Role of circular RNAs in preeclampsia (Review)

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Received October 10, 2023; Accepted June 25, 2024

DOI: 10.3892/etm.2024.12661

Abstract. Preeclampsia (PE) is a hypertensive disorder of pregnancy characterized by new-onset hypertension and proteinuria after 20 weeks of gestation, which affects 3-8% of pregnant individuals worldwide each year. Prevention, diagnosis and treatment of PE are some of the most important problems faced by obstetrics. There is growing evidence that circular RNAs (circRNAs) are involved in the pathogenesis of PE. The present review summarizes the research progress of circRNAs and then describes the expression patterns of circRNAs in PE and their functional mechanisms affecting PE development. The role of circRNAs as biomarkers for the diagnosis of PE, and the research status of circRNAs in PE are summarized in the hope of finding novel strategies for the prevention and treatment of PE.

Contents

1. Introduction

Circular RNAs (circRNAs) are covalently closed circular non-coding RNAs (ncRNAs) without a 5' cap and a 3' poly(A) tail (1). For decades, circRNAs were considered to be non-functional byproducts of mis-splicing (2,3). In recent years, circRNAs have been discovered in eukaryotes (4-8). With the maturity of sequencing technologies and algorithms, thousands of circRNAs have been identified, and experiments have confirmed that such RNAs are no longer 'splicing noise', but functional molecules (7,9-12). CircRNAs can share the microRNA (miRNA/miR) response elements targeted by mRNA, thereby regulating the expression of mRNA (13).

In addition, circRNAs have other biological functions, such as regulating gene transcription and translation, and binding to RNA-binding proteins (9). CircRNAs can regulate transcriptional and post-transcriptional gene expression in various diseases such as lung cancer and gastric carcinoma (14). These functional circRNAs are of significance for the maintenance of normal cell functions and the occurrence and development of abnormal biological functions. In addition to participating in the regulation of epigenetic, transcriptional or post-transcriptional biological processes of various cells, circRNAs also play important roles in the signal pathways of cellular processes (15,16).

Preeclampsia (PE) is defined as new-onset hypertension after 20 weeks of gestation, accompanied by proteinuria, headache, dizziness, nausea, vomiting and epigastric discomfort (17). PE is a serious obstetric emergency worldwide, with an annual incidence of 3-8%, and is a major cause of increased maternal and neonatal morbidity and mortality (18). Therefore, understanding the pathogenesis of PE remains imperative for obstetricians. A growing body of evidence supports that the pathogenesis of PE is multifactorial, including insufficient invasive ability of trophoblasts (19), failure of spiral artery remodeling (18), abnormal immune responses (18), inflammatory responses (20) and genetic factors (21). These pathogenic mechanisms can be regulated by epigenetics (21). As a type of ncRNA, circRNAs are widely involved in gene expression, protein/RNA splicing or modification or protein-coding process (22). Abnormally expressed ncRNAs associated with PE have been identified by genome-wide analysis of placental-derived circRNA (23). Studies have confirmed that circRNA plays an important role in regulating the development and function of the placenta and the pathogenesis of PE (24,25). The abnormal placental transcriptome of PE is affected by epigenetic regulation. However, the regulation of differentially expressed genes and transcripts on the occurrence and development of PE has not been fully clarified (26). The present review summarized studies on the role of circRNAs in the pathogenesis of PE.

2. Expression pattern and diagnostic value of circRNAs in PE

At present, in the field of PE, the study of circRNAs is mainly limited to diagnostic markers and pathogenesis. Risk factors

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Key words: preeclampsia, circular RNA, microRNA, trophoblast

for PE include a history of PE in a previous pregnancy, chronic kidney disease, hypertension, diabetes, autoimmune diseases such as systemic lupus erythematosus, initial onset PE, age >40 years, inter-pregnancy interval over 10 years, a body mass index >35 kg/m^2, polycystic ovary syndrome and multiple pregnancies (20). However, only 30% of individuals predisposed to PE can be detected based on these risk factors (27). Due to the heterogeneous presentation of PE, potential biomarkers are required for its early detection.

Shao *et al* (28) studied the expression of circRNA in the blood of 82 pregnant individuals at 8-20 weeks of gestation and revealed that the blood concentration of circ_101222 in patients with PE was significantly higher compared with that in healthy pregnant individuals. Other studies have analyzed the expression of several mRNAs, ncRNAs and circRNAs in the plasma or placentas of individuals with PE and healthy pregnant individuals to identify potential predictive markers of PE. The expression pattern of current potential circRNAs that may serve as diagnostic markers for PE is summarized in Table I.

Among all detected markers, hsa_circ_0036877 is recognized as a potential plasma biomarker for PE (29). Two biomarkers, hsa_circ_0004904 and hsa_circ_0001855, are involved in the pathogenesis of PE by activating miRNA sponges that directly target pregnancy-associated plasma protein A (PAPP-A). This indicates that PAPP-A is present in the plasma of individuals with PE (30). However, the limitations of circRNAs as diagnostic markers must be considered. Pregnancy is a process, and the level of molecular expression in the placenta dynamically changes. More detailed grouping and long-term studies are needed to determine the time point for screening circRNA as a diagnostic marker.

3. Mechanisms of circRNAs involved in PE

PE is a hypertensive disorder (31,32). Unfortunately, the etiology and pathogenesis of PE are still far from clear. However, accumulating evidence confirms that impaired spiral artery remodeling, placental dysfunction and insufficient trophoblast invasion may play critical roles in the development and progression of PE (33-35). Furthermore, extensive or shallow invasion of extravillous trophoblasts (EVTs) at the maternal-fetal interface has been identified as a major cause of placental failure, ultimately leading to PE (36,37). Restricted migratory activity of EVTs in the maternal decidua has been shown to impede trophoblast function, leading to PE (38). Some studies have investigated the pathogenesis of PE from the perspective of placenta (39,40). A large number of recent studies have shown that a variety of ncRNAs are associated with the pathogenesis of pregnancy disorders (41-45).

From the perspective of pathogenesis, abnormal placental development is one of the main causes of PE. Zhou *et al* (46) have revealed that circRNA_3286, circRNA_5593 and circRNA_3800 are downregulated in placental tissues of individuals with PE compared with healthy pregnant individuals. Melchiorre *et al* (39) have investigated the distribution of circRNAs in the placental tissues of individuals with PE and explored the potential impact of circRNA dysregulation on the progression of PE. A total of 300 circRNAs that are differentially expressed between individuals with PE and healthy pregnant individuals were identified. Reverse transcription-quantitative PCR results showed that hg38_circ_0014736 and hsa_circ_0015382 are highly upregulated, and hsa_circ_0007121 is downregulated in all patients with PE. The data showed that these three circRNAs are significantly associated with the regulation of transcription, proliferation, hypoxia response and protein binding (47). The studies on the role of circRNAs in the pathogenesis of PE are summarized in Table II, which is helpful to explore novel strategies for the treatment of PE.

In recent decades, researchers have confirmed that circRNAs are involved in a variety of diseases (48). However, to the best of our knowledge, there have been few studies on the role of circRNAs in the pathogenesis of PE (49-51). The different mechanisms are described in detail below.

Roles of circRNAs in regulating migration and invasion of trophoblasts. Insufficient invasion and migration abilities of trophoblasts are one of the major causes of PE (42,52). Studies have shown that circRNAs can affect the invasion and migration abilities of trophoblasts (53,54). Hsa_circ_0111277 spliced from PAPP-2A is highly expressed in the placentas of patients with PE. The expression level of Hsa_circ_0111277 is proportional to the placental weight and urinary protein level, suggesting that it may be involved in PE (55). Subsequently, an *in vitro* experiment has demonstrated that Hsa_circ_0111277 regulates the Notch-1 signaling pathway through the miR-494/high-temperature requirement-A serine peptidase 1 axis, thereby inhibiting the migration and invasion of HTR-8/Svneo and JEG-3 cells (55). Notch-1 signaling pathway play an important role in the migration and invasion of trophoblasts, decreased activity of which can significantly inhibit the invasive ability of trophoblasts (30,56).

However, hsa_circ_0002814 is downregulated in the placentas of individuals with PE. Overexpressed hsa_circ_0002814 elevates Notch-1 expression by suppressing miR-21 (57), which has also been shown to bind FUS protein, thus increasing soluble fms-like tyrosine kinase 1 (sFlt-1) and VEGF protein (58). Hsa_circ_0008726 is highly expressed in the plasma and placentas of patients with PE (59). It regulates LIM homeobox transcription factor family (LHX6) and RING1 and YY1-binding protein (RYBP) by adsorbing miR-1290 and miR-345-3p, respectively, and regulates the migration and invasion abilities of trophoblasts (60,61). Hsa_circ_0007121 mediates the progression of PE through the miR-182-5p/placental growth factor (62). CircLRRK1 has been identified to inhibit trophoblast proliferation, migration and invasion through the miR-223-3p/PI3K/AKT axis (12).

Involvement of circRNAs in the regulation of epithelial-mesenchymal transition of trophoblasts. Epithelial-mesenchymal transition (EMT) is a characteristic process during which polarized epithelial cells transform into a mesenchymal phenotype, including the changes in migration and invasion abilities (63). The EMT of trophoblasts is considered to be one of the steps before efficient spiral artery remodeling (64,65). Hsa_circ_0006772 is upregulated in the placentas of individuals with PE compared with that in the placentas of healthy pregnant individuals. Overexpressed hsa_circ_0006772 increases the expression of E-cadherin protein

Table I. Diagnostic values of circRNAs in PE.

ID	Gene symbol	Expression	Sample type	Area under ROC curve	Sensitivity	Specificity	(Refs.)	Study year
hsa_circ_0007121	-	Downregulated	Plasma	0.72	0.77	0.70	(47)	2018
hsa_circ_0036877	FURIN	Downregulated	Plasma	0.85	0.85	0.73	(29)	2018
hsa_circ_0055724	ANKRD36	Downregulated	Plasma	-	-	-	(139)	2022
hsa_circ_0003496	UBAP2	Downregulated	Plasma	-	-	-	(131)	2021
hsa_circ_0002814	HERC2	Downregulated	Plasma	-	-	-	(80)	2022
hsa_circ_0003286	GTF2H2B	Downregulated	Plasma	-	-	-	(140)	2018
hsa_circ_0004904	POLE2	Upregulated	Plasma	-	-	-	(30)	2018
hsa_circ_0001855	RNF38	Upregulated	Plasma	0.62	0.53	0.70	(30)	2018
hsa_circ_0029601	TPTE2	Upregulated	Plasma	0.87	0.71	0.80	(141)	2016
hsa_circ_0025992	SLC38A2	Upregulated	Plasma	0.81	0.54	0.93	(142)	2021
hsa_circ_0001326	PHLDB2	Upregulated	Placenta	0.79	-	-	(21)	2021
hsa_circ_0008726	DNAJB6	Upregulated	Plasma	-	-	-	(143)	2022
hsa_circ_0004904	POLE2	Upregulated	Plasma	-	-	-	(144)	2021
hsa_circ_0013301	HIAT1	Upregulated	Plasma	-	-	-	(145)	2021
hsa_circ_0007885	BRAP	Upregulated	Plasma	0.71	0.63	0.76	(64)	2022
hsa_circ_0058152	FN1	Upregulated	Plasma	0.78	0.87	0.56	(146)	2022

circRNA, circular RNA; PE, preeclampsia.

and decreases the expression of Vimentin protein, which are EMT-related protein markers. It sponges miR-762 to inhibit the miR-762 expression and elevates the level of Grhl2 protein, an EMT-related transcriptional factor (11). These findings demonstrate that circTNRC18 inhibits EMT of trophoblasts, suggesting that it may be involved in the progression of PE.

Regulation of cell proliferation and apoptosis by circRNAs. PAPP-A, a key regulator of insulin-like growth factor bioavailability, is essential for normal fetal development (66). Hsa_circ_0015382 is also derived from the splicing of PAPP-2A transcript, which is upregulated in the placentas of individuals with PE (67). By regulating the expression of tissue factor pathway inhibitor 2 (TFPI2), hsa_circ_0015382 not only inhibits the migration and invasion abilities of trophoblasts, but also inhibits the proliferation of trophoblasts and promotes their apoptosis (68). Hsa_circ_0001326 is highly expressed in the placentas of individuals with PE, which can modulate the level of p27 Kip1 by absorbing miR-186-5p (12). Overexpressed hsa_circ_0001326 significantly upregulates p27 Kip1, cleaves caspase 3 and downregulates cyclin-dependent kinase 2 (CDK2) and cyclin E1, suggesting decreased viability and proliferation of trophoblasts. While hsa_circ_0001326 induces G_0/G_1 cell cycle arrest is attenuated in the case of p27 Kip1 knockdown (69). These findings show that hsa_circ_0001326 may be involved in the progression of PE. Hsa_circ_0017068, as a post-transcriptional regulator of X-linked inhibitor of apoptosis protein, has been reported to regulate the proliferation, cell cycle and apoptosis of trophoblasts by targeting miR-330-5p (51).

Other functions of circRNAs involved in PE. In one study, a microarray analysis was performed using placental tissue from pregnant individuals with PE (70), the results of which revealed that hsa_circRNA_100782, hsa_circRNA_102682 and hsa_circRNA_104820 are highly upregulated in PE. The identified circRNAs have multiple binding sites for miRNA-17, indicating that these circRNAs can regulate the expression of miRNA-17 in human placental tissues. A previous study showed that increased expression of miRNA-17 in the placenta contributes to the development of PE by promoting trophoblast invasion (71). Therefore, the differential expression of circRNAs in the placenta may lead to the upregulation of miRNA-17 by activating the miRNA sponge, thereby enhancing the pathogenesis of PE. MiRNA-17 has been introduced as an angiogenesis-related miRNA and is highly expressed in PE (72).

The placentas of individuals with PE show endothelial cell swelling called endotheliosis and microvascular obstruction (73). PE has been implicated in altered expression of angiogenic and antiangiogenic factors, sFlt-1 or sVEGFR1, which is overproduced by the early placenta and secreted into the maternal peripheral blood. In the maternal bloodstream, it is considered to bind and neutralize VEGF and PlGF, a member of the VEGF subfamily, with high affinity, which results in a reduction of VEGF and PlGF in maternal blood and the disruption of VEGF signaling in endothelial cells due to reduced number of bound VEGF receptors (74-76). In conclusion, the disturbed balance between PIGF and sFlt-1 is one of the causes of PE. Hsa_circ_0063517 has a decreased expression in the placentas of patients with PE, and its knockdown reduces the expression of endothelin B receptor, VEGFA and VEGFR2 in HUVEC-12 and HMEC-1 cells by sponging miR-31-5p (77), which suggests that hsa_circ_0063517 is involved in the angiogenesis of placenta.

Table II. Mechanism studies of circRNAs in preeclampsia.

circRNA ID	Gene symbol	Expression	Cell	Target	Function	(Refs.)	Study year
hsa_circ_0055724	ANKRD36	Downregulated	Trophoblast	N-cadherin	Proliferation; migration; invasion	(147)	2022
hsa_circ_0003496	UBAP2	Downregulated	Trophoblast	FOXM1	Proliferation; migration	(60)	2021
hsa_circ_0002814	HERC2	Downregulated	Trophoblast	Notch-1, CPEB2, FUS/VEGF	Proliferation; invasion	(58)	2022
hsa_circ_0088227	PAPPA	Downregulated	Trophoblast	HOXA7	Proliferation; migration; invasion	(143)	2022
hsa_circ_0000284	HIPK3	Downregulated	Trophoblast	-	Migration; invasion; proliferation; angiogenesis	(148)	2019
hsa_circ_0003286	GTF2H2B	Downregulated	Trophoblast	-	Invasion	(46)	2018
hsa_circ_0032962	SMEK1	Downregulated	Trophoblast	PBX3	proliferation; migration; invasion; EMT	(143)	2021
hsa_circ_0005734	FAM53B	Downregulated	Trophoblast	KCMF1	Proliferation; migration; invasion	(149)	2022
hsa_circ_0017068	B3GALNT2	Downregulated	Trophoblast	XIAP	Proliferation; cell cycle; apoptosis	(150)	2022
hsa_circ_0063517	RANGAP1	Downregulated	Vascular endothelial cell	ETBR	Proliferation; migration; angiogenesis	(80)	2020
hsa_circ_0001326	PHLDB2	Upregulated	Trophoblast	p27 Kip1	Proliferation; migration	(12)	2021
hsa_circ_0001326	PHLDB2	Upregulated	Trophoblast	IL16	Proliferation; EMT; migration; invasion.	(151)	2021
hsa_circ_0008726	DNAJB6	Upregulated	Trophoblast	LHX6	Proliferation; migration; invasion	(143)	2022
hsa_circ_0008726	DNAJB6	Upregulated	Trophoblast	RYBP	Migration; invasion; EMT	(60)	2021
hsa_circ_0004904	POLE2	Upregulated	Trophoblast	ATG12, FUS/VEGF	Proliferation; invasion; autophagy	(144)	2021
hsa_circ_0007445	OPHN1	Upregulated	Trophoblast	THBS2	Proliferation; migration; invasion	(57)	2022
hsa_circ_0007611	FAM193B	Upregulated	Trophoblast	IL1RAP	Proliferation; angiogenesis	(152)	2022
hsa_circ_0007885	BRAP	Upregulated	Trophoblast	HIF-2α, sFLT1	Proliferation; invasion	(61)	2022
hsa_circ_0058152	FN1	Upregulated	Trophoblast	ATF2	Proliferation; migration; invasion; apoptosis	(149)	2022
hsa_circ_0015382	PAPPA2	Upregulated	Trophoblast	TFPI2	Proliferation; migration; invasion; EMT; apoptosis; cell cycle	(94)	2021
hsa_circ_0088196	TNC	Upregulated	Trophoblast	ABL1	Migration; invasion	(149)	2022
hsa_circ_0088196	TNC	Upregulated	Trophoblast	LIF, jak-stat	-	(153)	2019
hsa_circ_0000566	VRK1	Upregulated	Trophoblast	PTEN, Akt	Migration; invasion; EMT	(154)	2021
hsa_circ_0085296	RIMS2	Upregulated	Trophoblast	THBS2	Proliferation; migration; invasion; angiogenesis	(58)	2022
hsa_circ_0085296	RIMS2	Upregulated	Trophoblast	E-cadherin	Proliferation; migration; invasion	(80)	2020
hsa_circ_0111277	PAPPA2	Upregulated	Trophoblast	HTRA1, Notch-1	Migration; invasion	(55)	2020
hsa_circ_0011460	AK2	Upregulated	Trophoblast	PGT	-	(51)	2019
hsa_circ_0011460	AK2	Upregulated	Trophoblast	THBS2	Proliferation; migration; invasion	(145)	2021

Table II. Continued.

circRNA ID	Gene symbol	Expression	Cell	Target	Function	(Refs.)	Study year
hsa_circ_0011460	AK2	Upregulated	Trophoblast	HTRA1	Proliferation; migration; invasion	(94)	2021
hsa_circ_0006772	TNRC18	Upregulated	Trophoblast	Grhl2	Migration; EMT	(154)	2019

circRNA, circular RNA; LHX6, LIM homeobox transcription factor family; RYBP, RING1 and YY1-binding protein; EMT, epithelial-mesenchymal transition; TFPI2, tissue factor pathway inhibitor 2; XIAP, X-linked inhibitor of apoptosis protein; ETBR, endothelin B receptor.

Circ_0001438 aggravates human villous trophoblast dysfunction by mediating the miR-942/NLRP3 axis (78). It has been reported that circCRAMP1L, circSFXN1 and circ_0085296 are involved in the pathogenesis of PE to varying degrees (50,79,80).

4. Mechanisms and clinical application of circRNAs

Although the functions of most circRNAs remain unclear, only a small fraction of identified circRNAs have been studied for their biological significance (81-85). A study has shown that circRNAs have binding sites for microRNAs and RNAs, and can act as RNA sponges to regulate the expression levels of target genes (86). The most representative circRNA is ciRS-7, which contains >70 conserved binding sites for miR-7 (87-89). A study has shown that circCDR1as and circMTO1 bind to miR-7 and miR9, respectively, and affect gene regulation, thereby indirectly suppressing or stimulating tumors (90). In addition, subsequent studies have also demonstrated the presence and importance of ciRS-7 as a miR-7 sponge in a number of pathophysiological processes, such as insulin secretion, myocardial infarction, hepatocellular carcinoma and gastric cancer progression (88,91-93). Based on the aforementioned theory, artificial sponge technology is a method of manufacturing molecules that can specifically bind to target miRNAs so that they can specifically adsorb target miRNAs. According to the partial base sequence of the target miRNA, circRNAs are artificially processed, then packaged with plasmids and transfected into cells or tissues, while circRNA acts as a miRNA 'sponge' to adsorb a large number of target miRNAs (64). Fan *et al* (94) found that the expression of circNR3C2 significantly enhances the tumor suppressive effect of HRD1 by sponging miR-513a-3p.

CircRNAs can also regulate biological processes by binding to proteins such as transcription factors. After binding to peccadillo homolog 1, circANRIL affects exonuclease-mediated pre-ribosomal (r)RNA processing and ribosome biogenesis (95). Circ-Foxo3 binds to CDK2 and cyclin-dependent kinase inhibitor 1 to form a ternary complex, thereby inhibiting the function of CDK2 and blocking cell cycle progression (10,96). Circ-Foxo3 also has a high binding affinity to anti-aging inhibitor of DNA binding 1, transcription factor E2F1 and anti-stress proteins FAK and HIF1a, and retains them in the cytoplasm, leading to increased cellular senescence (10). Circ-poly(A)-binding protein nuclear 1 (PABPN1) binds to HuR, thus preventing HuR from binding to PABPN1 mRNA to reduce PABPN1 translation (61,97). However, not all circRNAs that interact with proteins inhibit protein function. Ectopic circ-Amotl1 interacts with and stabilizes the nuclear oncogene c-myc, thereby upregulating c-myc targets and promoting tumorigenesis (98,99).

An early study by Chen and Sarnow in 1995 (100) demonstrated that synthetic circRNAs can recruit the 40S ribosomal subunit and initiate the translation of detectable peptides in human cells through internal entry sites. Studies have shown that, if an internal ribosome entry site (IRES) is inserted upstream of the start codon, whether *in vivo* or *in vitro*, circRNAs that are similar to certain RNAs without a 5' cap structure and a 3' (polyA) tail structure can be translated into proteins (101,102). Although IRES-mediated translation was first discovered in RNA and DNA viruses, it has subsequently been discovered in mRNAs such as immunoglobulin heavy chain binding protein mRNA, fibroblast growth factor and VEGF mRNA (103-105).

At present, several translated circRNAs have been identified to play key roles in human diseases, especially cancer. In gliomas, circSHPRH, produced by the SNF2 histone linker PHD RING helicase (SHPRH) gene, encodes a novel 146-amino acid protein (SHPRH-146aa), which exhibits inhibitory activity during tumorigenesis and glioma activity and also serves as a biomarker (106-108). Another glioma study revealed that circLINC-PINT is derived from a long intergenic non-coding RNA p53-induced transcript (LINC-PINT), which encodes an 87-amino acid peptide (PINT87aa). It interacts with the PAF1 complex in the nucleus to inhibit the transcriptional elongation of multiple oncogenes, thus playing a tumor suppressor role in the control of cell proliferation and tumorigenesis (106).

There are also studies showing that circ-F-box and WD-repeat domain containing 7 (FBXW7) can inhibit the development of glioma (109,110). CircFBXW7 is produced by the tumor suppressor E3 ligase FBXW7, which encodes a 185 amino acid peptide (FBXW7-185aa), that plays the role of a tumor suppressor in glioma (111). Another recent study showed that FBXW7-185aa can inhibit the proliferation and migration of triple-negative breast cancer cells by increasing FBXW7 abundance and inducing c-Myc degradation (112).

In hepatocellular carcinoma, GSK3β-induced phosphorylation and degradation of β-catenin lead to activation of the Wnt pathway, which is associated with poor hepatocellular carcinogenesis and prognosis (113,114). In circBase, circβ-catenin is the only isoform that can be expressed in hepatocellular

carcinoma (115). Circβ-catenin produces a 370 amino acid peptide (β-catenin-370aa), and can promote the growth of liver cancer cells by activating the Wnt pathway (116,117).

Other studies have confirmed that circRNAs can activate the encoded protein through the m6a mechanism (118,119). The modification of m6A is completed by methyltransferase complexes such as methyltransferase-like (METTL)-3, METTL-14, Wilms Tumor 1-associated protein, RNA-binding motif protein 15 and zinc finger CCCH domain-containing protein 13 (4,120-124). Various internal or external factors, such as cell type, developmental stage, nutrient supply, circadian rhythm and environmental stresses initiate m6a translation (125). The 5'UTR m6A residue can directly recruit eukaryotic initiation factor 3, which is sufficient to recruit the 43S pre-initiation complex and bypass the m7G capping requirement to initiate translation, thus enabling translation initiation in the absence of the cap-binding factor eIF4E model (126).

Unlike conventional forward splicing, circRNAs originate from the same precursor as linear RNA transcripts, which is formed by a process called back splicing. Back-splicing creates a covalently closed loop that is characterized by a non-linear back-splicing junction between the splice donor and upstream splice acceptor, and it lacks a 5'cap and a 3' poly(A) tail (127). Due to this structural feature, circRNA can resist digestion by nucleic acid ribozymes (such as RNase R) and is more difficult to be degraded by exonuclease, so it is more stable compared with linear RNAs, with a longer half-life of up to 10 times that of linear RNA (128). These attributes make circRNA a potential biomarker for disease diagnosis and prognosis (85). CircRNA is stable and not easy to be degraded in blood and exosomes. It can be quantitatively detected by reverse transcription followed by qPCR (85). At the same time, compared with the complex antigen-antibody reaction and unclear parameters of protein detection, circRNAs are always expressed in a tissue- or cell-specific manner and can be detected by qPCR and *in situ* hybridization, which makes circRNA an ideal molecule for clinical diagnosis or prognosis detection of diseases, with landmark significance (1,7,129-131).

CircRNAs have been implicated in a variety of diseases, such as bone-osteosarcoma, colon-colorectal adenocarcinoma, kidney-renal cell carcinoma, liver-hepatocellular carcinoma, lung-lung adenocarcinoma and stomach-gastric adenocarcinoma (132). Due to the observed association between circRNA abundance and cancer, circRNA may serve as a cancer biomarker with good diagnostic performance (133). A study has also shown that circRNAs are present in human body fluids such as saliva, plasma, plasma and exosomes at relatively high steady-state levels, making them candidate biomarkers for non-invasive liquid biopsies (127). Zhang *et al* (79) found that circSATB2 is highly expressed in non-small cell lung cancer cells and tissues. CircSATB2 is highly expressed in plasma exosomes of patients with lung cancer with high sensitivity and specificity for clinical detection, and is associated with lung cancer metastasis (134). Wang *et al* (134) found that circRNA-002178 is detectable in the plasma exosomes of patients with lung adenocarcinoma (LUAD) and can be used as a biomarker for early diagnosis of LUAD. These studies provide a certain basis for the use of circRNAs as molecular markers for disease diagnosis and provide a new method for clinical screening of diseases.

5. Conclusion

PE is defined as new-onset hypertension after 20 weeks of gestation, so early diagnosis is crucial for PE. Due to the current lack of sufficient data or the heterogeneity of the recruited population, circRNA is not sufficient as a marker for PE monitoring and screening. Given the molecular advantages of circRNAs over linear RNAs, studies on circRNAs are more focused on possible screening purposes. Although some studies have reported the possible screening performance of circRNAs in the first or second trimester of pregnancy, a single circRNA has not been successfully used in any PE screening program (135-137). One study has found that the area under the curve (AUC) of plasma hsa_circ_0001855 is 0.62. While using the plasma protein PAPP-A in combination with hsa_circ_0001855 and hsa_circ_0004904, the AUC increases to 0.94, with a sensitivity of 0.87 and a specificity of 0.97 (30). In another study combining plasma hsa_circ_0007885 level, plasma sFLT1 level and abnormal uterine artery pulsatility index (UtA-PI), the AUC is 0.85, and the sensitivity and specificity are 0.80 and 0.86, respectively (138). The predictive power for PE is far stronger compared with any previous single molecular or ultrasound data (61). In summary, circRNAs can be combined with some specific molecules or clinical examination data such as PPAP-As, sFlt-1 and UtA-PI for prediction as a new strategy for early clinical diagnosis of PE.

The present review summarizes the study progress of circRNAs in PE in recent years. The endogenous competitive mechanism of circRNAs occupies the majority, which is of help for understanding the pathogenesis of PE. However, the research on circRNAs has only revealed the tip of the iceberg, such as RNA-binding proteins and encoded proteins, which have potential for the prevention and treatment of PE. With the development of sequencing technology, more circRNAs will be discovered and new methods will be used to study PE. We hope that this review has provided help for the diagnosis and treatment of PE.

Acknowledgements

Not applicable.

Funding

This work was supported by the National Natural Science Foundation (grant no. 81871173).

Availability of data and materials

Not applicable.

Authors' contributions

HJ contributed significantly to analysis and manuscript preparation, performed the data analyses and wrote the manuscript. ZL and TM revised the manuscript. All authors reviewed the

manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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