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INFLAMMASOMES: THEIR ROLE IN NORMAL AND COMPLICATED PREGNANCIES

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Abstract

Inflammasomes are cytoplasmic multi-protein complexes that coordinate inflammatory responses, including those that take place during pregnancy. Inflammasomes and their downstream mediators caspase-1 and IL-1β are expressed by gestational tissues (e.g. the placenta and chorioamniotic membranes) during normal pregnancy. Yet, only the activation of the NLRP3 inflammasome in the chorioamniotic membranes has been partially implicated in the sterile inflammatory process of term parturition. *In vivo* and *ex vivo* studies have consistently shown that the activation of the NLRP3 inflammasome is a mechanism whereby preterm labor and birth occur in the context of microbial- or alarmin-induced inflammation. In the placenta, the activation of the NLRP3 inflammasome is involved in the pathogenesis of preeclampsia and other pregnancy syndromes associated with placental inflammation. This evidence suggests that inhibition of the NLRP3 inflammasome or its downstream mediators may foster the development of novel anti-inflammatory therapies for the prevention or treatment of pregnancy complications.

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AN OVERVIEW OF THE INFLAMMASOMES

Inflammasomes are cytosolic multiprotein complexes that typically consist of a sensor molecule (e.g. a pattern recognition receptor), the adaptor protein (apoptosis-associated speck-like protein containing a caspase recruitment domain; ASC), and the pro-inflammatory caspase-1 (1). Inflammasome sensor molecules are responsible for recognizing pathogen-associated molecular patterns (PAMPs) or endogenous danger signals/alarmins/damage-associated molecule patterns (DAMPs) (2–11). Upon recognition, oligomerization of the inflammasome complex and activation of caspase-1 occur (2–7), which initiates downstream responses including the processing and release of interleukin (IL)-1β and IL-18 (12–18) as well as pyroptosis, a lytic form of cell death (19–22). Inflammasomes were thought to be exclusive to innate immune signaling (1, 23); however, recent reports showed that these platforms also promote adaptive immune responses (24–26). Several members of the nucleotide-binding oligomerization domain leucine-rich repeat-containing protein (NLR) family function as the sensor molecules of the inflammasome (1, 27, 28); therefore, it was initially thought that NLR signaling was inherent to inflammasome activation (2). Consequently, multiple NLR-dependent inflammasomes were described, namely nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing protein (NLRP)-1 (1), NLRP3 (28), and NLR family caspase-activation-and-recruitment domain (CARD)-domain-containing protein-4 (NLRC4) (27, 29). Yet, NLR-independent inflammasomes that are driven by alternative sensor molecules such as absent in melanoma-2 (AIM2) (30–33) and pyrin (34) have also been described.

To date, five distinct inflammasomes have been well characterized, each identified by its specific sensor molecule: NLRP1, NLRP3, NLRC4, AIM2, and pyrin (2–7). Other inflammasomes that require further characterization of their specific ligands, mechanisms of action, and roles in disease include NLRP6 (35), NLRP7 (36), NLRP12 (37), retinoic acid-inducible gene-I (RIG-I) (38, 39), and interferon-γ (IFNγ)-inducible protein-16 (IFI16) (40, 41). Next, we will provide a brief overview of the NLRP1, NLRC4, AIM2, pyrin, and NLRP3 inflammasomes.

The NLRP1 inflammasome was the first to be described (1) and exists as a single protein in humans, whereas mice express multiple NLRP1 paralogues (42). Initial reports showed that NLRP1 responds to the lethal toxin of *Bacillus anthracis* (42), and subsequent studies indicated that this inflammasome also responds to *Toxoplasma gondii* (43), *Listeria monocytogenes*, and *Shigella flexneri* (44). The NLRP1 inflammasome can also be activated by the microbial product muramyl-dipeptide, a component of peptidoglycan (45). Interestingly, mutations in NLRP1 have been associated with severe inflammatory skin disorders (46), which may be due to the high expression of this molecule in keratinocytes (46). Therefore, the NLRP1 inflammasome is implicated in host defense against pathogens and skin homeostasis.

NLRC4 was first characterized as an apoptotic-protease activating factor-1 (APAF1)-related protein (27), and was shown to induce inflammasome activation in response to *Salmonella typhimurium* infection in mice (29). Subsequent reports indicated that the murine NLRC4 inflammasome was activated in response to flagellin (47) as well as multiple components of

the bacterial type 3 secretion system (T3SS) (48). The NLRC4 inflammasome is unique in that it relies on multiple NLR family apoptosis inhibitory proteins (NAIPs) (49) to detect specific bacterial proteins (e.g. T3SS rod protein in mice (48, 50) and T3SS needle subunit in humans (48). NAIPs can then interact with NLRC4 to trigger the assembly of this inflammasome (48, 50). Humans express only one NAIP with at least two reported isoforms (51), which recognize *Chromobacterium violaceum* and *Salmonella* flagellin (48, 51). The assembly of the NLRC4 inflammasome may also require the phosphorylation of NLRC4 (52), highlighting the complexity of the mechanisms by which this inflammasome is activated.

The AIM2 inflammasome is unique in that it is activated by cytosolic DNA of microbial or host origin independently of NLRP3 and TLR signaling (30–32, 53). In the absence of cytosolic DNA, AIM2 exists in an auto-inhibitory state with its HIN200 domain tightly bound to the pyrin domain (PYD) (54, 55). The binding of cytosolic DNA to HIN200 releases the protected PYD, allowing for self-oligomerization and interaction with ASC in order to initiate inflammasome assembly (54, 55). The AIM2 inflammasome orchestrates host defense against DNA viruses such as cytomegalovirus and vaccinia virus, as well as infections with intracellular bacterial pathogens (30–32, 53, 56, 57). In addition, the AIM2 inflammasome is implicated in the pathogenesis of psoriasis (58) and prostate cancer (59). Hence, the AIM2 inflammasome participates in host defense and tumor progression (5).

The most recently discovered of the well characterized inflammasomes is the Pyrin inflammasome (34, 60). This inflammasome indirectly responds to *Burkholderia cenocepacia* and *Clostridium difficile* (34, 60) by sensing the bacterial modification and inactivation of Rho GTPases (60). Such modifications include glycosylation, adenylation, and ADP-ribosylation, all of which result in activation of the Pyrin inflammasome; yet, direct interactions between Rho and Pyrin have not been detected (60). Interestingly, recent reports indicate that the activation of the Pyrin inflammasome can occur in response to microtubule disruption and other cytoskeletal modifications resulting from microbial infection, rather than in response to the pathogen itself (61, 62). More recently, it was shown that specific bile acid analogs can directly activate the Pyrin inflammasome, suggesting a new mechanism whereby the production of bile acid metabolites by gut microbiota could affect host innate immune responses (63). Therefore, the Pyrin inflammasome can participate in host defense responses and gut homeostasis.

The most widely studied of the inflammasomes is the NLRP3 inflammasome (23, 28, 64–66). This inflammasome has two key characteristics: first, it can be activated by a wide range of unrelated molecules, including PAMPs (64, 67) and both endogenous and exogenous DAMPs or alarmins (23, 66, 68), as has been previously reviewed (11). Second, the NLRP3 inflammasome is highly expressed in innate immune cells such as macrophages, neutrophils, and dendritic cells (23, 69, 70), as well as in multiple tissues (23, 68, 71–73). Notably, classical or canonical activation of the NLRP3 inflammasome requires two distinct steps: priming and assembly (74, 75). The priming step is initiated by inflammatory stimuli via surface PRRs such as TLRs, which induce NF-κB activation resulting in the increase of NLRP3 and pro-IL-1β (65, 76). The second step includes multiple signaling events occurring upon recognition of the PAMP or DAMP which, in turn, promotes the assembly of

the inflammasome complex, the cleavage of caspase-1, and subsequent processing and release of IL-1β and IL-18 (11). The activation of the NLRP3 inflammasome has been associated with multiple cellular events including potassium efflux (77, 78), lysosomal rupture (79), mitochondrial dysfunction (80), calcium influx (81, 82), and decreased cellular cAMP levels (82), many of which seemed to depend on the activating stimulus. A later study suggested that potassium efflux is a common cellular event associated with NLRP3 inflammasome activation by showing that multiple microbial and endogenous signals induce a drop in cytosolic potassium that is sufficient to activate this inflammasome (83). Yet, even potassium efflux-independent pathways of NLRP3 inflammasome activation have been described (84). Further studies are required to elucidate all of the cellular pathways associated with the canonical activation of this inflammasome.

In addition to the canonical activation pathway of the NLRP3 inflammasome, this inflammasome can also be indirectly triggered by caspase-11 in mice (85) (or the homologues caspase-4 and caspase-5 in humans (85, 86)), which has been termed the non-canonical activation pathway (87). The non-canonical pathway was first described in murine macrophages infected with *Escherichia coli, Citrobacter rodentium*, and *Vibrio cholera* (87). This report showed that caspase-11 was required for the non-canonical activation of the NLRP3 inflammasome, which subsequently leads to the cleavage of caspase-1 and release of IL-1β and IL-18 (87). Notably, in the non-canonical pathway, caspase-11 directly recognizes and binds to intracellular lipopolysaccharide (LPS) (88, 89), resulting in its oligomerization and activation by auto-proteolytic cleavage (90). Active caspase-11 can then directly induce the cleavage of gasdermin D (GSDMD) to cause pyroptosis (e.g. release of caspase-1-processed IL-1β and IL-18) (87, 91).

In summary, inflammasomes mediate central processes during host defense against pathogens and immunoregulation, whose processes are essential for homeostasis (92). Hence, aberrations in inflammasome activation can be implicated in the pathogenesis of disease (92). In this review, we focus on describing the role of inflammasomes during normal pregnancy and its complications, including preterm labor and birth, the leading cause of perinatal morbidity and mortality worldwide (93, 94), and pregnancy disorders associated with placental inflammation.

INFLAMMASOMES DURING NORMAL PREGNANCY

Inflammation is a key process in reproductive success since it is required for implantation (95), pregnancy maintenance (96), and parturition (97–99). Therefore, it is tempting to propose that inflammasomes are involved in each of the above processes and, consequently, their components are expressed in the gestational tissues.

Inflammasome components in the gestational tissues

Inflammasome components have been detected during pregnancy in both maternal and fetal compartments. Initial reports showed that NLRP3 (100–102), NLRC4 (103), and NLRP1 (102) are expressed by peripheral leukocytes of pregnant women. In the placenta (organ serving as the lungs, liver, and kidney for the fetus (104)), a tissue-wide survey revealed that multiple sensor molecules including *NLRP1, NLRP3*, and *NLRC4* were expressed (105). In

the first trimester, *in vitro* studies have shown that placental cells (e.g. trophoblasts) expressed *NLRP1*, *NLRP3*, and *NLRC4* (106, 107), as well as *NLRP2* (108). At term (≥37 weeks of gestation), placental tissues also expressed these sensor molecules (106, 109–114). Mirroring the expression of the NLRs, the adaptor protein ASC (or PYCARD) is also expressed in the placenta throughout pregnancy (105–107, 113, 114). The chorioamniotic membranes (also known as the extraplacental membranes: fetal tissues forming the amniotic cavity (115)) expressed sensor molecules of the inflammasome, namely NLRP1 (116), NLRP3 (109, 116), NLRC4 (116), and AIM2 (116), as well as ASC (117). Immune cells infiltrating the chorioamniotic membranes (e.g. choriodecidual leukocytes) also expressed ASC (117). Moreover, NLRP3 is expressed by myometrial tissues from women at term pregnancy (118). Together with the fact that inflammatory caspases (caspase-1 and caspase-4) have been detected in the human placenta (110–113, 119, 120), chorioamniotic membranes (110, 116, 117, 121, 122), and myometrium (121), this evidence indicates that gestational tissues possess the machinery to initiate inflammasome-mediated immune responses during pregnancy. Figure 1 includes a schematic representation of the inflammasomes reported in the chorioamniotic membranes during normal pregnancy.

Inflammasomes in term parturition

Parturition represents a form of physiological inflammation (98, 123), which is considered sterile in nature given that the majority of women who undergo labor do not have culturable microorganisms in the amniotic cavity (124). This concept is supported by numerous studies showing an increased bioavailability of cytokines (125–134) and chemokines (135–139) in the amniotic fluid, maternal circulation (140, 141), and gestational tissues such as the placenta (142–144), chorioamniotic membranes (123, 144–152), myometrium (146, 148, 150, 151, 153), and cervix (146, 148, 151, 154, 155) during labor. This sterile inflammatory process occurs in conjunction with an influx of innate and adaptive immune cells into the choriodecidua (cell layer attached to the chorioamniotic membranes) (146, 156–167), myometrium (168–173), and cervix (148, 168, 174–182). Recent reports have established that inflammasomes also participate in the pro-inflammatory milieu of parturition (116, 117, 183). Next, we discuss the evidence supporting such a concept.

The first link between the inflammasome and parturition was reported in 2008 by Gotsch et al. (183) who measured caspase-1 in amniotic fluid (biological fluid with physiological and immune properties that surrounds the fetus throughout gestation (184–186)). These authors reported that the inflammasome-dependent caspase-1 was detected in amniotic fluid of women at term pregnancy, but not in the second trimester (183). In addition, caspase-1 concentrations in amniotic fluid were further increased in women with spontaneous labor at term (183). These findings are in line with reports showing that the main downstream product of the inflammasome, IL-1β, is elevated in women during the physiological process of labor at term (126, 127, 144). Yet, amniotic fluid concentrations of IL-18 do not increase during term parturition (187). In addition, amniotic fluid concentrations of the adaptor protein ASC and the effector protein of pyroptosis GSDMD are also increased in women with spontaneous labor at term (188, 189). The findings described above led us to hypothesize that the chorioamniotic membranes, tissues that surround the amniotic cavity, display an increased expression of the sensor molecules, the adaptor protein, and

inflammatory caspases in the process of parturition at term. Consistent with this hypothesis, we and others found that the chorioamniotic membranes expressed NLRP1, NLRP3, AIM2, and NLCR4 (116) as well as the inflammatory caspase-1 (116, 121) and caspase-4 (116). Yet, only the priming and activation of the NLRP3 inflammasome, as evidenced by the upregulation of the sensor molecule and increased amounts of the active forms of caspase-1 and mature IL-1β, was observed in the chorioamniotic membranes of women with labor at term (116). The assembly of the NLRP3 inflammasome was later confirmed by localization of ASC/caspase-1 complexes and ASC specks (a readout of inflammasome activation (190)) in the chorioamniotic membranes and choriodecidual leukocytes of women with labor at term (117, 188). Subsequent studies also suggested that the NLRP3 inflammasome is involved in the inflammatory process of labor in the myometrium (118). The final piece of evidence showing a partial role for the NLRP3 inflammasome in the physiological process of labor was generated when pregnant dams were treated with an inhibitor of NLRP3 inflammasome assembly, MCC950 (191), and arrest of labor (i.e. dystocia) was observed in a subset of animals (192). Collectively, the abovementioned studies indicate that the activation of the NLRP3 inflammasome in the amniotic cavity and surrounding tissues occurs as part of the sterile inflammatory milieu that accompanies physiological labor at term (Figure 1).

Not all term pregnancies occur in the absence of pathology. A subset of women with labor at term are diagnosed with acute histologic chorioamnionitis (193). This placental lesion is associated with intra-amniotic infection (i.e. microorganisms in the amniotic fluid and inflammation) or sterile intra-amniotic inflammation (i.e. inflammation without detectable microorganisms in amniotic fluid) (194). Acute histologic chorioamnionitis is characterized by the invasion of neutrophils and macrophages into the chorioamniotic membranes (195), and is associated with elevated concentrations of pro-inflammatory cytokines such as IL-1β in amniotic fluid (196, 197). Therefore, we hypothesized that inflammasomes may be involved in the process of parturition associated with acute placental inflammation. In line with this hypothesis, NLRP3 and NLRC4 as well as the active/mature forms of caspase-1, IL-1β, and IL-18 were increased in the chorioamniotic membranes of women with labor at term and acute chorioamnionitis compared to those without this placental lesion (198). Enhanced inflammasome assembly in the chorioamniotic membranes of women with acute chorioamnionitis was later confirmed by detection of ASC/caspase-1 complexes (117). Furthermore, amniotic fluid concentrations of the adaptor protein ASC are increased in women with acute histologic chorioamnionitis at term (199). These descriptive findings are consistent with *in vitro* studies showing that the incubation of the chorioamniotic membranes with microbial products (e.g. LPS) induces the processing of the active forms of caspase-1 and the release of IL-1β, which is blocked by caspase-1 inhibitors (109, 121, 198, 200). These studies suggest that the NLRP3 and NLRC4 inflammasomes may be involved in the pathological inflammatory process of labor at term associated with microbial invasion. Yet, further *in vivo* studies are needed to investigate whether these inflammasomes are indeed implicated in the acute inflammation of the placental tissues at term pregnancy.

INFLAMMASOMES IN PRETERM LABOR AND BIRTH

Spontaneous preterm labor is a syndrome of multiple etiologies (201), which commonly leads to preterm birth, the leading cause of perinatal morbidity and mortality worldwide (93, 202, 203). The best studied cause for preterm labor is intra-amniotic inflammation (204–213), which can occur as a consequence of microbial invasion of the amniotic cavity (i.e. intra-amniotic infection) or as a result of elevated concentrations of danger signals or alarmins in amniotic fluid (i.e. sterile intra-amniotic inflammation) (214, 215). Both clinical conditions are characterized by increased cytokine concentrations (125, 127, 128, 135–137, 187, 216–222) and elevated numbers of immune cells (186, 223–230) in amniotic fluid. One of the central players in this intra-amniotic inflammatory response is IL-1β (127, 221), given that this cytokine orchestrates the production of labor mediators such as prostaglandins (231–237). Indeed, the administration of IL-1β induces preterm birth in mice (129, 238, 239) and non-human primates (207, 240–244). The abovementioned studies led us to investigate whether inflammasomes, the primary machinery of IL-1β processing, were implicated in the intra-amniotic inflammatory response that accompanies preterm labor and birth. Next, we discuss the evidence indicating a role for the inflammasome in intra-amniotic infection- and sterile intra-amniotic inflammation-associated preterm labor and birth.

Intra-amniotic infection-associated preterm labor and birth

The first evidence suggesting a role for the inflammasome in the mechanisms that lead to preterm labor and birth in the context of intra-amniotic infection was generated by Gotsch et al. (183). These authors reported that amniotic fluid concentrations of caspase-1 were increased in women with preterm labor and intra-amniotic infection compared to those without this clinical condition (183). Such findings were in line with prior studies showing that amniotic fluid concentrations of IL-1β (125, 127, 221, 245, 246) and IL-18 (187, 247) were also elevated in women with preterm labor and intra-amniotic infection. This clinical evidence led us to investigate whether inflammasomes were involved in the pathophysiology of preterm labor/birth in the context of inflammation induced by microbes. First, we showed that women with preterm labor and birth and acute chorioamnionitis (a readout of intra-amniotic infection (195, 248, 249)) displayed priming of the NLRP3 inflammasome as evidenced by the upregulation of NLRP3, caspase-1, caspase-4, IL-1β, and IL-18 in the chorioamniotic membranes (250). Next, the activation of the NLRP3 inflammasome was confirmed by increased concentrations of active caspase-1 and caspase-4 and mature forms of IL-1β and IL-18, as well as enhanced formation of ASC/caspase-1 complexes in the chorioamniotic membranes of women with preterm labor and acute chorioamnionitis (250). The increased concentrations of active caspase-4 suggest that non-canonical inflammasome activation may occur in the context of preterm labor resulting from intra-amniotic infection due to Gram-negative bacteria. Recently, we also found that amniotic fluid concentrations of the adaptor protein ASC (251) and the effector molecule of pyroptosis GSDMD (252) were increased in women with preterm labor and intra-amniotic infection compared to those without this clinical condition. Both ASC and GSDMD are also overexpressed by the chorioamniotic membranes of women with preterm labor and intra-amniotic infection. Together, these data provide descriptive evidence supporting a role for the NLRP3

inflammasome in the pathophysiology of intra-amniotic infection-associated preterm labor and birth.

Causal links between the activation of the NLRP3 inflammasome and preterm labor and birth in the context of infection include the following: 1) the intra-uterine administration of peptidoglycan and poly I:C increased the expression of NLRP3 and caspase-1, as well as increased amounts of active caspase-1, in the uterine tissues (253); 2) the deficiency of *Nlrp3* protects against group B streptococcus-induced preterm birth (254); 3) the combined injection of MHV-68 and LPS induces preterm birth (255, 256) by causing exaggerated inflammation in the fetal membranes, which was suggested to occur in part through the activation of the NLRP3 inflammasome (200); and 4) the ultrasound-guided intra-amniotic administration of LPS induced priming and activation of the NLRP3 inflammasome in the fetal membranes prior to preterm birth, which was ameliorated by blocking the assembly of the NLRP3 inflammasome using MCC950 (257). Preliminary data from our group suggest that the NLRP3 inflammasome is implicated in host defense mechanisms against genital mycoplasmas (Motomura et al., unpublished data). It is worth mentioning that inhibition of the inflammasome in the context of intra-amniotic infection does not fully prevent adverse pregnancy and neonatal outcomes (257), indicating that the blockade of multiple pathways (including other inflammasomes) may be necessary to restore the normal timing of parturition. Further studies are required to investigate whether clinically-isolated bacterial cultivars associated with preterm labor and birth induce the activation of the NLRP3 inflammasome *in vivo*, and whether conventional treatments are effective for prevention of adverse pregnancy outcomes.

Sterile intra-amniotic inflammation-induced preterm labor and birth

A link between the NLRP3 inflammasome and the mechanisms leading to sterile intra-amniotic inflammation-associated preterm labor and birth was first hypothesized upon the observation that placentas from women with intra-amniotic inflammation without detectable microorganisms are diagnosed with acute chorioamnionitis (214, 215) and display characteristics of NLRP3 inflammasome activation (250). This hypothesis was confirmed by recent reports showing that women with preterm labor and sterile intra-amniotic inflammation have increased concentrations of ASC (251) and GSDMD (252) in amniotic fluid and the chorioamniotic membranes. These clinical observations led us to investigate the mechanisms whereby danger signals or alarmins, molecules that initiate sterile inflammation (258–260), trigger inflammatory processes in the amniotic cavity and chorioamniotic membranes. First, we showed that the ultrasound-guided intra-amniotic administration of the classical alarmin HMGB1, a molecule that is present in amniotic fluid of women with preterm labor (261), induces preterm birth in mice (262). Next, using an *ex vivo* model of intra-amniotic inflammation, we reported that HMGB1 causes the priming and activation of the NLRP3 inflammasome in the chorioamniotic membranes (263). Recently, we also provided *in vivo* evidence that the alarmin S100B can induce sterile intra-amniotic inflammation by activating the NLRP3 inflammasome in the fetal membranes prior to inducing preterm birth (192). Importantly, by inhibiting the assembly of this inflammasome using MCC950, S100B-induced preterm birth can be prevented in most cases (192). Furthermore, we have generated data showing that the ultrasound-guided intra-

amniotic injection of the alarmin IL-1α induces preterm labor and birth via the NLRP3 inflammasome (Motomura et al., unpublished data). These findings have clinical implications given that we have proposed to use inhibitors of the NLRP3 inflammasome as a therapeutic strategy for sterile intra-amniotic inflammation, a condition that currently lacks treatment (192). Additional studies are required to investigate whether other alarmins [e.g. heat shock protein 70 (HSP70) (264)] present in amniotic fluid of women with preterm labor and sterile intra-amniotic inflammation can activate the NLRP3 inflammasome in the fetal membranes, inducing preterm labor and birth.

Figure 2 includes a representation of the proposed role for the canonical and non-canonical NLRP3 inflammasome pathways in the pathophysiology of preterm labor and birth in the context of intra-amniotic infection or sterile intra-amniotic inflammation.

INFLAMMASOMES IN PREGNANCY COMPLICATIONS ASSOCIATED WITH PLACENTAL INFLAMMATION

Given that inflammasome components are expressed by placental cells, as reviewed above, early studies have suggested that inflammasomes are implicated in the inflammatory responses associated with placental disease. Mulla et al. and Xie et al. were the first to demonstrate that NLRP3 inflammasome activation in trophoblasts (106) and peripheral blood (100) was implicated in the pathogenesis of preeclampsia. Indeed, it has been shown that peripheral monocytes from women with preeclampsia display enhanced expression of NLRP1 and NLRP3 (102, 265, 266), and polymorphisms in their coding genes are associated with the development of this syndrome (267, 268). In addition, women with preeclampsia had elevated levels of total cholesterol and uric acid, cellular metabolites that act as alarmins when released extracellularly (269, 270), which can potentially activate the NLRP3 inflammasome in the syncytiotrophoblast layer of the placenta (112). Descriptive studies have also shown that placentas from women with severe preeclampsia display higher expression of NLRP3, caspase-1, and IL-1β compared to normotensive pregnant women (120, 271). Further, *in vivo* studies (119, 272–275) have provided a link between alarmin-induced activation of placental NLRP3 inflammasomes and the resulting placental inflammation-associated pregnancy complications. In line with this evidence, a recent study using murine models and human tissues showed that endothelial-derived extracellular vesicles induce NLRP3 inflammasome activation, triggering a preeclampsia-like syndrome that can be attenuated by inhibition of this pathway (276). Taken together, these findings suggest that NLRP3 inflammasome activation is implicated in the placental inflammatory processes associated with the pathophysiology of preeclampsia (Figure 3).

Moreover, *in vitro* and *in vivo* studies have shown that inflammatory stimuli (e.g. LPS or uric acid) induce the activation of the NLRP3 inflammasome in the placenta (107, 277), which may also contribute to the mechanisms of disease of other pregnancy complications associated with placental inflammation such as anti-phospholipid syndrome (277–279), gestational diabetes (280), and fetal growth restriction (119). Recent studies showed that the NLRP7 inflammasome is a key regulator of placental development and hypoxia, the impairment of which can lead to fetal growth restriction (281). This finding suggests that the

NLRP7 inflammasome, which has been previously shown to be activated by microbial products (36), may also be triggered by non-microbial signals resulting from hypoxic conditions in the placenta (281) (Figure 3). Yet, further studies are required to investigate whether the inhibition of inflammasomes can be considered as a strategy to prevent placental inflammation-associated disorders.

CONCLUSION

Growing evidence has consistently shown that inflammasomes are implicated in the physiological and pathological inflammatory processes of pregnancy. Several inflammasomes have been detected in the gestational tissues; yet, only the NLRP3 inflammasome in the chorioamniotic membranes has been implicated in the mechanisms that lead to the sterile inflammatory process of term parturition. The premature activation of the NLRP3 inflammasome in the chorioamniotic membranes is now established to be an important mechanism whereby microbes or danger signals induce preterm labor and birth. The activation of the NLRP3 inflammasome in the placenta has also been involved in the pathogenesis of preeclampsia and other placental disorders. This evidence could foster the development of novel anti-inflammatory therapies based on the inhibition of the NLRP3 inflammasome for the prevention or treatment of pregnancy complications.

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3Non-standard abbreviations:

AIM2	absent in melanoma-2
ASC	apoptosis-associated speck-like protein containing a caspase recruitment domain
DAMPs	damage-associated molecule patterns
GSDMD	Gasdermin D
LPS	Lipopolysaccharide
MCC950	sodium salt is a potent selective inhibitor of NLRP3
NAIPs	NLR family apoptosis inhibitory proteins
NLR	nucleotide-binding oligomerization domain leucine-rich repeat-containing protein

NLRC4	NLR family caspase-activation-and-recruitment domain (CARD)-domain-containing protein-4
NLRP	nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing protein
PAMPs	pathogen-associated molecular patterns
PRRs	pattern recognition receptors
T3SS	Type 3 secretion system

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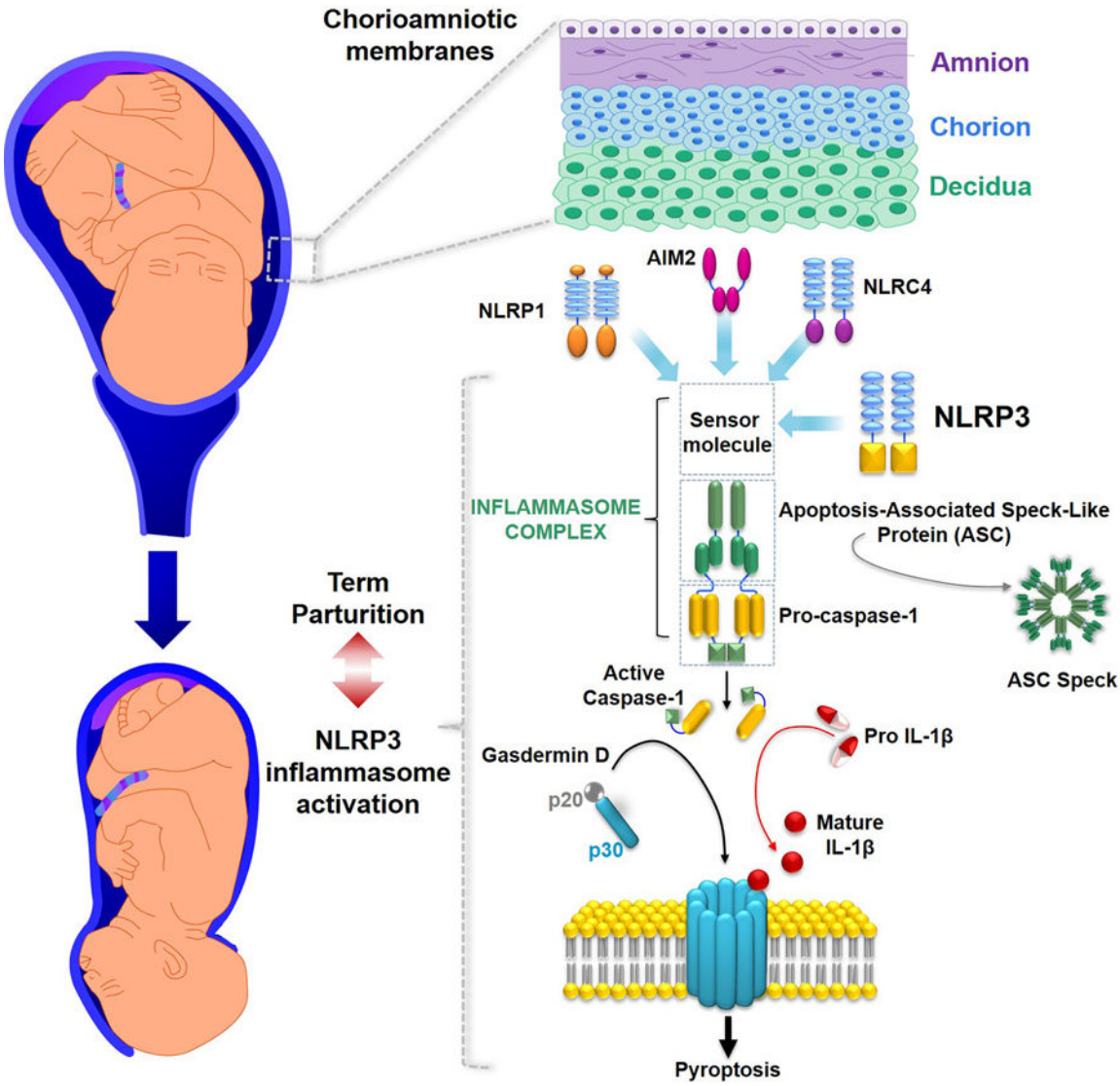

Figure 1. Inflammasomes in the chorioamniotic membranes during normal parturition.

Representative image of the chorioamniotic membranes (amnion, chorion, and decidua) surrounding the amniotic cavity containing the fetus and amniotic fluid. The NLRP1, AIM2, NLRC4 and NLRP3 sensor molecules have been detected in the chorioamniotic membranes during normal pregnancy. The activation of the NLRP3 inflammasome leading to pyroptosis has been implicated in the physiological mechanisms of term parturition.

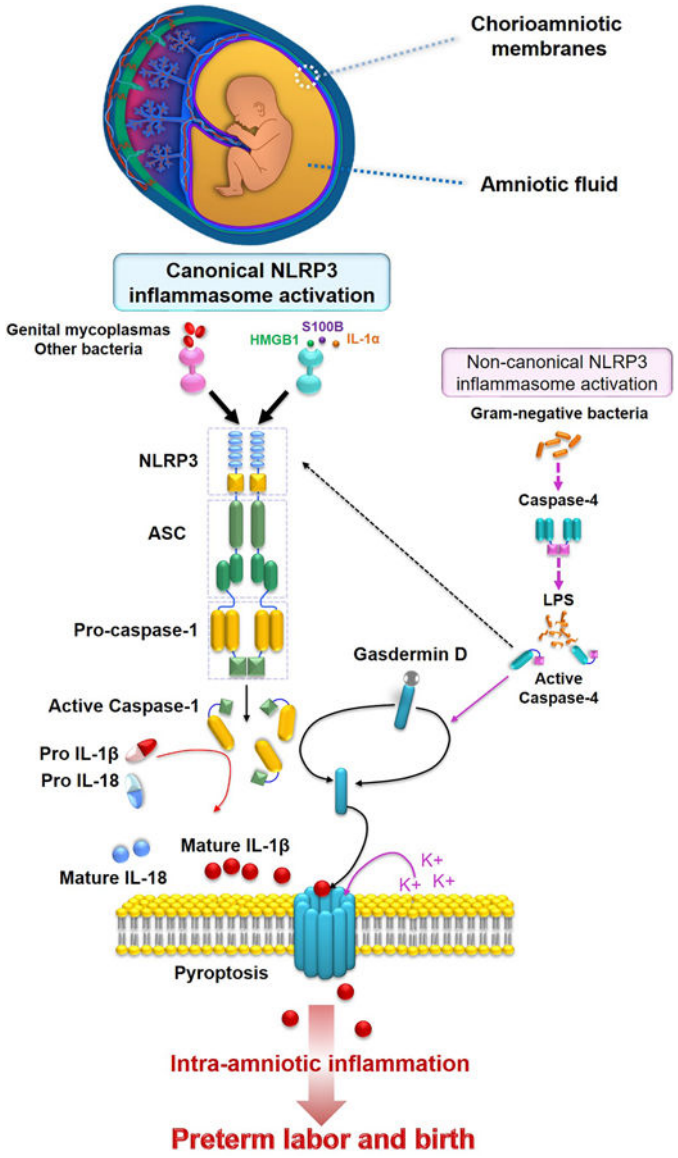

Figure 2. The NLRP3 inflammasome in preterm labor and birth.

Bacteria (e.g. genital mycoplasmas) or alarmins (e.g. HMGB1, S100B, or IL-1α) can activate the canonical NLRP3 inflammasome pathway in the chorioamniotic membranes, which results in the release of active caspase-1 and mature forms of IL-1β and IL-18 into the amniotic fluid. Gram-negative bacteria may also activate the non-canonical NLRP3 inflammasome pathway. Detection of extracellular ASC and gasdermin D in the chorioamnioitic membranes and amniotic fluid have also been reported as readouts of inflammasome activation and pyroptosis, respectively.

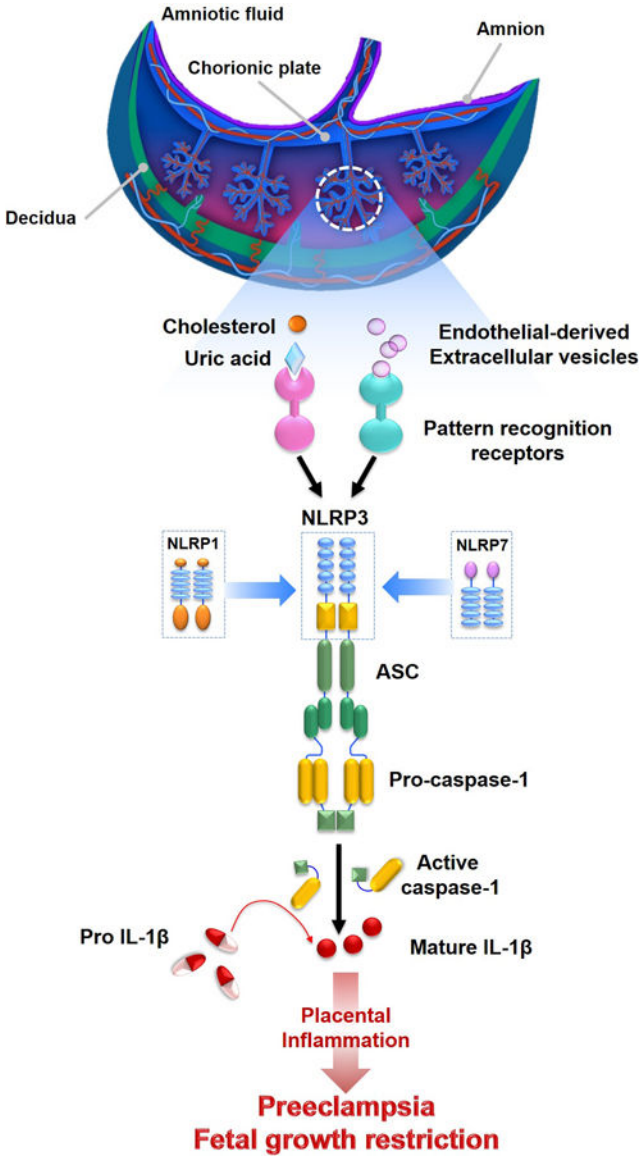

Figure 3. Inflammasomes in placental inflammation.

Endothelial-derived extracellular vesicles and/or alarmins (e.g. cholesterol or uric acid) can activate the NLRP3, NLRP1, and NLRP7 inflammasomes in the placenta, leading to the processing and release of active caspase-1 and mature IL-1β. The resulting inflammation may lead to placental diseases such as preeclampsia and fetal growth restriction.