Thieme

The NFκB Signaling Pathway Is Involved in the Pathophysiological Process of Preeclampsia

Der NFκB-Signalweg ist am pathophysiologischen Prozess der Präeklampsie beteiligt

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ABSTRACT

The high prevalence of preeclampsia (PE) is a major cause of maternal and fetal mortality and affects the long-term prognosis of both mother and baby. Termination of pregnancy is currently the only effective treatment for PE, so there is an urgent need for research into its pathogenesis and the development of new therapeutic approaches. The NFκB family of transcription factors has an essential role in inflammation and innate immunity. In this review, we summarize the role of NFκB in normal and preeclampsia pregnancies, the role of NFκB in existing treatment strategies, and potential NFκB treatment strategies.

ZUSAMMENFASSUNG

Die hohe Prävalenz von Präeklampsie (PE) ist eine wesentliche Ursache mütterlicher und fetaler Mortalität und wirkt sich auch auf die Langzeitprognose von Mutter und Kind aus. Der Schwangerschaftsabbruch stellt zurzeit die einzig effektive Therapie gegen PE dar. Damit besteht ein dringender Bedarf nach weiterer Forschung zur Pathogenese von PE sowie zur Entwicklung neuer Therapieansätze. Die NFκB-Familie der Transkriptionsfaktoren spielt eine wichtige Rolle in Entzündungsprozessen und für die angeborene Immunität. In dieser Übersichtsstudie fassen wir die Rolle von NFκB bei normalen und Präeklampsie-Schwangerschaften sowie die Bedeutung von NFκB in bereits existierenden Therapien und potenzielle NFκB-Behandlungsstrategien zusammen.

Introduction

Preeclampsia (PE) is a hypertensive disorder of pregnancy (HDP), characterised by oedema, proteinuria, and hypertension-related symptoms, and can only be diagnosed after the 20 th week of pregnancy [1]. PE is a common syndrome in pregnancy, affecting approximately 3–5 % of pregnancies worldwide. The incidence of PE has been increasing for nearly 30 years [2]. It can lead to fetal growth restriction (FGR), abortion, low birth weight and other fetal and neonatal complications. Besides, it can adversely affect the long-term prognosis of mother and baby and even lead to maternal and infant death, such as increased risk of chronic hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, kidney disease, thromboembolism, hypothyroidism, and even impaired memory in the later maternal period and [3] increased risk of obesity in offspring and others metabolic diseases with PE. When PE presents with severe symptoms of eclampsia or haemolysis, elevated liver enzymes and low platelets (HELLP syndrome), maternal mortality is even higher. Some researchers have found that the onset of PE is related to maternal immune imbalance and placental inflammation [4]. However, the pathogenesis of PE is not fully understood in humans because of this special period of pregnancy. The only treatment currently available is termination of the pregnancy. Low-dose aspirin in early pregnancy has been shown to prevent PE, but only if taken before 16 weeks' gestation [5, 6, 7]. Thus, it is crucial to screen during the first trimester in order to effectively prevent PE [8]. However, due to the lack of comprehensive understanding of the pathogenesis of PE, existing screening protocols are inaccurate. It is therefore important to have a thorough understanding of the pathogenesis of PE.

PE has a complex pathogenesis involving a number of different mechanisms. The main causes of PE are oxidative stress at the maternal–fetal interface, maternal inflammation, insufficient remodelling of the uterine spiral arteries and vascular endothelial injury [9, 10, 11]. All these mechanisms are mediated by NFκB. During pregnancy, women experience a physiological inflammatory response that can promote remodelling of the uterine spiral arteries by regulating trophoblast infiltration. Overactivation of the inflammatory response leads to immune imbalance and vascular endothelial damage, which promotes the development of pregnancy complications associated with PE [2, 12]. Therefore, in this review, we systematically elaborate on the role of NFκB in the development and treatment of PE.

The NFκB family consists of seven proteins, RelA (p65), RelB, c-Rel, NFB1 (p105/p50), and NFB2 (p100/p52), which are encoded by five distinct genes and affect the expression of over 400 genes [13, 14]. It plays an important role in normal and complex pregnancies by regulating pathways such as inflammation, oxidative stress, cell proliferation, differentiation, apoptosis, and angiogenesis [15]. In resting cells, NFκB is present in the cytoplasm and bound to its inhibitor (IkB), which dissociates by phosphorylation in an environment rich in reactive oxygen species and cytokines. NFκB is translocated from the cytoplasm to the nucleus where it recognises and binds to specific DNA sequences and acts as a transcription factor regulating the expression of inflammatory factors and MMPs (Matrix Metalloproteinases) [16, 17]. There are studies suggesting that the development of PE may be a familial risk, which may be due to genetic and epigenetic changes [18, 19]. Compared to women with no family history of PE, NFκB expression in PE is increased by 23.35 percent [20].

NFκB Signal Pathway in Normal Gestation and PE

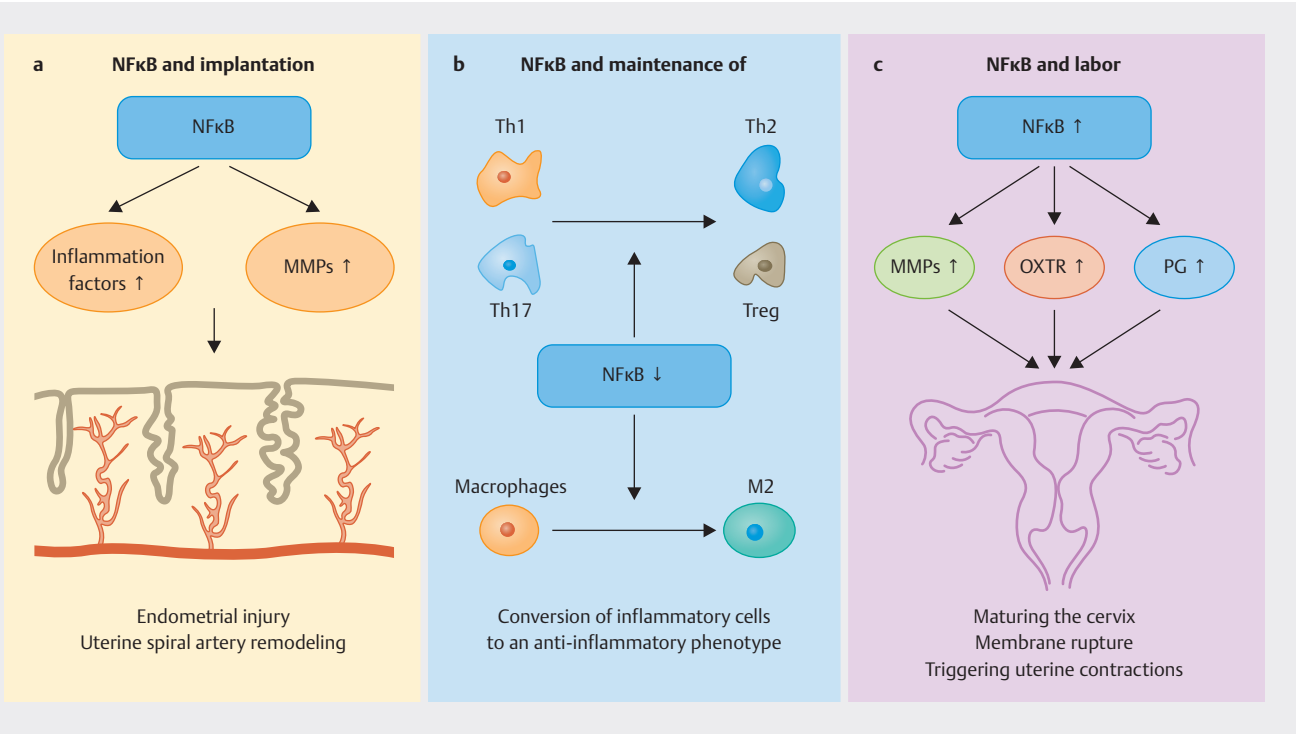
Semi-allogeneic fetuses exposed to maternal immune systems during pregnancy are usually not rejected and develop in the mother's womb until birth. The fetal–maternal interface is the site of regulation of this substantial immune tolerance and the placental chorionic villi are critical for this management. For a normal pregnancy, inflammation must be tightly controlled. Macrophages help to maintain pregnancy by promoting tolerance to semi-allogeneic fetuses and maintaining the homeostatic environment necessary for healthy fetal development [21, 22]. Macrophage differentiation can also be regulated by the NFκB pathway.

Normal gestation

In order to help control the window of implantation, NFκB is upregulated in the decidua prior to fertilisation. When the embryo implants, there is a severe inflammatory response, which may be triggered by the production of paternally derived alloantigens in the embryo [23]. The uterus releases pro-inflammatory cytokines during the implantation window to activate and attract numerous immune cells to the endometrium, causing local endometrial injury that aids effective implantation [24, 25]. Studies support the idea that endometrial biopsies performed during the natural cycle prior to IVF treatment can significantly increase the likelihood of implantation and clinical pregnancy [25]. Furthermore, higher NFκB expression in the first trimester is associated with increased MMP expression. MMPs are important extracellular matrix (ECM) remodeling proteinases that control uterine remodeling, a process that is essential for healthy pregnancies [26]. High MMP-9 levels promote uterine ECM degradation and relax intercellular connections, promoting extravillous trophoblast cells to invade and uterine spiral artery remodeling [27, 28].

NFκB expression is also increased in late pregnancy, which can enhance cervical maturation, induce membrane rupture, and cause uterine contractions [15, 29]. When labor begins, inflammatory cytokines in the chorion are increased and act on the myometrium via the NFκB pathway, boosting oxytocin receptor expression and starting labor [30]. At the same time, MMP activates at the start of labor by lysing the cytoskeletal substrate, triggering muscular contraction. By inhibiting the biological role of progesterone, a pregnancy-maintaining factor, and promoting the expression of oxytocin receptors and prostaglandin synthase, myometrial inflammation plays a significant role in labor [31, 32, 33].

During pregnancy maintenance, maternal inflammatory levels were largely suppressed and NFκB transcript levels decreased, which was associated with increased regulatory T cells. A subset of T cells called "Treg" cells play a role in regulating the immune system and preventing organ rejection [34, 35]. Th1 and Th17 effector cells differentiate into regulatory T cells at this stage and mediate the development of immune tolerance [29]. The expression of the Foxp3 gene and cytokines (e.g. IL-2 binding) are associated



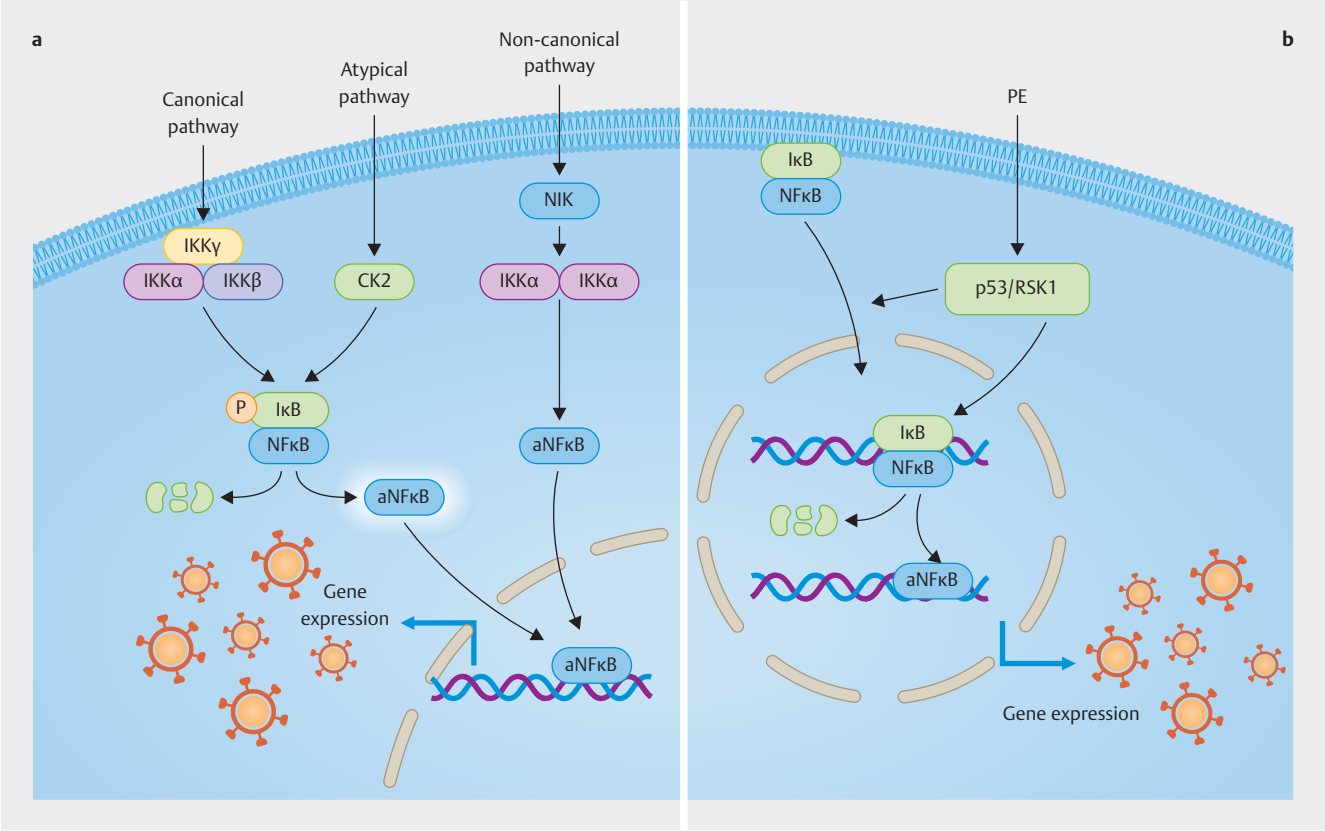
▶ **Fig. 1** Mechanism of action of NFκB in normal pregnancy. (**a**) In the first trimester, pre-eclampsia expression increases significantly, secreting a large number of inflammatory factors and MMPs, promoting endometrial damage and spiral artery remodelling, and enabling embryos to implant successfully. (**b**) During pregnancy maintenance, NFκB levels decrease, immune cells differentiate towards the anti-inflammatory phenotype, Th1 and Th17 differentiate into T2 and Treg cells, and macrophages differentiate towards the M2 phenotype, inducing maternal immune tolerance to the fetus. (**c**) NFκB levels rise again in the third trimester, promoting the expression of prostaglandins, MMPs and oxytocin receptors, inducing cervical maturation, leading to rupture of the membranes and uterine contractions.

with the differentiation of Treg [36]. Meanwhile, placental macrophages differentiate towards the M2 phenotype under NFκB mediation. M2 macrophages promote tissue repair, angiogenesis and homeostasis, whereas M1 macrophages are generally considered to be anti-inflammatory. The intense maternal inflammatory response is thus suppressed [37, 38] (▶ **Fig. 1**).

PE pregnancy

NFκB is generally activated at the beginning of pregnancy by the action of IKKα and IKKβ proteins [39]. NFκB inhibitors are degraded by the combined action of IKKα and IKKβ, together with IKKγ. IKKα is a key activator of NFκB in the canonical and non-canonical pathways. CK2α, the catalytic subunit of the CK2 protein, is the key activator of the atypical NFκB activation pathway [40]. Activators (IKKα and CK2α) are decreased and inhibitors (IκBβ and IκBα) are increased in PE placenta, which may mean that all three NFκB activation pathways are downregulated in PE [14]. Interestingly, the role of IKKα depends on its localization, i.e., activating NFκB in the cytoplasm and terminating NFκB-mediated gene expression in the nucleus [41]. Therefore, depletion in the cellular IKKα level may influence the nuclear transcriptional activity of NFκB, leading to elevated concentrations of factors whose genes are regulated by NFκB (▶ **Fig. 2a**). One possibility is that the NFκB inhibitors whose levels are elevated in this paper may favor NFκB activation by switching from an inhibitory role to a chaperone-like function, thus supporting the transport of NFκB in an inactive form into the nucleus [14]. The levels of p53/RSK1 in HTR8/SVneo cells cultured with PE serum were elevated. The p53/RSK1 complex is known to activate NFκB by its phosphorylation at Ser536, independent of the cytoplasmic degradation of the kappa B inhibitor. This suggests that factors existing in the serum of pre-eclamptic women influence the activation of NFκB by the p53/RSK1 pathway in hypoxic conditions [42] (▶ **Fig. 2b**). However, experimental data were obtained from placentas obtained during late pregnancy. The activation pathway of NFκB in early and mid-pregnancy is still worth exploring.

Several studies have shown that, compared to normal pregnancy, NFκB in the placenta and maternal circulation of PE women is significantly increased, which leads to an increase in maternal inflammation levels [43, 44, 45, 46]. Hofbauer cells (HBCs) are natural macrophages of the human placenta, predominantly with an anti-inflammatory M2 phenotype. However, under the influence of persistent inflammation during pregnancy, there is a transition to the M1 phenotype, which may be based on an increase in NFκB expression [47]. Syncytiotrophoblast dysfunction is a key feature in PE, reports have observed disruption of syncytiotrophoblast apical microvilli, indicating a loss of apical polarity, which can be disrupted by pro-inflammation [48].



▶ **Fig. 2** NFκB activation pathway in cells. (**a**) Canonical, atypical, and non-canonical activation pathways for NFκB. IKKα, IKKβ, and IKKγ are activators of NFκB in the canonical and non-canonical pathways. CK2 is the activator of the atypical NFκB activation pathway. IκB is an inhibitor of the NFκB pathway. (**b**) Activation pathway of NFκB in HTR8/SVneo cells cultured with PE serum [40].

Pro-inflammatory or Anti-inflammatory Factors Affect NFκB Signaling Pathway

The NFκB signaling pathway is regulated by a variety of regulators in human. The risk factors for PE are similar to those for cardiovascular diseases, such as elderly pregnancy, obesity, metabolic disorders, kidney disease, autoimmune diseases [49], and a family history of preeclampsia. These factors can lead to placental inflammation. However, the exact aetiology of PE is unclear, but it has been hypothesized that while genetic and environmental factors both affect how the condition develops, genetic factors have a greater impact [50]. In addition, a number of special pathogens, such as periodontal pathogens and gut microbes, are also involved in the development of PE through the NFκB pathway [11, 51].

Periodontal pathogens

A large number of clinical studies have found a positive correlation between periodontitis and the incidence of PE [52, 53]. One of the "key pathogens" in the aetiology of periodontitis is Porphyromonas gingivalis, which is also the most common pathogenic bacterium in amniotic fluid and placental tissue [54, 55]. Transmission of specific periodontal bacteria to placental tissue via the bloodstream stimulates upregulation of Toll-like receptor 4 (TLR-4) expression and downregulation of Peroxisome proliferator-activated receptor γ (PPAR-γ) expression. This in turn increases NFκB activity in placental tissue, ultimately promoting the development of PE [51, 56]. The possibility that these bacteria are part of the placental microbiome is controversial, as there is no agreement on whether the placental microbiome is present in healthy full-term pregnancies [57, 58]. However, periodontal disease during pregnancy is significantly associated with unfavorable short- and long-term offspring outcomes, which may be due to epigenetic changes [57]. Early diagnosis and treatment of periodontal disease in the first trimester or even before conception may be helpful in preventing and effectively minimising problems with conception and obstetrical issues [59, 60].

Gut microbe

Studies have shown that patients with PE have significant dysbiosis and a reduced diversity of gut bacteria. Among these, the intestinal flora associated with LPS production was significantly elevated in the intestinal flora of the PE group. Alterations in the gut microbiota may alter the profile of short-chain fatty acids released by bacteria, potentially leading to metabolic syndrome and hypertension [61, 62, 63, 64]. Early pregnant rats exposed to ultra-low doses of lipopolysaccharide (LPS) develop PE due to placental TLR4 activation [65]. LPS induces Prostaglandin-endoperoxide synthase

2 (PTGS2) and LncRNA BC030099 manipulates the inflammatory response via the NFκB pathway [33, 66].

Genetic factors

Placental omics analysis provides clues for exploring the occurrence and therapeutic targets of PE at the genetic level. Daniel Vaiman et al. identified 16 specific genes associated with placental disease, such as PKN3, PTTG1, etc., through a new method, which are involved in the development of PE through various pathways [67]. The NFκB pathway can be activated by the expression of inflammation-related genes such as NEMO, which is a key regulator of NFκB activation [68]. Agata Sakowicz et al. suggest that the presence of identical NEMO gene variants in the maternal and fetal genomes may increase the likelihood that PE offspring will develop PE [69]. This view may provide new insights into the genetic causes and pathogenesis of PE.

Over the past few years, microRNAs (miRNAs) have emerged as important regulators of gene expression in inflammatory and immune responses. Numerous miRNAs modify the activity of NFκB either by targeting upstream and downstream NFκB activating kinases or other NFκB signaling elements [13]. For example, MiR-517–3 p, which has high levels in the placenta of PE, targets the mRNA encoding TNFAIP3-interacting protein 1 (TNIP1), an inhibitor of the NFκB pathway, to activate NFκB pathway. Activation of NFκB increases production of the cytokine TNF superfamily member 15 (TNFSF15), leading to the upregulation of anti-angiogenic soluble vascular endothelial growth factor receptor 1 (sFlt-1). The Cajal bodies (CBs) are upstream regulators of miR-517–3 p, highly expressed in PE [13, 70]. By suppressing the production of HDAC2, miR-23a was able to stimulate the NFκB pathway [71]. In addition to inhibiting downstream phosphorylated AKT (p-AKT) and NFκB expression, unidirectional miR-219a can also inhibit downstream VEGF/NFκB signaling to inhibit trophoblast proliferation and invasion [72]. And other microRNAs, such as miR-21, miR-155, miR-31–5 p and miR-138, are involved in the development of PE through the NFκB pathway [73, 74, 75, 76, 77].

Despite lacking the ability to encode proteins, long non-coding RNAs regulate disease progression, possibly by affecting microRNA function [78, 79]. Placental overexpression of the lncRNA MIR503 host gene (MIR503 HG) is a microRNA-competitive endogenous RNA (ceRNA) whose cna inhibits the phosphorylation of IκB and the nuclear translocation of the NFκB signaling subunit p65 to regulate NFκB pathway [80].

Other factors

Many physical and social factors can also contribute to the development of PE, such as race or ethnicity, economic level, maternal disease, genetic polymorphisms and amniotic stretch [81, 82]. One interesting study found that polyhydramnios and multiple gestations were associated with an increased risk of preterm birth [83]. Justin et al. believe that stretching causes a downregulation of nuclear factor-E2-related factor 2 (Nrf2), accompanied by activation of the NFκB, leading to a pro-inflammatory state, which in turn leads to membrane thinning [84]. This may be explained by the subsequent infiltration of white blood cells that produce MMPs [85]. Studies have found that MTHFR (methylenetetrahydrofolate reductase) polymorphisms and diabetes can lead to impaired placental development [86], which may also be one of the reasons for the occurrence of PE, but the specific mechanism is still worth studying.

Protective factor

PPARγ, a transcription factor involved in glycolipid metabolism [87], is involved in placental cell metabolism, anti-inflammatory pathways, and oxidative stress [88]. PPARγ can regulate NFκB signal, inhibit its DNA binding activity, and promote its degradation [89, 90]. In multiple studies, PPARgamma appears to be downregulated in the placenta of PE patients [91, 92]. Due to the decrease in PPAR-γ, NFκB is overactivated, resulting in the release of pro-inflammatory factors such as IL-6, IL-8, and TNF-α from the placenta [93], resulting in vascular dysfunction and maternal PE [56]. In addition, abnormal expression of the PPAR gene is also associated with increased cardiovascular risk in PE offspring. Decreased PPAR expression increases the sensitivity of blood vessels to Ang II. Adult children with complicated pregnancies are more sensitive to Ang II, resulting in endothelial dysfunction [94, 95].

Some interesting studies suggest that smoking may reduce the risk of PE [96, 97]. In animal studies, LPS-induced PE-like symptoms in pregnant rats are greatly reduced by nicotine activation of alpha7 nicotinic acetylcholine receptors (7nAChRs). In human blood samples have shown that activating 7nAChR reduces NFκB activation in monocytes from PE patients and balances the production of pro-inflammatory and anti-inflammatory cytokines [98, 99]. This idea has also been supported by in vitro experiments in which nicotine significantly reduced activation of NFκB and increased the survival of endothelial cells, which may reduce the likelihood of developing PE in smokers [100]. However, smoking is not regarded as a therapy option for PE due to the negative effects of nicotine on health.

NFκB Signaling Influences PE Development

Poor placental implantation and remodelling of the maternal spiral arteries are associated with PE. The inability of the placental spiral artery to remodel properly and the inappropriate infiltration of trophoblast cells into the maternal decidua are considered to be the early stages of PE formation. Impaired trophoblast activity hinders the remodelling of the uterine spiral artery, which may lead to placental oxidative stress and the release of inflammatory factors into the maternal circulation, causing systemic vascular endothelial damage and further PE-related pregnancy complications [22]. Therefore, many of the molecules that regulate trophoblast and endothelial function may influence the development of PE.

Trophoblast cell function

In PE, overexpression of Fas, ANKRD37 and triggering receptor expressed on myeloid cells-1 (TREM-1) contributes to the development of PE by preventing trophoblast cell invasion and migration, through the NFκB pathway [101, 102, 103]. These substances cause NFκB to be activated and interact with lnc-SLC4A1–1, resulting in an increase in CXCL8 mRNA expression. CXCL8 can promote TNF-α and IL1 β. The release of cytokines activates inflammation-

related pathways, ultimately leading to increased cell apoptosis and reduced proliferation of trophoblasts, inhibiting their migration and vitality [104]. In addition, the activation of the NFκB pathway can also inhibit the invasion of trophoblast cells by increasing the production of PTEN [105]. By controlling NFκB pathway in PE, reducing the expression of PTGS2 and FPR2 can inhibit the pro-invasive and pro-inflammatory effects of LPS on trophoblast invasion [106, 107].

Matrix metalloproteinase

The activation of the PI3 K/AKT and ERK1/2 pathways in human trophoblast cells promotes NFκB translocation to the nucleus, activates MMP-9 promoter transcription after binding to DNA, and increases MMP-9 levels in trophoblast cells. Meanwhile, NFκB indirectly enhances MMP-2 activity by controlling enzymes associated with post-translational processing, such as increasing the expression of MT-MMP (model metalloproteinase) [17, 108]. Many studies have shown that MMP-2, MMP-9 are associated with uterine artery remodelling by promoting trophoblast cell proliferation, migration and invasion [109, 110]. There are significant differences in the levels of serum MMP-2 and MMP-9 at different stages of pregnancy. MMP-2 is most highly expressed in the first trimester and is involved in early placental formation. MMP-9 expression is lowest in the first trimester and highest in the second and third trimesters, which may be related to the promotion of placental and fetal development by MMP-9 [111]. After PE, serum MMP-2 levels are significantly increased and MMP-9 levels are significantly decreased [112]. Ongoing research shows that the expression of MMPs can be regulated by a variety of substances, such as JSH-23 and MIR503 HG, which can reduce MMP levels by inhibiting the NFκB signaling pathway [11, 66, 80]. Nuclear receptor coactivator 6, a transcriptional coactivator, can activate NFκB to induce MMP-9 transcription [113].

The levels of MMP-2 and MMP-9 are also associated with autophagy. Autophagy regulates trophoblast invasion by targeting NFκB activity [114]. NFκB signaling is generally thought to occur prior to autophagy activation [115], but studies have also shown that autophagy itself has the ability to degrade NFκB signaling components through various signaling pathways [116, 117, 118].

Endothelial cell function

eNOS can catalyze the synthesis of NO by vascular endothelial cells and maintain vasodilation by activating PKG [119, 120]. NFκB is a key factor in impairing vascular function and remodelling in human chronic inflammatory diseases by affecting endothelial progenitor cells (EPCs) and endothelial cell function [121]. Placental dysplasia can lead to placental dysfunction, resulting in the release of STBEV into the maternal bloodstream, which causes endothelial failure by activating NFκB, causing oxidative and nitrative stress and reducing eNOS expression and NO bioavailability [122]. Through interactions with IKK, GSTP1 can suppress NFκB signaling. This reduces iNOS expression and stimulates apoptosis, which controls NO-mediated ROS production [123]. By blocking the p38 MAPK/ NFκB pathway, cathepsin C downregulation improves HUVEC function. Endothelial cell dysfunction is protected by cathepsin C knockdown, which also offers a novel and promising strategy for the treatment of PE [9].

NFκB Pathway: Targets for Drug Therapy in PE

Common drugs act on NFκB

Many drugs can target NFκB pathway to improve PE-like symptoms. Aspirin is the drug most commonly used clinically to prevent PE. Aspirin inhibits activation of the NFκB pathway by preventing NFκB nuclear translocation and binding to DNA motif elements or by binding to the IKKα protein as a competitive inhibitor of ATP [44, 124, 125]. Aspirin prevents redox-sensitive NFκB/miR-155/eNOS axis thereby reversing TNF-α-mediated downregulation of eNOS and endothelial failure [126].

Magnesium sulphate is one of the most commonly used drugs in obstetrics and is often used to lower blood pressure, prevent eclampsia and protect fetal nerves. Magnesium sulphate also has an inhibitory effect on the NFκB pathway [124, 127]. In animal studies, $MgSO_4$ was found to protect cranial nerves in PE rats by inhibiting the NFκB/ICAM-1 signaling cascade [128]. In addition, magnesium salts can also reduce the placental hyperinflammatory response in an NFκB-dependent manner [129].

Other anti-inflammatory, antineoplastic and vitamin supplementation therapies have also been tried to treat PE by targeting NFκB. Such as sulfasalazine and vitamin D supplementation, both have been shown to inhibit the NFκB pathway and reduce PE-like symptoms in animal models [130, 131]. Through the PPARγ–NFκB axis, rosiglitazone can reduce trophoblast-associated inflammation [95]. Metformin (MET) has been shown to improve LPS-induced PE symptoms and placental damage. This process may inhibit TLR4/NFκB/PFKFB3 signaling in the trophoblast to treat PE by reversing glucose metabolic reprogramming and NLRP3 inflammasome-induced pyroptosis [132, 133]. Therefore, metformin and other NFκB signaling inhibitors may be potential treatments for PE.

Potential treatment options

In addition, targeting substances upstream of NFκB to block its mechanism of action has been shown in a large number of cell and animal studies to prevent or treat PE or improve the poor prognosis of PE. Such as USP14, Mammalian ste20-like kinase 1 (MST1) and proteinase-activated receptors-1 (PAR-1). USP14 expression levels are significantly upregulated in placental tissues of PE patients, which can activate NFκB. Through the development of drugs targeting USP14 may be helpful in the prevention of PE [134]. MST1, part of the tumor necrosis factor (TNF-α) receptor 1 signaling complex, reduces the effect of TNF-α on NFκB signaling. Leonurine (LNR) is one of the active components of motherwort [135], which can exert anti-inflammatory and anti-apoptotic effects by upregulating MST1 and inhibiting NFκB signaling [136, 137]. MMP-1 can encourage the release of IL-8 from vascular smooth muscle, and it is markedly enhanced in the PE circulation. Recruitment of neutrophils might be aided by IL-8 [138]. Neutrophil expression of PAR-1 is specific for pregnancy. PAR-1 activates ROCK and then activates NFκB, causing vascular endothelial inflammatory injury [139]. PE may be prevented by blocking the

PAR-1 pathway or by reducing MMP-1 levels in the maternal circulation.

Traditional Chinese medicine treatment

In animals, cells and even clinical trials, some Chinese herbal preparations and their active ingredients have shown effective therapeutic benefits. Apocynin, Astragaloside IV (AsIV) and Fisetin could reduce PE-like symptoms such as hypertension and proteinuria, possibly by reducing inflammation through the TLR4/NF-B pathway [140, 141, 142]. In placental tissue from pre-eclamptic rats, astragalus injection can successfully inhibit the expression of sFlt-1, NFAT-5 and NFκB and increase the expression of PlGF and MMP-9 [110]. By controlling NLRP1 and NLRP3 inflammosomes in monocytes and activating the TLR4/NFκB pathway, silybin (SB) may be able to treat PE. However, its safety is questionable [143, 144].

Physiologic substances for PE

In addition to medication, the development of PE may also be regulated by physiological substances. One study found decreased vagus nerve activity in women complicated by PE [145]. ACh greatly reduced p38 MAPK and NFκB phosphorylation, as well as hypoxia-induced ROS production and subsequent apoptosis. According to Wang Zheng et al., ACh therapy can increase the activity of the vagus nerve and may be beneficial in the treatment of PE [146, 147]. The increase in estrogen and progesterone (PG) during pregnancy allows the uterus and placenta to improve vascularisation. PG regulates the expression of inflammation-related genes and proteins by inhibiting NFκB activation in macrophages, exerts an immunomodulatory effect on monocytes in pre-eclamptic women. Immunomodulation may be an alternative treatment for PE [148, 149]. Endogenous melatonin production is inhibited by hypoxia/reoxygenation (H/R), which reduces syncytiotrophoblast vitality. To prevent H/R-induced damage, exogenous melatonin therapy may be an option. This would increase placental cell survival and benefit fetal outcomes [150].

Drug carriers

Early pregnancy is the period of placental formation and also the susceptibility period for fetal teratogenesis. Poor placental formation is an irreversible process. Therefore, the treatment of PE is mainly focused on improving symptoms. Many NFκB inhibitors cannot be used directly to prevent and cure PE because many small-molecule drugs may have unknown effects on the fetus across the placental barrier in early pregnancy. To stabilise the maternal circulation and avoid placental metastasis, Adrian C. Eddy and colleagues have developed a drug delivery method based on the bioengineered protein ELP (elastin-like polypeptide). The usefulness of this system for small molecule, peptide and protein therapies used during pregnancy is enhanced by the adaptability of ELP to fuse with various therapeutic agents [151].

Conclusion

NFκB affects the ability of trophoblasts to proliferate, invade and migrate by affecting the expression of MMPs, which may lead to inadequate remodelling of the spiral arteries and changes in placental villous morphology and function in early pregnancy. Note that the NFκB activation pathway in the placenta of women with PE in the third trimester differs from that in other cells and tissues. This difference may be related to the development of the P53/RSK1 complex [124] and may be due to the prolonged inflammatory state of the maternal placenta. However, the period of activation and transformation of the NFκB pathway is still unknown. It is interesting to note that cellular metabolic reprogramming is closely linked to TLR4/NFκB signaling. When the NFκB signaling pathway is activated, the energy metabolism within cells shifts from aerobic metabolism to glycolysis, which may also be related to the occurrence of PE [133].

Drugs targeting NFκB have shown therapeutic effects on PE in a large number of experiments, but considering their impact on the fetus, their use in the human body is still very cautious. In the future, it may be possible to reduce the impact of drugs on the fetus by constructing drug carriers, or to make drugs only act on the mother by affecting placental immunity and drug metabolism.

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Contributors' Statement

Yaxi Li prepared the manuscript. Jing Wang, Xiaolei Liang provided writing guidance. Qinying Zhu, Xue Qin, Yi Li revised the manuscript. Ruifen He, Junhong Du provided drawing guidance. All authors have approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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