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Role of the NLRP3 Inflammasome in Preeclampsia

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Reproduction involves tightly regulated series of events and the immune system is involved in an array of reproductive processes. Disruption of well-controlled immune functions leads to infertility, placental inflammation, and numerous pregnancy complications, including preeclampsia (PE). Inflammasomes are involved in the process of pathogen clearance and sterile inflammation. They are large multi-protein complexes that are located in the cytosol and play key roles in the production of the pivotal inflammatory cytokines, interleukin (IL)-1β and IL-18, and pyroptosis. The nucleotide-binding oligomerization domain, leucine-rich repeat-, and pyrin domain-containing 3 (NLRP3) inflammasome is a key mediator of sterile inflammation induced by various types of damage-associated molecular patterns (DAMPs). Recent evidence indicates that the NLRP3 inflammasome is involved in pregnancy dysfunction, including PE. Many DAMPs (uric acid, palmitic acid, high-mobility group box 1, advanced glycation end products, extracellular vesicles, cell-free DNA, and free fatty acids) are increased and associated with pregnancy complications, especially PE. This review focuses on the role of the NLRP3 inflammasome in the pathophysiology of PE.

Keywords: NLRP3 inflammasome, pregnancy, preeclampsia, interleukin-1β, inflammation

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INTRODUCTION

Reproduction, including development of oocyte and sperm, ovulation, corpus luteum function, fertilization, implantation, placentation, maintenance of pregnancy, and parturition, is essential for species maintenance, and reproductive events for next generation are tightly regulated (1). Pregnancy has been studied extensively over the years (2). From the perspective of the maternal immune system, a conceptus is a semi-allogeneic tissue that must be rejected; however, that does not generally happen. It was quickly ruled out that the fetus is shielded from the maternal immune system via the placenta acting as a physical barrier because the fetal extravillous trophoblast cells deeply penetrate the uterine mucosa and directly communicate with various maternal immune cells to avoid rejection (3).

Inflammation is basically a complex protective immune response to harmful stimuli such as pathogens, damaged or dead cells, and irritants (4). This response is tightly regulated by the host, enabling survival after infection or injury and maintaining tissue homeostasis. However, excessive inflammation may cause chronic or systemic inflammatory diseases. On the other hand, the immune system also contributes to the regulation of reproductive function and pregnancy (5). Immune-mediated processes such as tissue growth, remodeling, and differentiation are crucial to maintain pregnancy (1, 5). Disruption of well-controlled immune functions leads to infertility, placental inflammation, and numerous pregnancy complications, such as preeclampsia

(PE), obesity during pregnancy, gestational diabetes mellitus (GDM), spontaneous abortion, and recurrent pregnancy loss (6–8).

There is an increasing body of evidence to suggest that inflammation and immune cells are involved in both physiology and pathophysiology of pregnancy. Since infection is not involved in the majority of the phenomena related to pregnancy physiology and pathology, it remains unclear why inflammation is involved. Recently, there have been numerous reports of inflammasome mechanisms that control sterile inflammation involved in pregnancy pathologies. Inflammasomes are large multi-protein complexes found in the cytosol that play key roles in the production of the pivotal inflammatory cytokines, interleukin (IL)-1β and IL-18, and pyroptosis (inflammatory cell death) [(9–11); **Figure 1**]. In particular, nucleotide-binding oligomerization domain, leucine-rich repeat-, and pyrin domain-containing 3 (NLRP3) inflammasome is a key mediator of sterile inflammation. Excessive activation of the NLRP3 inflammasome contributes to the pathogenesis of a wide variety of diseases, such as diabetes, atherosclerosis, and obesity-induced insulin resistance (12–17). The present review focuses on the role of the NLRP3 inflammasome in placental inflammation and pregnancy complications, especially PE.

IMMUNE CELLS INVOLVED IN PREGNANCY

The most important immune cells that induce pregnancy immune tolerance is CD4+ regulatory T cells (Tregs) (18). The transcription factor, forkhead boxP3 (Foxp3), is a master regulator of the development and function of Tregs (19). The frequency of Foxp3+Tregs increases during normal pregnancy in the decidua and peripheral blood in humans and mice (20–22). Shima et al. (23) used an animal model to demonstrate that $CD4^+CD25^+Foxp3^+$ Tregs play a critical role in regulating immune tolerance at the implantation site to support implantation and successful pregnancy. The frequency of Tregs is lower in human pregnancy complications such as PE or miscarriage (24). In addition, seminal fluid induces and accumulates paternal-specific Tregs that are involved in the preimplantation uterus, and insufficient expansion of Tregs against paternal antigens may trigger spontaneous abortion (25).

Natural killer (NK) cells, particularly decidual NK cells, are also essential immune cells involved in establishing pregnancy; they are the most abundant leukocyte population during the first trimester of human pregnancy (1, 26). Decidual NK cells directly communicate with extravillous trophoblast cells and other immune cells in the fetal-maternal boundary area, and promote fetal tolerance and pregnancy progression (26).

Monocytes also accumulate in the decidua, in a process that involves communication with trophoblast cells (1, 27). They can differentiate into dendritic cells (DCs) in the decidua during murine and human pregnancy (28, 29). DCs regulate immune tolerance by inducing effector T cell apoptosis and expansion of Tregs due to reduced antigen presentation, reduced expression of co-stimulatory molecules, or enhanced production of anti-inflammatory IL-10 (1, 30). Monocytes also differentiate into macrophages depending on the tissue, and polarization of macrophages is well-understood (inflammatory M1 and anti-inflammatory M2 type macrophages). It has been suggested that dysfunction of decidual macrophages and dysregulation of M1/M2 balance are critical events in the pathogenesis of PE. Moreover, activation of NLRP3 inflammasome in the reproductive organs including placenta is known to occur by these macrophages.

MECHANISMS OF NLRP3 INFLAMMASOME ACTIVATION

Inflammasomes recognize various inflammation-inducing stimuli, such as endogenous danger/damage-associated molecular patterns (DAMPs) and exogenous pathogen-associated molecular patterns (PAMPs). They tightly regulate the production of proinflammatory cytokines such as IL-1β and IL-18 (9, 13, 31). The NLRP3 inflammasome is the most widely studied and is activated in response to a wide array of stimuli, including exogenous and endogenous danger signals [(9, 11); **Figure 1**]. The NLRP3 inflammasome is typically composed of NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1 as an IL-1β-converting enzyme (32). Activation of NLRP3 in response to danger signals leads to nucleation of ASC into prion-like filaments via pyrin domain (PYD)–PYD interactions (33). ASC is then linearly ubiquitinated for NLRP3 inflammasome assembly, followed by procaspase-1 interaction with ASC using caspase recruitment domain (CARD)-CARD interactions, forming its own prion-like filaments (34). Activated caspase-1 (a cysteine protease) cleaves the precursor cytokines, pro-IL-1β and pro-IL-18, generating the biologically active cytokines, IL-1β and IL-18, respectively (9–11). Moreover, active caspase-1 is able to induce pyroptosis as an inflammatory form of cell death due to cleaved gasdermin D (GSDMD) (35, 36). Caspase-1 proteolytically cleaves GSDMD into a N-terminal domain and C-terminal domain. Cleaved N-terminal domain of GSDMD binds to phosphatidylinositol phosphates and phosphatidylserine in the cell membrane, forming a 10–20 nm pore and induces a lytic form of cell death, pyroptosis (36). Another feature of gasdermin D-dependent pyroptosis is the release of IL-1β and IL-18 via GSDMD-forming cell membrane pore.

The production and secretion of mature IL-1β are regulated via two steps, including the transcription of pro-IL-1β and proteolytic processing into a mature form IL-1β by inflammasomes (9–11). Prior to its activation, NLRP3 must be primed in most cell types. Nuclear factor κB (NF-κB)-activating stimuli, such as lipopolysaccharide (LPS), upregulate mRNA expression of *NLRP3* and *IL-1β*, resulting in elevated expression of NLRP3 and pro-IL-1β protein (9–11). On the other hand, another priming step facilitates the rapid induction of the NLRP3 inflammasome via deubiquitination of NLRP3 (37, 38).

The upstream mechanisms of NLRP3 activation have been elucidated by many studies, and include the release of cathepsins into the cytosol after lysosomal destabilization,

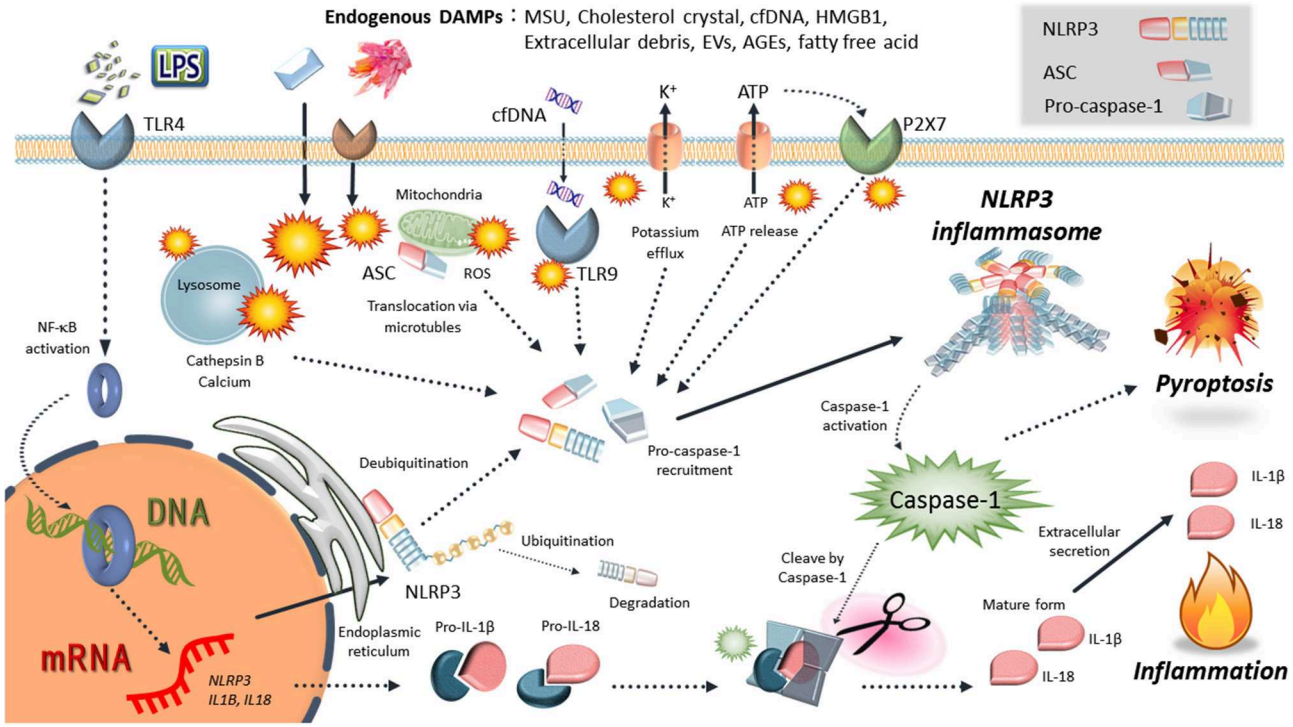

FIGURE 1 | Schematic mechanisms of NLRP3 inflammasome activation. NLRP3 is activated by various endogenous DAMPs: uric acid crystals (MSU), cholesterol crustal, cell-free DNA (cfDNA), high-mobility group box 1 (HMGB1), extracellular debris, extracellular vesicles (EVs), advanced glycation end-products (AGEs), and free fatty acid. Various events such as intracellular ATP release, NLRP3 deubiquitination, relocalization, reactive oxygen species (ROS) generation, mitochondrial dysfunction, lysosome rapture, and cathepsin release occur depending on the effects of damage-associated molecular patterns (DAMPs). Then, inflammasome components, including NLRP3, ASC, and procaspase-1, form the NLRP3 inflammasome complexes. Finally, activated caspase-1 induces the inflammatory form of cell death known as pyroptosis and cleaves the precursor cytokines pro-IL-1β and pro-IL-18, generating the biologically active cytokines IL-1β and IL-18.

potassium efflux, generation of mitochondrial reactive oxygen species (ROS), and release of mitochondrial DNA (39, 40). Cytosolic leakage of cathepsin B via lysosomal rupture is essential for NLRP3 inflammasome activation, especially by endogenous DAMPs (41). Leakage of cathepsin B also leads to potassium efflux and mitochondrial damage. Potassium efflux and reduced potassium concentration within cells result in NLRP3 inflammasome activation (10). In response to potassium efflux, NEK7 (a member of the family of mammalian NIMA-related kinases) directly interacts with NLRP3 inflammasome (42, 43). Cellular and mitochondrial ROS production also act as NLRP3 inflammasome activators (44, 45). Furthermore, recent studies have demonstrated that the NLRP3 inflammasome is tightly regulated by multiple mechanisms, including ubiquitination, phosphorylation, nitrosylation, microRNAs, and endogenous regulators (e.g., pyrin-only proteins and CARD-only proteins) (9, 46–48).

Following NLRP3 activation through the above mentioned regulatory mechanisms, NLRP3 relocates from endoplasmic reticulum to the mitochondria, where it forms complexes with ASC (49). IL-1β and IL-18 secretion is regulated by caspase-1 activation by many NLRP3 inflammasome activators, including monosodium urate (MSU) crystals, silica crystals, asbestos, and cholesterol crystals (12, 13, 31, 50). Additionally to the canonical pathway of the NLRP3 inflammasome, the inflammasome activation can also be indirectly triggered by caspase-11 in mice (or the homologs caspase-4 and caspase-5 in humans), which has been termed the non-canonical inflammasome pathway (51). In this non-canonical pathway, caspase-11 directly recognized and binds to intracellular LPS, resulting in its oligomerization and activation by autoproteolytic cleavage (35). Then, caspase-11 can directly induce the cleavage of GSDMD to induce pyroptosis (35, 36). Details of the structure and activation mechanism of the NLRP3 inflammasome are refer to following great reviews (10, 17, 39, 40, 52).

PREECLAMPSIA AND THE NLRP3 INFLAMMASOME

PE is a pregnancy-specific hypertensive syndrome that complicates around 5–10% of all pregnancies worldwide (53), and is a leading cause of maternal and fetal morbidity and mortality. It is characterized by the onset of hypertension and proteinuria in the third trimester of pregnancy, and is associated with 12% of infants with fetal growth restriction (FGR) and approximately 20% of preterm deliveries (54). The clinical manifestations of PE reflect widespread systemic inflammation

and endothelial dysfunction, resulting in vasoconstriction, end-organ ischemia and increased vascular permeability (55). The placenta has been shown to play a central role in the pathogenesis of PE due to the rapid disappearance of disease symptoms after delivery. Thus, placenta-derived circulating factor(s) may induce excessive inflammation and endothelial defects, leading to PE (56).

During normal pregnancy, trophoblast cells invade, and remodeling of maternal spiral arteries and the fetoplacental unit produce angiogenic factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), to support the developing placenta (57, 58). Inadequate trophoblast remodeling of spiral arteries, which is a key feature of PE, is believed to result of dysregulation in placental angiogenesis and maternal immune response (55). Following that, various inflammatory factors are produced by the diseased and hypoxic placenta, which activates systemic inflammatory responses (27, 59). It is widely recognized that antiangiogenic factors, including soluble endoglin (sEng; a coreceptor for transforming growth factor β) and soluble fms-like tyrosine kinase (sFlt-1; a receptor for VEGF), induce PE-like phenomena (57, 60). Indeed, overexpression of sEng and sFlt-1 in pregnant rats leads to severe PE symptoms including hypertension, proteinuria, renal and endothelial dysfunction, hemolysis, elevated liver enzymes, and FGR (60).

Pathophysiological changes of PE include inflammation and immune cell activation (61–63). The main pathological features of PE include a general inflammatory response by cytokines, such as IL-1β, IL-6, IL-8, and tumor necrosis factor-α (TNFα) (7, 64, 65). Siljee et al. (66) reported that IL-1β has a potential to improve prediction of PE during the first trimester. A decreased frequency of peripheral Tregs is characteristic immune cell dynamics seen in PE patients (6). On the other hand, M2-like immunomodulatory macrophages are abundantly present in the decidua in healthy pregnant women and participate in spiral artery remodeling via the angiogenic factors, VEGF and PlGF (27). Increased numbers of M1-like inflammatory macrophages are observed in PE patients and may be associated with increase in inflammatory cytokines, decreased spiral artery remodeling, and increased production of sFlt-1 and sEng (27).

In recent years, there has been a rapid increase in reports that the NLRP3 inflammasome is involved in the pathogenesis of PE (**Figure 2**). Higher expression of components of the NLRP3 inflammasome has been reported in peripheral blood mononuclear cells and placental tissue from PE patients compared with that of healthy normal pregnant women (67–69). In addition to immune cells, human trophoblast cells express NLRP3, ASC and caspase-1 that are components of the NLRP3 inflammasome (70–72). IL-1β secretion is induced in response to nigericin or nano-silica crystals, typical activators of the NLRP3 inflammasome, in human trophoblast cells (71, 72).

HYPERTENSION AND THE NLRP3 INFLAMMASOME IN PE

Maternal hypertension is a characteristic of PE and the renin–angiotensin system has been implicated in its pathogenesis of PE (73, 74) generated a mouse model of PE-like symptoms by mating females expressing human angiotensinogen with males expressing human renin, resulting in mice exhibiting maternal hypertension, proteinuria, and FGR. Angiotensin II (AngII) is a strong vasoconstrictor that contributes to hypertension and stimulates sFlt-1 production and secretion from the placenta in mice (75). Infusion of AngII in pregnant mice can lead to high maternal blood pressure, proteinuria, and FGR (75, 76). Deficiency of NLRP3 inflammasome components attenuates the development of AngII-induced hypertension, but does not affect FGR, proteinuria, or sFlt1 levels (76).

Furthermore, during non-pregnant conditions, infusion of AngII induces hypertension with activation of NLRP3 inflammasome in the aorta, and NLRP3 deficiency attenuated AngII-induced hypertension via inhibition of NLRP3 inflammasome activation in mice (77). A murine experimental hypertension model (uninephrectomy and treatment with deoxycorticosterone acetate and 0.9% NaCl in the drinking water) induced activation of the NLRP3 inflammasome in kidney and specific NLRP3 inhibitor, MCC950, inhibited the NLRP3 inflammasome and inflammation, resulting in improvement of hypertension in mice (78). In rats, salt-induced hypertension occurs partly due to the role of NLRP3 inflammasome activation in the hypothalamic paraventricular nucleus, while blockade of brain NLRP3 attenuates the hypertensive response (79). An absence of ASC also reduces pulmonary hypertension induced by hypoxia (80). These findings suggest that the NLRP3 inflammasome contributes to the development of hypertension in both pregnant and non-pregnant situations. On the other hand, NLRP3 inflammasome has been shown to contribute to a wide range of acute and chronic kidney diseases (81); the importance of NLRP3 inflammasome in renal pathologic abnormalities in PE pathology is not well-understood.

ACTIVATION OF NLRP3 INFLAMMASOME BY DAMPS IN PE

Release of DAMPs from various cells during stress has been implicated in pregnancy complications. In PE patients, many DAMPs, such as, cholesterol, uric acid crystals (MSU), extracellular DNA, high-mobility group box 1 (HMGB1), extracellular cell debris, advanced glycation end-products (AGEs), and free fatty acids, have been detected in higher levels in the peripheral blood and placenta (**Figure 2**) and act as NLRP3 inflammasome activators.

CHOLESTEROL AND THE NLRP3 INFLAMMASOME IN PE

Cholesterol crystals activate inflammatory responses and promote inflammatory cell infiltration, resulting in progression of atherosclerosis and development of cardiovascular disease (16, 82). Cholesterol crystals also cause lysosome rupture, resulting in the release of cathepsin B to the cytosol, and are a candidate activator of the NLRP3 inflammasome (82, 83).

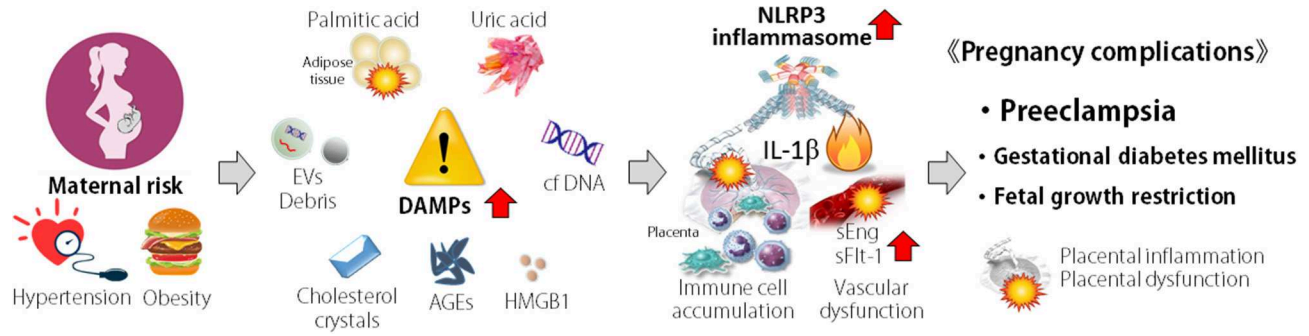

FIGURE 2 | Concept of association of NLRP3 inflammasome in pathogenesis of pregnancy complications. Maternal risk such as hypertension and obesity are associated with the elevation of damage-associated molecular patterns (DAMPs). DAMPs activate NLRP3 inflammasome, accumulate immune cells, and induce inflammatory cytokine production and vascular dysfunction in placenta. These events result in placental inflammation and dysfunction, leading to pregnancy complications, such as preeclampsia, spontaneous abortion, recurrent pregnancy loss, and fetal growth restriction.

Maternal cholesterol serum levels are elevated in PE and cholesterol accumulates in placenta of PE patients, along with increased levels of NLRP3 and IL-1β expression (84, 85). In an *in vitro* human placental explant experiment, treatment with cholesterol crystals significantly increased the release of IL-1β, and cholesterol crystal-induced IL-1β secretion was suppressed by treatment with MCC950, as a specific inhibitor of the NLRP3 inflammasome (84). Cholesterol crystals also strongly activated the NLRP3 inflammasome in macrophages and induced IL-1β secretion, dependent on activation of the NLRP3 inflammasome (82, 83, 86). In addition to macrophages, cholesterol crystals markedly increase the formation and activation of NLRP3 inflammasome in endothelial cells, as demonstrated by increased colocalization of NLRP3 with ASC or caspase-1, enhanced caspase-1 activity, and elevated IL-1β secretion in mice (87). These findings indicate that cholesterol induces placental inflammation via the NLRP3 inflammasome pathway in human placenta, suggesting the contribution of enhanced NLRP3 inflammasome activation to harmful placental inflammation in PE.

MSU AND THE NLRP3 INFLAMMASOME IN PE

Saturation of uric acid in body fluids results in the formation of MSU crystals. These are identified as danger signals from dying cells, resulting in an acute and/or chronic inflammatory response known as gout, which is associated with the deposition of MSU crystals (41, 88) demonstrated that MSU crystals activate the NLRP3 inflammasome, resulting in the production of active IL-1β and neutrophil accumulation in mice, suggesting a pivotal role for inflammasomes in inflammatory diseases. In terms of the mechanisms of NLRP3 inflammasome activation, MSU crystals are taken up by phagocytosis and lysosomal damage is induced, resulting in the release of cathepsin B and stimulation of ROS production from mitochondria (89).

Elevated levels of MSU in the maternal circulation have been shown in many pregnancy complications, especially PE (69, 84, 90, 91). In human first trimester trophoblast cell lines, IL-1β was produced in response to MSU crystals via the NLRP3 inflammasome (91). Brien et al. (91) reported that MSU crystals induce a proinflammatory profile with predominant secretion of IL-1β and IL-6 in human placental explants, and these effects were IL-1-dependent, as confirmed using a caspase-1 inhibitor and IL-1 receptor antagonist. In addition, administration of MSU crystals to pregnant rats induced placental inflammation (increase IL-1β, IL-6, and TNFα production, and macrophage accumulation) and FGR. Indeed, MSU crystals elicit an increase in the recruitment of macrophages and neutrophils with IL-1β secretion in the NLRP3 inflammasome-dependent manner (41, 92). These findings suggest that higher levels of MSU in PE patients trigger placental inflammation via NLRP3 inflammasome activation, resulting in the pathogenesis of PE.

EXTRACELLULAR DNA AND THE NLRP3 INFLAMMASOME IN PE

Extracellular released cell-free DNA (cfDNA) circulating in the blood, which is considered a product of apoptosis and/or necrosis, acts as a DAMP and is related to many types of inflammatory diseases (93, 94). Toll-like receptor 9 (TLR9), originally identified as a sensor of exogenous DNA fragments, contributes to cfDNA-mediated inflammatory processes (95). It is activated by bacterial DNA rich in unmethylated CpG motifs, and can also be activated by DNA from mammalian cells such as nucleic and mitochondrial DNA. Therefore, TLR9 signaling is of interest as a candidate molecule responsible for the first signal in sterile inflammation (96). It was previously reported that cfDNA released from apoptotic hepatocytes activates TLR9 systems, which in turn triggers a signaling cascade that increases transcription of the genes encoding pro-IL-1β and pro-IL-18. Furthermore, mice lacking components of the NLRP3 inflammasome showed reduced amounts of cfDNA and improved liver injury (96). Pan et al., reported that mitochondrial

DNA is directly recognized and binds with NLRP3, resulting in the formation of NLRP3 inflammasome complex and its activation (97).

During pregnancy, the amount of total cfDNA and cf-fetal DNA (cffDNA) is significantly increased in the maternal blood depending on the stage of pregnancy (98). There are also significant associations between elevated cfDNA and cffDNA with pregnancy complications such as PE and FGR (98–104). We recently showed that expression levels of TLR9 and the amount of cffDNA from the placenta were higher in PE patients compared with that in women with normal placenta (NP), and PE-derived cffDNA stimulated levels of inflammatory cytokine, including IL-1β and sEng secretion depend on TLR9 signaling, compared with NP-derived cffDNA (105). Moreover, a synthetic TLR9 ligand activated inflammatory responses including IL-6 secretion together with stimulation of sFlt1 secretion, while inhibition of TLR9 reduced sFlt1 secretion in human trophoblast cells (106). In mice, administration of a TLR9 ligand induces PE-like symptoms, such as hypertension, proteinuria, placental inflammation, and FGR. Moreover, injection of human fetal DNA, but not adult DNA, induces placental inflammation, fetal resorption, and preterm birth in pregnant mice, and notably, these adverse effects are improved in TLR9-knockout mice (107). These findings suggest that excessive extracellular DNA acts as a DAMP and causes pregnancy complications, especially PE, via TLR9 signaling.

In trophoblast cells, cfDNA is also capable of detecting danger signals via the intracellular DNA sensor, interferon-inducible protein 16 (IFI16). Indeed, IFI16 agonist poly(dA:dT) stimulates sFlt-1 and sEng production in human trophoblast cells in an IFI16-dependent manner (108). Extracellular DNA plays an essential role in the induction of inflammatory responses; however, further research is required to clarify the role of extracellular DNA in NLRP3 inflammasome activation in pregnancy complications.

HMGB1 AND THE NLRP3 INFLAMMASOME IN PE

HMGB1 is an important DAMP that acts as an architectural chromatin-binding factor and is generally located in the nucleus of most cell types under physiological conditions (109). When cells are exposed to stress, HMGB1 is translocated into the extracellular milieu and elicits inflammatory responses via the production of proinflammatory mediators and accumulation of inflammatory cells. HMGB1 interacts with TLR2, TLR4, and receptor for AGE (RAGE), resulting in elevated levels of HMGB1 in tissues and serum associated with the development of inflammation during pathological conditions (110). It is reported that HMGB1 induces the formation of the NLRP3 inflammasome (111). HMGB1 also activates the NLRP3 inflammasome since that stimulation with HMGB1 induces the release of IL-1β with increase in NLRP3 inflammasome component, these effects can be attenuated by inhibition of the NLRP3 inflammasome (112). In addition, Deng et al. (113) demonstrated that HMGB1 directly binds LPS and targets its internalization into the lysosomes of cells via the RAGE, resulting activation of caspase-11-dependent non-canonical inflammasome signaling. On the contrary, NLRP3 inflammasome activation accelerates atherosclerosis induced by HMGB1 secretion, indicating that HMGB1 is a key downstream signaling molecule of NLRP3 inflammasome activation (114). Therefore, the vicious cycle of HMGB1 and the NLRP3 inflammasome may exacerbate inflammation and pathological conditions.

In peripheral blood, HMGB1 concentrations are significantly elevated in PE patients compared with those of healthy pregnant and non-pregnant women (115, 116). Compared with healthy placenta, protein and mRNA expression of HMGB1 and its receptor RAGE, are increased in severe PE placentas (116). In human trophoblast cells, HMGB1 stimulates inflammatory cytokine production dependent on NF-κB activation and ROS signaling via TLR4 (117). In human placenta, treatment with PE serum increased the expression and release of HMGB1, which induced endothelial cell activation (118). In addition, HMGB1 treatment increased NLRP3 protein expression and activation of caspase-1, resulting in an increase of mature IL-1β secretion in human chorioamniotic membranes (119). These findings indicated that HMGB1 contributes to placental inflammation and NLRP3 inflammasome activation as endogenous DAMPs, leading to PE. Interestingly, the expression levels of HMGB1 in the uterus are lowest during the expected time of implantation, and exogenous administration of HMGB1 leads to pregnancy failure accompanied by induction of inflammatory responses in rats, indicating a role of excessive extracellular HMGB1 in PE as well as infertility (120).

PLACENTAL DEBRIS AND THE NLRP3 INFLAMMASOME IN PE

The outer layer of the placenta is covered by a single syncytiotrophoblast that forms the maternal-fetal interface (1). When portions of the syncytiotrophoblast become damaged, cellular debris is extruded into the maternal blood in membrane-enclosed vesicles (121). During normal healthy pregnancy, trophoblastic debris is produced by programmed cell death/apoptosis in the placenta. This extracellular debris is believed to induce a tolerogenic response in maternal endothelial and immune cells (122). On the other hand, extracellular debris from PE placenta mainly originates from necrotic cell death, and exposing endothelial cells to necrotic trophoblastic debris leads to their activation (123). The amount of trophoblastic debris shed into the maternal blood is greatly increased in PE patients compared with that in healthy pregnant women (108).

It is likely that trophoblastic debris includes various types of danger signals, such as DNA, RNA, adenosine, HMGB1, and MSU (118, 124). The degree of trophoblastic debris from human placenta is increased by treatment with PE serum and antiphospholipid antibodies, resulting in the activation of endothelial cell activation and induction of immune cell adhesion (118). Interestingly, necrotic, but not apoptotic, trophoblastic debris contains IL-1β protein, whereas much of the trophoblastic debris is dead cell corpses that might not be able to produce new

proteins (124). On the other hand, adenosine in trophoblastic debris and cell surface adenosine receptor A2B signaling also contributes to the pathogenesis of PE (125). Iriyama et al. (125) demonstrated that chronically elevated placental adenosine leads to the hallmark features of PE (hypertension, proteinuria, and FGR) in a mouse model. Moreover, elevated adenosine in PE patients is correlated with Th1/Th2 imbalance, and adenosine directly induces sFlt-1 production from placenta (126). Baron et al. (127) showed that extracellular adenosine activates the NLRP3 inflammasome and IL-1β secretion by interaction with adenosine receptors and through adenosine cellular uptake using nucleotide transporters. These findings suggest that adenosine signaling in debris activates NLRP3 inflammasome in placenta, resulting in PE.

EXTRACELLULAR VESICLES AND THE NLRP3 INFLAMMASOME IN PE

Extracellular vesicles (EVs) are also produced and released by living cells and can be detected in all biological fluids, including blood. EVs are nanosized particles that are traditionally classified into subtypes, such as exosomes, microvesicles, and apoptotic/necrotic bodies (debris). EV cargo includes bioactive molecules such as protein, lipids, and nucleic acid (DNA, mRNA, microRNA, and non-coding RNA) (128). Significantly higher levels of syncytiotrophoblast-derived EVs are found in the peripheral blood of women with PE compared with women with normal pregnancies (129). EVs isolated from PE patients differ phenotypically and functionally from those isolated from healthy pregnant women (130). Indeed, syncytiotrophoblast-derived EVs (including exosomes) from patients with PE contain higher levels of sFlt-1, sEng, and neprilysin, and treatment with EVs from PE patients impairs angiogenesis of endothelial cells and changes the characteristics of monocytes *in vitro* (131, 132). In addition, exosomes from PE patients cause vascular dysfunction and directly result in adverse PE-like birth outcomes in mice (131). Kohli et al. (133) demonstrated that administration of EVs led to accumulation of activated platelets and induced activation of NLRP3 inflammasome within the placenta, resulting in a PE-like phenotype in pregnant mice. Intriguingly, genetic deletion of NLRP3 inflammasome or pharmacological inhibition of inflammasome abolished this PE-like phenotype, indicating the pathogenesis of PE by EVs was dependent the NLRP3 inflammasome.

FREE FATTY ACID AND THE NLRP3 INFLAMMASOME IN PE

Obesity is a major risk factor for PE and FGR (134, 135). Obesity represents low-grade chronic systemic inflammation (136), and maternal obesity increases the risk of the offspring developing obesity and insulin resistance in the later stages of life (137–141). The NLRP3 inflammasome is involved in the pathogenesis of obesity-related inflammatory diseases, including metabolic syndrome, type 2 diabetes, and cardiovascular diseases (12, 13, 31, 50). There are many common mechanisms between PE and obesity-related pregnancy complications, and obesity accelerates the systemic features of PE.

Free fatty acids levels are elevated in the plasma of obese humans (142), and it has been proposed that they act to promote inflammatory responses by directly engaging TLRs and inducing the NF-κB-dependent production of inflammatory cytokines (143, 144). In particular, one of the major saturated fatty acids, palmitic acid (PA), causes intracellular crystallization, which in turn activates the NLRP3 inflammasome via lysosomal dysfunction in macrophages (145). PA also induces NLRP3 inflammasome activation by generating ROS and inducing autophagy dysfunction, resulting in secretion of mature IL-1β (144, 146, 147). Similar to other crystalline molecules, intraperitoneal administration of PA crystal induces neutrophil recruitment in an IL-1β-dependent manner (145).

Serum PA levels are increased in women with PE and FGR (148–150). Treatment with free fatty acid solution to mimic the plasma of PE patients induces lipid droplet accumulation, mitochondrial dysfunction, and apoptosis in human umbilical vein endothelial cells (149). In addition, PA induces activation of the NLRP3 inflammasome, resulting in the secretion of mature IL-1β by human trophoblast cells (147). NF-κB activation and IL-6 production are associated with higher levels of lipid accumulation in the placenta of obese women compared with those of lean women (151). These findings suggest that saturated fatty acids directly induce placental inflammation, resulting in PE.

AGEs AND THE NLRP3 INFLAMMASOME IN PE

AGEs are heterogeneous, reactive, and irreversibly crosslinked molecules formed from the non-enzymatic glycation of proteins, lipids, and nucleic acids (152, 153). They interact with RAGE and/or TLR4 to induce inflammatory responses (154, 155). AGE-RAGE interactions may increase and perpetuate the inflammatory condition, leading to obesity, diabetes mellitus, and cardiovascular and kidney diseases. Both *in vivo* and *in vitro* experiments have demonstrated that AGEs stimulate NLRP3 inflammasome activation and IL-1β secretion in human umbilical vein endothelial cells, kidney, and pancreatic islets (117, 156, 157). Ablation of the NLRP3 inflammasome improved AGE-induced abnormal insulin sensitivity, pancreatic islet damage, and inflammatory responses (158). These findings suggest that consumption of AGEs increases obesity-related dysfunction via NLRP3 inflammasome activation.

Increasing evidence indicates that AGEs and IL-1β are associated with PE and obesity in pregnant women (134, 135, 159–161). In human placenta, AGEs increase *in vitro* release of IL-1β, IL-6, IL-8, and TNFα depend on NF-κB activation (162). We also demonstrated that in human placental tissues, AGEs directly increase both the transcription and secretion of IL-1β (117). In addition, AGEs stimulate pro-IL-1β production, resulting in the acceleration of mature IL-1β secretion by NLRP3 inflammasome activation in human trophoblast cells. AGEs also induce sFlt-1 production through RAGE signaling, suggesting a

direct link with the pathology of PE (163). Antoniotti et al. (164) reported that AGEs led to activated inflammatory responses in endometrial cells, impaired decidualization, compromised implantation of blastocyst, and suppressed trophoblast invasion. Therefore, AGEs adversely may impact not only PE but also endometrial function and embryo implantation.

OTHER PREGNANCY COMPLICATIONS ASSOCIATED WITH THE NLRP3 INFLAMMASOME

GDM is also classed as an obesity-related pregnancy complication. In GDM, high levels of serum glucose are associated with increased inflammation in blood as well as placenta (165). Excess glucose induces IL-1β secretion from human trophoblast cells depending on the NLRP3 inflammasome (166). In addition to the placenta, caspase-1 activation and mature IL-1β secretion are higher in the adipose tissue of pregnant patients with GDM compared with healthy pregnant women (167), and treatment with caspase-1 inhibitor suppresses IL-1β secretion, suggesting the contribution of NLRP3 inflammasome activation in GDM.

Inflammation of the maternal-fetal interface such as intra-amniotic inflammation or chorioamnionitis, which can be induced by intra-amniotic infection or DAMPs, is a causal link to spontaneous preterm birth, which is a leading cause of perinatal mortality and morbidity (168). In a non-primate rhesus macaques chorioamnionitis model induced by intra-amniotic injection of LPS, the amnion upregulated neutrophil accumulation via the chemoattractant IL-8 in an IL-1-dependent manner (169). In a mouse model of intra-amniotic inflammation-induced preterm birth, the NLRP3 inflammasome was activated following IL-1β secretion in the fetal membranes and decidua basalis (170). In addition, IL-1β blockade decreased inflammation-induced preterm labor in mice (171). These findings suggest that the NLRP3 inflammasome plays a pivotal role in inflammation of the maternal-fetal interface associated with preterm birth, and IL-1 is a potential therapeutic target for these conditions.

To understand the role of the NLRP3 inflammasome in normal pregnancy and pregnancy complications, please refer the essential review (172).

CONCLUSION

Accumulating evidence suggests that the NLRP3 inflammasome plays an essential role in the pathogenesis of pregnancy inflammatory complications. Various types of DAMPs act as danger signals to activate the NLRP3 inflammasome in reproductive organs, resulting in pregnancy inflammatory complications (**Figure 2**). Once activated, the NLRP3 inflammasome drives the robust release of mature IL-1β, initiating a positive feedback loop that results in the accumulation of other immune cells (neutrophils and macrophages) and an increase in the "danger" cytokines and chemokines. Considering the potential for excessive NLRP3 inflammasome and IL-1β production, it is not unexpected that several negative regulatory mechanisms exist in nature to control inflammasome function. Understanding how the NLRP3 inflammasome regulates pregnancy complications and how to control excessive NLRP3 inflammasome activation is essential for the identification of new targets for the treatment of reproductive dysfunction.

AUTHOR CONTRIBUTIONS

KS and TK wrote the manuscript. MT critically revised the manuscript. All authors read and approved the final manuscript.

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