Preeclampsia and COVID-19: the Role of Inflammasome Activation

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Abstract

Purpose of Review It is well established that controlled immune activation and balance is critical for women's reproductive health and successful pregnancy outcomes. Research in recent decades in both clinical and animal studies has demonstrated that aberrant immune activation and inflammation play a role in the development and progression of women's reproductive health and pregnancy-related disorders. Inflammasomes are multi-protein cytoplasmic complexes that mediate immune activation. In this review, we summarize current knowledge on the role of inflammasome activation in pregnancy-related disorders.

Recent Findings Increased activation of inflammasome is associated with multiple women's health reproductive disorders and pregnancy-associated disorders, including preeclampsia (PreE). Inflammasome activation is also associated with the novel coronavirus disease 2019 (COVID-19) disease caused by the SARS-Cov-2 virus. We and others have observed a positive association between increased PreE incidences with the onset of the COVID-19 pandemic. Here, we present our recent data indicating increased inflammasome activation, represented by caspase-1 activity, in women with COVID-19 and PreE compared to normotensive pregnant women COVID-19.

Summary The role of inflammation in pregnancy-related disorders is an area of intense research interest. With the onset of the COVID-19 pandemic and the associated increase in PreE observed clinically, there is a greater need to identify mechanisms of pathophysiology and targets to treat this maternal disorder. Inflammasome activation is associated with PreE and COVID-19 infection and may hold therapeutic potential to improve outcomes associated with PreE and curb the morbidity attributed to PreE.

Keywords Inflammasome · Preeclampsia · COVID-19 · NLRP3

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Introduction

Inflammation in the female reproductive system contributes to various disorders of pregnancy and reproductive health [1–4]. Inflammasomes are cytoplasmic, multi-protein complexes that mediate innate and adaptive immune responses and inflammation [5, 6]. As members of the innate immune system, inflammasomes recognize patterns indicative of infection or changes in cellular homeostasis and initiate responses by the immune system to eliminate pathogens and repair tissue damage to restore homeostasis. Recent studies have identified associations between various women's reproductive disorders, particularly in pregnancy, and inflammasome expression and activation [2, 7–11]. More recently, the discovery of inflammasomes has peaked research interest in investigating the roles of this novel immune modulating complex in these reproductive and pregnancy-associated disorders and complications. This review will summarize

the recent studies investigating the role of inflammasome activation in reproductive disorders with a special emphasis on preeclampsia (PreE). The advances in our understanding of how inflammasomes contribute to these women's health-related issues may provide novel targets and therapeutic strategies to improve women's reproductive health and pregnancy-related outcomes.

Inflammasomes and the Immune System

Normal pregnancy requires a controlled state of inflammation in order for proper placentation and vascular remodeling to occur during the initial stages of pregnancy [12]. These immune changes promote tolerance of the semi-allogenic fetus, while also still protecting the mother from external infectious diseases. In pregnancy-related disorders and complications, the immune changes that occur are associated with chronic immune activation and inflammation that contribute to pathological changes in reproductive tissue and pathophysiology in women and their offspring. Both clinical and preclinical studies have identified the roles of various factors of the immune system including innate and adaptive immune cells and cytokines in contributing to these disorders.

Inflammasomes are formed by a complex of proteins consisting of a sensor protein, an adaptor protein, and caspase-1. The sensor proteins are named based on their structural domain: (1) the nucleotide-binding domain and leucine-rich repeat containing proteins (NLRs); (2) the absence in melanoma 2 (AIM2)-like receptors (ALRs); and (3) the pyrin receptor. The adaptor protein, apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD), also known as Pycard (ASC) contains the PYD (pyrin domain) and CARD (caspase activation and recruitment domain) which serves as the connector protein to bring the sensor protein and caspase-1 together in the inflammasome complex [5, 6, 13•]. The inflammasomes that have been described to date include NLRP1, NLRP3, NLRC4, NLRP7, NLRP12, AIM2, and PYD. Other sensor proteins that have been proposed include human NLRP2, NLRP7, and IF116, and murine NLRP6 and NLRP9b in mouse [13•, 14]. These inflammasomes have recently been reviewed elsewhere [13•].

Canonical activation of inflammasomes includes the recruitment of the sensor protein, ASC, and pro-caspase 1 into a single multi-protein complex within the cytoplasm. After the inflammasome is assembled, caspase-1 is auto-cleaved into enzymatically active caspase-1 p20 and p10 subunits [13•, 15]. The active caspase then goes on to cleave inactive forms of the pleiotropic cytokines interleukin-1 beta (IL-1β) and IL-18 into their active forms to be secreted from cells. More recently, it has been discovered that caspase-1 also cleaves a protein, gasdermin D, which initiates

pyroptosis, inflammatory cell death that is induced following inflammasome activation [16].

Inflammasomes and Preeclampsia

PreE is a disease defined by new onset hypertension after 20 weeks of gestation in combination with organ dysfunction and is a major contributor to maternal and fetal morbidity worldwide [17, 18]. The exact mechanisms underlying the development of PreE are not known. However, endothelial dysfunction and a pro-inflammatory state resulting from placental ischemia caused by shallow trophoblast invasion and insufficient uterine spiral artery remodeling is a well-accepted mechanism [19, 20]. Recent studies are beginning to report elevations in inflammasomes or related mediators among women with PreE or women who are at risk for developing PreE [21–23]. As much of the data and studies have focused primarily on NLRP3 inflammasomes, the remainder of this review will also be composed of mostly NLRP3 studies.

NLRP3 and PreE

NLRP3 inflammasomes are intracellular protein complexes associated with the innate immune system. Overactivation of NLRP3 inflammasomes contributes to a variety of disorders such as atherosclerosis, diabetes, and obesity-induced insulin resistance [24]. NLRP3 inflammasomes can be activated via transcriptional dependent and independent pathways through endogenous or exogenous damage-associated molecular patterns (DAMPs) [25•] (Fig. 1). Regardless of the activation pathway, women with PreE have evidence of a number of inflammatory events that can activate each component of the NLRP3 inflammasome, which may provide some foundation as to why immune system dysfunction is prevalent among women with PreE [26].

There have been numerous reports of elevations in placental and systemic NF-κB among women with PreE compared to normotensive women [27]. From these studies one can theorize that with elevated levels of NF-κB, there is also an increase in the translation of NLRP3. Women with PreE have increased levels of circulating cellular debris, protein aggregates, hypoxia factors and more soluble factors such as uric acid and cholesterol; all of which have been reported to activate NLRP3 at a higher rate in comparison to other inflammasomes [28, 29]. In regard to women with PreE, studies have reported that cholesterol and uric acid can cause placental and decidual inflammation by activating NLRP3 [28, 30–32]. Along similar lines, Weel et al. reported that PreE women had significantly higher placental expression of NLRP3,
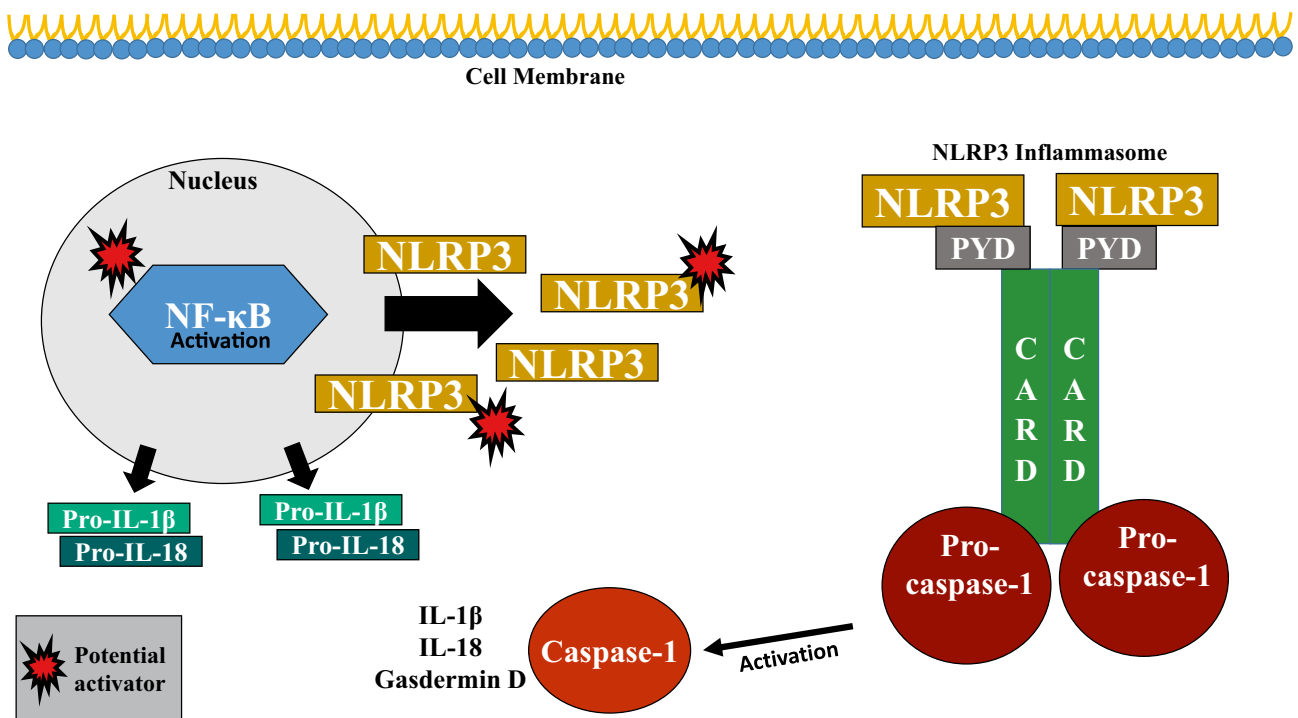
Fig. 1 Mechanisms of NLRP3 inflammasome assembly via priming and activation. The priming signal works to activate nuclear factor kappa B (NF-κB) which in turn stimulates translation of NLRP3 and release from the nucleus. Once NLRP3 is in the cytoplasm, it can be activated via a variety of activation signals or DAMPs (i.e., uric acid, cholesterol, extracellular debris, extracellular vesicles, reactive oxygen species). Upon activation, there is a conformational change leading to formation of the NLRP3 inflammasome. The CARD-CARD interaction leads to the cleavage of caspase-1, which in turn activates IL-1β, IL-18, and gasdermin D

caspase-1, and IL-1β compared to normotensive women [21]. In addition to uterine and placental tissues expressing NLRP3, a recent study by Ozeki et al. reported that human umbilical vein endothelial cells (HUVECs) isolated directly from women with PreE had evidence of a greater NLRP3 response relative to HUVECs isolated from normotensive women [33], suggesting that circulating factors, in particular S100A9, directly stimulate NLRP3 activity in endothelial cells.

HELLP (hemolysis elevated liver enzyme low platelet) syndrome is a severe obstetric complication that affects 15–20% of women with PreE and 1–2% of women without PreE [34]. Unlike PreE, the diagnosis of HELLP requires evidence of significant organ, thrombosis, and coagulopathy via a series of laboratory diagnoses. Even though at the time of this review, there are not any published reports of inflammasome activity among women with HELLP syndrome, there is also evidence to support a role for NLRP3 inflammasome activation in the pathogenesis of this disorder. Heme, which is increased in women with HELLP syndrome, has been found to stimulate activation of HUVEC NLRP3 inflammasomes [35]. Women with HELLP also have a a high degree of apoptosis which is mediated though the death receptor Fas ligand [36]. Activation of this pathway contributes to DAMPs which lead to activation of the NLRP3 inflammasome and eventually pyroptosis [37].

Preclinical Studies

Similar to what has been reported among pregnant women, NLRP3 inflammasomes are also activated in rodents due to numerous factors. A variety of PreE animal models have been used to provide more insight into immunological mechanisms associated with PreE [38–40]. A study by Zeng et al. which utilized a PreE rat model reported that PreE rats had higher mRNA expression of NLRP3 in uterine tissues compared to normal pregnant rats [41]. This group also found that both uterine protein expression of caspase-1 along with mRNA expression of caspase-1 and IL-1β were increased, leading them to conclude that the NLRP3 inflammasome has a key role in regulating uterine inflammation. Similarly IL-17, which we have previously reported to have a key role in mediating the hypertensive and immune response in PreE was recently reported to also regulate NLRP3 inflammasome activation [42, 43]. Chang et al. reported that in a PreE mouse model inhibition of fatty acid binding protein 4 prevents the Treg (T regulatory)/Th17 (T helper) imbalance, IL-17A production, and NLRP3 inflammasome activation [44].

Inflammasome, Spontaneous Miscarriage, and Preterm Labor

In addition to their roles in pregnancy disorders such as PreE and HELLP syndrome, inflammasomes have also been linked to recurrent pregnancy loss as well as missed abortions and spontaneous preterm labor. It is estimated that 21% of preterm births from women in the USA occur in women with PreE, a risk factor for spontaneous preterm labor [45, 46]. Several studies have suggested that inflammasome activation is an important component driving spontaneous preterm labor. Elevated levels of pro-inflammatory mediators that are downstream of inflammasome activation such as HMBGI, caspase-1, IL-1β, and IL-18 were found in women that underwent spontaneous preterm labor [47–49]. Direct evidence of increased NLRP1, NLRP3, and NLRC4 expression have been found in chorioamniotic membranes from women that experienced acute histologic chorioamnionitis in spontaneous preterm labor [47]. The authors in those studies proposed that inflammation associated with spontaneous preterm labor is driven by inflammasome activation, triggering production of IL-1β and IL-18 [47, 48]. These findings suggest that inflammasome-driven inflammation in the chorioamniotic membrane can induce spontaneous preterm labor. Given the amount of immunological crosstalk between reproductive disorders, the role of inflammasomes provides yet another avenue of potential linkage among women affected by reproductive complications.

Coronavirus Disease 2019 (COVID-19), Inflammasome Activation and PreE

Inflammasomes have a role in regulating inflammation which makes them crucial in inflammatory diseases or diseases where inflammation plays a role [50]. The exact role and incidence of this becomes evident when focusing on COVID-19, a disease commonly associated with hyperinflammation. Among the first clues for inflammasome activation in patients with COVID-19 was the noted cytokine storm in patients with severe COVID-19 which is composed of cytokines often activated via NF-κB and IL-1β pathways [51••]. As data began emerging, there was also a direct correlation between high circulating IL-18 levels, COVID-19 severity and increased mortality [52]. The specific mechanism by which SARS-Co-V2 activates inflammasomes, and NLRP3 in particular, is still unknown. Previous studies examining the SARS-Co-V-2 virus have indicated that NLRP3 is assembled and activated in response to changes in plasma permeability to calcium and potassium ions and increases in mitochondrial reactive oxygen species [53, 54].

Pan et al. recently reported that the N protein of SARS-CoV-2 selectively interacts with NLRP3 and not with NLRP1 or NLRC4 or AIM2 proteins [55]. This group also reports that the N protein promotes the assembly of the NLRP3 inflammasome through promotion of ASC oligomerization. The N protein is responsible for packaging the viral genome into a nucleocapsid protein located within the phospholipid bilayers, which is covered by spike proteins [56]. Due to COVID-19, there has been an upsurgence of research into this virus and into the N protein. A recent study [62] has suggested that the N protein itself can regulate immune function to either an immunosuppressive state or an overactive state. Along these same lines, it has been suggested that NLRP3 inflammasome–mediated pyroptosis and the cytokine
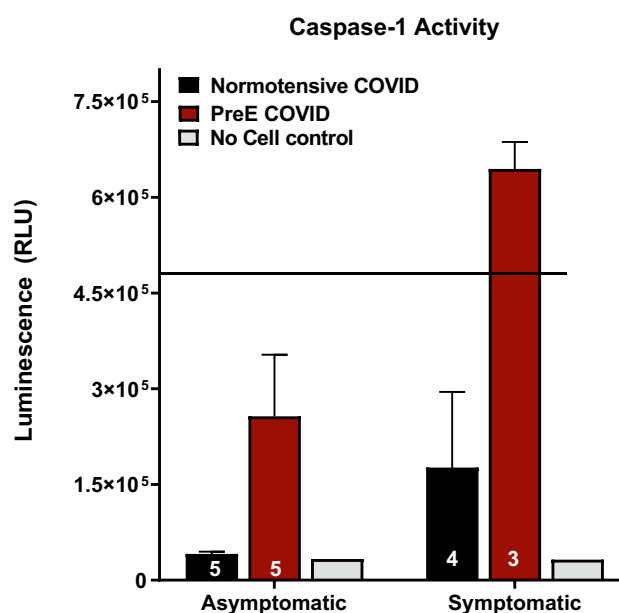
Fig. 2 Caspase-1 activity in endothelial cells exposed to sera from COVID pregnant patients. Serum was collected from women consented and enrolled in an IRB-approved study and placed over semiconfluent HUVECs for 24 h, as previously described [60]. Following 24 h of exposure to experimental media (50% Dulbecco modified Eagle's medium (Invitrogen), 50% medium 199 (Invitrogen), 1% antimycotic-antibiotic solution (Invitrogen), and 10% patient serum) basal media (media without any serum) were placed on cells for 24 h before a sample of the media was collected for caspase-1 evaluation. All cell culture experiments were performed in duplicate, and media samples were assayed in duplicate for caspase-1 activity via the Caspase-Glo 1 Inflammasome assay (Promega, Madison, WI). Luminescence was recorded after 90 min. The number of patients whose serum was evaluated is represented in white within the respective bar located on the bar graph. All the data are represented as mean±standard error mean. Gestational age at serum collection for normotensive women was 39.1±0.27 weeks (range 37.1–40 weeks), 34.58±0.99 weeks (range 30.2–38.4 weeks) for COVID positive preeclamptic women, and 34.8±2.1 weeks (range 30.6–38.4 weeks) for non-COVID positive preeclamptic women

Table 1 Approved pharmacological treatments for women at risk for PreE or who have been diagnosed with PreE that can also decrease the impact of inflammasome activation

Therapy	Pregnancy use	Potential impact on inflammasomes
Corticosteroids	Administered to increase surfactant release in babies who are at risk for premature birth	Betamethasone decreased levels of IL-1β and IL-18 in the amniotic fluid from sheep infused with lipopolysaccharide [61]
Aspirin	Administered to prevent or delay the onset of PreE in women who are considered high-risk for PreE	Aspirin prevented the nuclear translocation of NF-κB from monocytes exposed to serum from women with PreE [62]
Magnesium sulfate ($MgSO_4$)	Administered to prevent seizures	$MgSO_4$ has been shown to inhibit NLRP3 inflammasome activation, IL-1β upregulation, and pyroptosis in human monocytic cell line [63]; placentas from PreE women administered $MgSO_4$ secreted less IL-1β compared to PreE women not administered $MgSO_4$ [64]

storm only occur in individuals with an impaired immune system, suggestive of an initial low grade inflammation prior to the onset of infection [62]. This theory has been used to explain some of the differences in symptoms (asymptomatic vs symptomatic) that has been reported between patients with COVID-19 [58]. The combination of these studies, along with the fact that COVID-19 is associated with an increased risk of PreE or HELLP syndrome (both published studies [59•] and observations from our own patient population), led us to question if there was evidence of NLRP3 activation among women with COVID-19 and PreE.

To determine if there was evidence of inflammasome activation among pregnant women with COVID-19, we measured caspase-1 activity in the cell culture media. Previous studies have reported that circulating factors from women with PreE stimulate HUVECs in vitro to produce a variety of vasoconstrictive and inflammatory markers [60]. We conducted this assay to see if (1) pregnant women diagnosed with COVID-19 at term had evidence of inflammasome activation, (2) if PreE in the presence of a COVID-19 diagnosis at term was associated with inflammasome activation, and (3) if there were differences between symptomatic vs. asymptomatic patients. As shown in Fig. 2, serum from women with PreE induced more caspase-1 activity in cultured HUVECs relative to normotensive women. There was also a difference in caspase-1 activity between symptomatic and asymptomatic women regardless of their PreE diagnosis. Specifically, inflammasome activation is increased in women who were symptomatic for COVID-19. Furthermore, only COVID-19 positive symptomatic women diagnosed with PreE had caspase-1 levels higher than PreE women without COVID-19 (mean caspase-1 activity is denoted by black line). As caspase-1 is activated by inflammasome complex formation and activated via both the non-canonical and canonical pathways,

it serves as an essential marker of inflammasome function and activity [61].

Inflammasome Targeted Therapy

Not only has NLRP3 activation been shown to increase inflammation, but several in vivo studies have also shown inhibition of NLRP3 activation can reduce the abnormal inflammatory cascade seen in PreE [44, 65–68]. Currently, there are several potential therapeutic approaches for inhibiting the inflammasome or targeting pro-inflammatory cytokines. However, as many of these therapies pose a potential danger to the growing fetus; there is often no direct treatment that can be safely administered during pregnancy. There is also a large body of evidence indicating a decrease in the maternal immune response shortly after delivery of the placenta, which decreases the need for pharmaceutical therapy. However, there are a few therapies that are administered during pregnancy that may have an indirect effect on inflammasome activity (Table 1).

Conclusions

The pathophysiology of PreE is still unclear; however, there is a clear consensus on the involvement of the immune system in the disease process. Understanding the role of the inflammasome(s) and how potential inflammasome inhibition could mitigate other immune pathways and pyroptosis warrants further investigation. New data, demonstrating a link between inflammasome activation and COVID-19 and the increased risk for women with COVID-19 to develop PreE, further highlights the need to better understand the role of inflammasomes in PreE to possibly identify new and novel therapeutic interventions thereby potentially decreasing maternal and fetal mortality and morbidity.

Compliance with Ethical Standards

Conflict of Interest Denise C. Cornelius, Xi Wang, Ashley Griffin, Rachael Morris, and Kedra Wallace declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with animal subjects performed by any of the authors. Human samples were collected after informed consent was signed and women were enrolled in an Institutional Review Board approved study 2020–0134 (COVID + patients) and 2014–0256 (COVID − patients).

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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•• Of major importance

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