of CCAT1, the expression levels of E2F1, cyclin D, CDK2, and CDK4 in JEG3 cells were significantly reduced, while inhibition of CCAT1 led to significantly increased expression of E2F1, cyclin D, CDK2, and CDK4 in BeWo cells, suggesting that CCAT1 may be involved in the regulation of placental trophoblasts in PE, and thus play a role in the pathogenesis of PE (Deng et al., 2015).

lncRNAs Regulate Angiogenesis and Decidualization

Impaired decidual function can lead to failure of trophoblast infiltration into blood vessels and insufficient placental function, thereby increasing the risk of PE. The expression level of lncRNA SPRY4-IT1 is 2.8 times higher in the placentas of PE patients than in normal pregnancy. Silencing of SPRY4-IT1 with small interfering RNA (siRNA) leads to an increase in its migration phenotype and a decrease in cell apoptosis. At the same time, siRNA silencing of SPRY4-IT1 results in decreased tube formation ability, while overexpression of SPRY4-IT1 enhances tube formation (Zou et al., 2013). Knockout of SPRY14-IT1 leads to decreased gene and protein expression levels of E-cadherin

and β -catenin, as well as increased vimentin expression. The mechanism of those effects may be the binding of SPRY14-IT1 to the cytoplasmic RNA-binding protein HuR, and the resulting complex directly binding to β -catenin mRNA (Zuo et al., 2016). The interaction between HuR and β -catenin proteins leads to an imbalance in β -catenin mRNA expression, which has been verified in other cell types (Chou et al., 2015). Knockdown of SPRY14-IT1 can lead to down-regulation of Wnt3 and Wnt5B, the downstream targets of β -catenin. Strict regulation of Wnt/ β -catenin signaling plays important roles in maintaining the phenotype of epithelial cells and the development of cell-cell connections. The loss of this pathway leads to type 1 EMT. The EMT of extravillous trophoblasts is a key step in the invasion of maternal decidua tissue, and is essential to uterine spiral artery recasting and successful pregnancy (Gude et al., 2004). Expression of SPRY4-IT1 is associated with the formation of an endothelial cell-like tubular network, which is an important process in angiogenesis; in particular, high expression of SPRY4-IT1 in the placenta of patients with PE may be related to the process of uterine spiral artery recasting.

Phosphoglycerate kinase 1 (PGK1) is an enzyme involved in the glycolytic pathway, which is the main metabolic process undertaken by DCs. The sequences of lncRNA PGK1P2 and PGK1 are similar. Normal decidualization is essential for normal pregnancy. In one study, PGK1 and PGK1P2 mRNA expression and PGK1 protein level were lower in decidua of severe PE than in the normal pregnancy control group. Further research showed that PGK1 and PGK1P2 are a pair of ceRNAs targeting miR-330-5p. They play a crucial role in human decidualization by regulating angiogenesis and glycolytic metabolism. Lack of PGK1 and PGK1P2 in the decidua inhibits the decidualization process and may subsequently lead to PE (Tong et al., 2018).

lncRNAs Participate in Inflammation and Immune Regulation

lncRNA MALAT1 is also involved in immune regulation and inflammation. MALAT1 reduces the secretion of inflammatory factors TNF- α and IL-6, and inhibits the expression of TGF- β and NF- κ B in trophoblastic cells (Zhang Y. et al., 2020). lncRNA H19 plays role in inflammatory diseases (Wang W.T. et al., 2016). Excessive inflammation of maternal endothelial cells is a characteristic of PE (Chen et al., 2016). The placental tissues of PE patients have higher levels of lncRNA H19 than healthy controls. Overexpression of lncRNA H19 activates PI3K. The PI3K/AKT/mTOR pathway reduces cell viability and promotes autophagy in trophoblasts, but increases cell invasion (Xu J. et al., 2018). lncRNA DC is expressed exclusively in human DCs and induces DC differentiation and maturation by promoting the phosphorylation of STAT3 (Wang P. et al., 2014). lnc-DC and p-TAT3 increase in PE, and overexpression of lnc-DC inhibits trophoblast invasion, increases p-STAT3 levels, and increases the ratios of tissue inhibitor of metalloproteinase (TIMP)-1 to MMP-9 and TIMP-2 to MMP-2 (Zhang W. et al., 2020). In addition, overexpression of lnc-DC can cause excessive maturation of DCs in patients with PE and increase the abundance of Th1 cells, indicating that lncRNA DC has immunomodulatory activity (Zhang W. et al., 2017).

CircRNAs IN PE

CircRNA

Circular RNA is a closed circRNA with no 5' cap and with a 3' poly-A tail (Memczak et al., 2013). The sequence of circRNA is highly conserved, and its circular structure resists degradation by exonucleases. Its structure is relatively stable and highly expressed, and it plays roles in gene transcription and post-transcriptional regulation (Memczak et al., 2013). The length of circRNAs is in the range of 200–2,000 bp, and most are about 500 bp. circRNA is a type of endogenous RNA that is transcribed by RNA polymerase II (Zhang et al., 2018), and can be divided into non-coding and coding circRNAs. Coding circRNA has an open reading frame that generally contains at least one internal ribosome entry site (Li et al., 2019c). The closed-loop structure can be formed through the reverse splicing mechanism, wherein the upstream 5' splice site and downstream 3' splice site are connected by linear mRNA; therefore, canonical spliceosome signaling may be involved in the regulation of circRNA biogenesis (Chen, 2016). circRNA expression is tissue-specific, and diverse types of circRNA are expressed (Xia et al., 2017). According to the source of splicing, circRNA can be divided into exon source, intron source, or exon and intron source types (Han et al., 2018). Most circRNAs are derived from exons, and a small number are formed through direct circularization of introns. The main biological functions of circRNA are as follows. As a miRNA sponge, circRNA is rich in miRNA-binding sites and can function as ceRNA. circRNA can absorb miRNA through sponging or base complementation and inhibit its binding to mRNA, increasing mRNA expression (Han et al., 2018). By participating in the regulation of linear splicing (Hansen et al., 2013), it functions alongside RNA polymerase II as a cis-acting element and regulatory gene in transcription (Zhang Y. et al., 2013). Moreover, circRNA can interact with RNA-binding proteins as a scaffold to promote, align, and regulate RNA functions (Memczak et al., 2013) play roles in transcription and translation (Pamudurti et al., 2017), and act as an m6A recognition protein, known as YTH N6-methyladenosine RNA binding protein 3 (YTHDF3). It can bind to the modified start site of circRNA and recruit translation initiation factors such as eIF4G2 for translation (Yang et al., 2017).

CircRNAs in the Pathogenesis of PE

As a novel type of ncRNA, circRNA has notable advantages for development and application as a clinical biomarker. Although few studies on circRNA in the pathogenesis of PE have been conducted, it has been revealed that circRNA in the plasma and placenta tissue of patients with PE can block the inhibitory effect of miRNA on its target mRNA by binding to miRNA, thereby regulating mRNA expression. This mechanism may allow circRNA to participate in the pathogenesis of PE.

Deng et al. (2019) integrated RNA sequencing data from human placentas with severe PE and normal pregnancies, and found that 180 circRNAs were differentially expressed in placentas with severe PE, including 94 up-regulated and 86 down-regulated circRNAs. Most of the detected circRNAs have

not been annotated. Bioinformatics analysis of differentially expressed circRNAs shows that most are involved in vasodilation, blood vessel size regulation, protein transport and localization, and cancer pathways. circRNA mainly acts in a regulatory role as a sponge of miRNA. ceRNA inhibits its binding to mRNA and increases mRNA expression. The circ_0085296 level was elevated in PE placental tissue, while miR-144 was down-regulated (Zhu et al., 2020). Up-regulation of circ_0085296 inhibits trophoblast proliferation, invasion, and migration. miR-144 directly binds to circ_0085296 and E-cadherin, and circ_0085296 acts as a sponge of miR-144 to regulate the expression of E-cadherin. Moreover, miR-144 inhibition and E-cadherin overexpression weaken the effect of circ_0085296 on cellular processes in trophoblast cells. hsa_circ_011277 (Ou et al., 2020), hsa_circ_0011460 (Deng et al., 2019), and hsa_circ_0006772 (Shen et al., 2019) are significantly elevated in the placenta of PE patients. circ_011277 reduces the inhibitory effect of miR-494-3p by regulating the expression of Htra serine peptidase 1 (HTRA1) and Notch1 (Ou et al., 2020), while hsa_circ_0011460 directly targets the solute carrier organic anion transporter family member (PGT) interaction (Deng et al., 2019). hsa_circ_0006772 has a negative regulatory effect on trophoblast migration and EMT. Meanwhile, the hsa_circ_0006772 sponge miR-762 inhibits the activity of miR-762 and increases the protein level of the EMT-related transcription factor grainyhead like transcription factor 2 (Grhl2) (Shen et al., 2019). hsa_circ_0000284 (Zhang Y. et al., 2019) and hsa_circ_0003286 (Zhou et al., 2018) were reduced in PE placental tissue. After siRNA transfection to silence hsa_circ_0000284, the migration, invasion, proliferation, and tube formation activities of HTR8/SVneo cells were inhibited, while siRNA transfection silencing hsa_circ_0003286 significantly reduced cell invasion.

Expression of hsa_circ_0036877 in the placenta was lower in pregnant women with PE than in normal pregnant women, but that in peripheral blood was higher in pregnant women with PE than in normal pregnant women (Hu et al., 2019). hsa_circ_0036877 combines miR-519d-3p and miR-15b-5p, and may act as a miRNA sponge in the pathogenesis of PE (Hu et al., 2018). Syncytial trophoblast cell necrosis is a direct result of unbalanced regulation of apoptosis, and leads to increased release of trophoblast granules into the circulating blood of patients with PE (Huppertz et al., 2006). hsa_circ_0036877 may be an extracellular nucleic acid derived from the placenta. The marked increase in apoptosis of syncytial trophoblast cells may explain the low expression of hsa_circ_0036877 in the PE placenta but high expression in circulating blood.

Liu et al., 2019 analyzed differentially expressed circRNA, lncRNA, miRNA, and mRNA based on RNA sequencing data from placenta tissues and data in the Gene Expression Omnibus (GEO) database using gene set enrichment analysis and other bio-informatics methods. The results showed that the JAK/STAT signaling pathway was activated and miR-100-5p was down-regulated in both PE sequencing data and GEO data, and the expression levels of lncRNA-1492, hsa_circ_0088196, and leukemia inhibitory factor (LIF), which have targeted regulatory relationships with miR-100-5p, were up-regulated. A luciferase reporter experiment demonstrated the presence of

a ceRNA regulatory network in PE, wherein lncRNA-1492 and hsa_circ_0088196 target the inhibitory effect of miR-100-5p on LIF, and up-regulated LIF activates the JAK/STAT pathway, promoting the development of PE.

During early pregnancy before the onset of PE, prediction, effective intervention, prevention, and control of the disease are of great significance (Lavalée, 2015). circRNA has characteristics of stability, universality, specificity, and conservation, making it a more suitable biomarker than other RNA types (Lasda and Parker, 2014). A prospective study of circRNA expression in the blood cells of PE patients before 20 weeks of pregnancy and healthy pregnant women showed that PE patients had significantly higher hsa_circ_101222 (Zhang Y.G. et al., 2016). Analysis using bioinformatics prediction (Liu et al., 2019) indicated that hsa_circ_101222 may interact with miR-181, which is closely related to the pathogenesis of PE (Liu et al., 2012), while the miRNA response elements of hsa_circ_0001855 and hsa_circ_0004904 were identified as miR-138-5p, miR-30c-1-3p, miR-623, miR-30c-2-3p, miR-134-3p, miR-29a-5p, and miR-765, all of which target pregnancy-associated plasma protein A (PAPP-A), and miR-29a-5p, and are closely related to the pathogenesis of PE (Stubert et al., 2014). The area under the receiver operating characteristic curve for the two circRNAs combined with PAPP-A can reach 0.940 (95% confidence interval: 0.869–1.000), suggesting that hsa_circ_0004904 and hsa_circ_0001855 in combination with PAPP-A are promising biomarkers for the prediction of PE.

CONCLUSION

Preeclampsia is asymptomatic in the early stage, so early diagnosis is essential for PE. To identify potential biomarkers of PE, many groups focused on non-coding RNAs in maternal plasma and serum. As regards miRNAs and lncRNAs in maternal blood, there are still no sufficient data to understand if they can be used as promising markers for PE monitoring and screening, since almost all of the case-control designs only considered the affected cases and the unaffected cases. Besides, the population recruited by PE is heterogeneous, including variation in the definition of PE and the timing of screening during pregnancy, so the possible independent positive predictive value of miRNAs and lncRNAs is unclear. Additionally, abnormal expression of miRNAs and lncRNAs is only found in symptomatic PE cases. Because the true incidence is not provided, miRNAs and lncRNAs are currently useless for the possible implementation of screening purposes. Considering the molecular advantages of circRNAs, studies on circRNA are more focused on possible use for screening purposes, and are generally better designed, as they consider a wider number of cases. The first study to report circRNA analysis in pregnant women with PE before the onset of symptoms found that hsa_circ_0004904 and hsa_circ_0001855 were significantly elevated in pregnant women with PE compared with healthy pregnant women. The area under the curve of the combined model was 0.94 in the predicted PE subject (Jiang et al., 2018). Unfortunately, even though some papers reported the possible screening performance of circRNAs at the first or second trimester of pregnancy, circRNAs have not been used successfully

for any screening program for PE considering the small cohort of patients studied. Further prospective studies with larger samples from different gestational stages are needed to understand the possible role of circRNAs in predicting and monitoring PE. The abnormal expression of PLGF, PAPP-A, PP13, and sFlt-1 in the pathological process of PE has potential value in the prediction of PE. In addition to the above factors, there are more biological indicators in the clinical application value of PE that have been found. Considering the economy and efficiency of clinical application, multi-index combined prediction, including PAPP-A, PP13, sFlt-1, circRNAs, and other biological indicators, combined with maternal history, ultrasound, and so on, may have a greater application prospect.

The pathogenesis of early- and late-onset PE is different, and the role of non-coding RNAs in them may also be different. Deep sequencing compared the expression profiles of tissue and circulating miRNAs in pregnant women with early- and late-onset PE, and found differential expression of miRNA in the two groups of tissues (Timofeeva et al., 2018). In early-onset PE, miR-431, miR-518a-5p, and miR-124 were up-regulated in the placenta tissues (Lykoudi et al., 2018), and miR-423-5p was up-regulated in the circulating blood (Timofeeva et al., 2018), whereas miR-544 and miR-3942 were down-regulated in the placenta tissues (Lykoudi et al., 2018). In late-onset PE, miR-383 and miR-1183 were up-regulated in the placenta tissues (Lykoudi et al., 2018), whereas miR-23b-5p and miR-99b-5p were down-regulated in the circulating blood (Mavreli et al., 2020). However, the functional significance of these miRNAs in the pathogenesis of PE has not been confirmed and elucidated. Although great efforts have been made to explore the pathogenesis of miRNA in PE, most of the samples obtained are from patients with early-onset PE, and few studies have been devoted to comparing the pathogenesis of miRNA in early- and late-onset PE. Further exploration and clarification of the similarities and differences of non-coding RNA involved in the pathology of early- and late-onset PE can provide new ideas for explaining the pathogenesis of PE.

In summary, from the proliferation, invasion, and migration of trophoblast cells to cell cycle progression, changes in the above-described ncRNA expression above may affect the functions of those cells and eventually lead to PE. The discovery of early diagnostic markers is key to early pregnancy intervention. With the development of sequencing technologies, methods for detecting differentially expressed ncRNAs in the placenta and plasma of PE patients have been rapidly established. As research into the expression and function of ncRNA remains in its infancy, exploring the reasons underlying the differences between early- and late-onset PE, the discovery of additional PE-related or PE-specific ncRNAs, and corresponding target gene investigations will be major directions of future research. These studies will help clarify the pathological mechanism of PE and provide a new target for its early prevention.

AUTHOR CONTRIBUTIONS

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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