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NLRP3 inflammasome: a new therapeutic target for high-risk reproductive disorders?

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Abstract

The NOD-like receptor protein 3 (NLRP3) inflammasome is a key regulator of the host's immune response, and many immune and metabolic disorders are linked to its activation. This review aimed to investigate and clarify the relationship between this inflammasome and high-risk reproductive disorders. Papers cited here were retrieved from PubMed up to August 2020 using the keywords "NLRP3" or "NALP3", "caspase-1", "endometriosis", "gestational diabetes", "interleukin (IL)-18", "IL-1β", "pre-eclampsia (PE)", "preterm birth", "polycystic ovarian syndrome (PCOS)", "recurrent spontaneous abortion (RSA)", and combinations of these terms. The results show that NLRP3 inflammasome is associated with various high-risk reproductive disorders and many inflammatory factors are secreted during its activation, such as IL-1β induced during the development of endometriosis. PCOS is also associated with activation of the NLRP3 inflammasome, especially in overweight patients. It also participates in the pathogenesis of RSA and is activated in fetal membranes before preterm birth. The placentas of pregnant women with PE show higher expression of the NLRP3 inflammasome, and gestational diabetes mellitus occurs simultaneously with its activation. Current evidence suggest that the NLRP3 inflammasome plays an important role in female reproductive disorders. New treatment and management methods targeting it might help reduce the incidence of such disorders and improve neonatal outcomes.

Keywords: NLRP3 inflammasome; Endometriosis; Polycystic ovarian syndrome; Recurrent spontaneous abortion; Preterm birth; Pre-eclampsia; Gestational diabetes mellitus; Reproductive disorders

Introduction

Inflammation is a defense response induced by potentially harmful stimuli that usually requires the participation of multi-protein complexes known as inflammasome. The NOD-like receptor protein 3 (NLRP3) inflammasome can recognize a variety of pathogenic microorganisms and stress-related endogenous signaling molecules. It is mainly expressed and activated in dendritic cells and macrophages, where it plays an important regulatory role as a pro-inflammatory factor of the host's innate immune system. Many immune and metabolic disorders involve activation of the NLRP3 inflammasome activation,[1,2] such as atherosclerosis, gout, kidney disease, obesity, type 2 diabetes, and inflammatory bowel disease. Some studies suggest that activation of the NLRP3 inflammasome is linked to endometriosis, polycystic ovary syndrome (PCOS), recurrent spontaneous abortion (RSA), preterm birth, pre-eclampsia (PE) and gestational diabetes mellitus (GDM). This article reviews the progress of research into the role of this inflammasome in such reproductive disorders.

Mechanism of NLRP3 Activation

The NLRP3 inflammasome is a member of the nucleotide-binding oligomerization domain, leucine-rich repeat (LRR)-containing protein family. It contains a central nucleotide-binding and oligomerization domain, a C-terminal LRR domain, and an N-terminal pyrin domain. Its activation requires two steps. The first or priming signal, such as lipopolysaccharide (LPS), induces the expression of NLRP3 and Pro-interleukin (IL)-1β and Pro-IL-18. The second activating signal involves many activators, such as cholesterol, uric acid and ATP, and exogenous stimuli such as asbestos, ultraviolet light, pathogenic microorganisms and their metabolites.[3] In this step, the C-terminal senses a variety of endogenous stimuli, and binds to the pyrin domain (PYD) of apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) through

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its N-terminal PYD. Pro-caspase-1 is recruited to self-splice and generate the activated caspase-1 (p10/p20 complex). Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, then the latter two are secreted from cells to activate the downstream inflammatory response.[4]

The mechanisms involved in activating the NLRP3 inflammasome remain unclear. Possible processes include changes in intracellular calcium concentration,[5] lysosomal damage,[6] mitochondrial damage,[7] potassium ion efflux,[8] and reactive oxygen species (ROS) production.[9] The main function of this inflammasome is to initiate assembly of the inflammatory complex, and ASC serves as an adaptor protein of the inflammasome to connect upstream NLRP3 and downstream caspase-1. When the NLRP3 inflammasome becomes over-activated, it induces pyroptosis by generating excessive inflammatory factors and participates in the development of certain diseases.

NLRP3 and Reproductive Disorders

NLRP3 and endometriosis

Endometriosis (EMs) is a common gynecological disease. About 10% to 15% of women of childbearing age exhibit EMs, and about 30% of infertile women are affected by this disease.[10,11] Many recent studies have suggested that immune factors play important roles in its pathogenesis. Hypothyroidism, susceptibility to vaginal candidiasis, autoimmune diseases, fibromyalgia, chronic fatigue syndrome, headaches, arthralgias and myalgias, asthma and allergies are more common comorbidities in women with EMs than in women without it. Therefore, a possible link between endometriosis and autoimmunity has been suggested.[12] Peritoneal fluid samples from women with EMs show defectively activated macrophages and natural killer (NK) cells, which alter the recognition and clearance of endometrial cells. Macrophages secrete different products such as growth factors, enzymes, prostaglandins, and cytokines that stimulate the adhesion of endometrial tissue to mesothelial cells, promoting the invasion of extracellular matrix creating islands of endometrial cells where they can proliferate.[13] Previous studies have shown that inflammation is an important pathophysiological basis for EMs.[14] The intra-abdominal inflammatory environment and immune abnormalities are closely related to ectopic endometrial hyperplasia. Inflammation is a response from living tissues to infection or damage. Bullon *et al*[12] proposed that abnormal activation of inflammasome is closely related to the occurrence of endometriosis. As an important inflammatory mediator in inflammatory responses, the NLRP3 inflammasome is an important component of inflammasomes.[15] The same study also explored whether the NLRP3 inflammasome acts in the pathogenesis of EMs by establishing an EMs model: when the NLRP3 level was reduced, the production of inflammatory cytokines was inhibited.[13] Ahn *et al*[16] analyzed the genes associated with inflammation and immunity in patients with endometriosis, including 579 genes involved in human immunity and inflammation and 15 housekeeping genes. They found that 396 genes were upregulated in ectopic endometrial tissues, including those encoding caspase-1, IL-18, and NLRP3.

NLRP3 inflammasomes secrete many inflammatory factors, such as IL-1β, which are associated with the occurrence and development of EMs.[17,18] Bullon *et al*[12] and Sikora *et al*[19] reported that the concentrations of IL-1β in the extrauterine tissues and peritoneal fluid from patients with EMs were significantly higher than those from healthy women. Another study suggested that IL-1β upregulates the expression of cyclooxygenase-2 and increased the release of vascular endothelial growth factor (VEGF) in endometrial stromal cells and that this might promote the formation of EMs.[20] Zhao *et al*[21] found that a large amount of inflammatory cell infiltration occurred in an animal model of EMs compared with a sham-treated group and that the levels of inflammatory cytokines (IL-1β, IL-6, and tumor necrosis factor [TNF]-α) in the EMs group were significantly higher than in controls.

There are few studies about the treatment of EMs targeting the NLRP3 inflammasome. Thus, the oncogene Astrocyte elevated gene-1 (AEG-1) promoted inflammation in cases of EMs by reducing the cytokine signaling-1 (SOCS1) level and stimulating formation of the NLRP3 inflammasome. While silencing AEG-1 alone increased SOCS1 levels, the levels of inflammatory cytokines decreased, thereby inhibiting the formation of the NLRP3 inflammasome.[21] However, the effects of NLRP3 inhibitors on the occurrence and development of EMs need further study.

NLRP3 and PCOS

PCOS is a common endocrine and metabolic disorder of women of childbearing age, and is associated with cardiovascular diseases, hyperandrogenism, insulin resistance, obesity, metabolic syndrome, and reproductive abnormalities. At present, the etiology of PCOS remains controversial and many studies have suggested that chronic inflammation is involved. Clinical studies have found that factors involved in chronic inflammation, such as ILs, TNF-α, plasminogen activator inhibitor type (PAI)-1, and monocyte chemoattractant protein (MCF)-1, are increased in the peripheral blood of patients with PCOS to varying degrees.[22] Inflammatory factors can lead to the reconstruction of ovarian tissue and alter normal follicular development.[23-25] There is also compelling evidence that the rates of apoptosis of ovarian granulosa cells (GCs) in antral follicles in women with PCOS are significantly increased compared with healthy controls.[26] Wang *et al*[27] suggested that hyperandrogenism is the main cause of infertility as a result of PCOS, hyperandrogenism can drive the generation of the NLRP3 inflammasome, which results in the secretion of inflammatory mediators, and induced low-grade inflammation in mice with PCOS. Some women with PCOS appear to have increased levels of androgen, oxidative stress, free fatty acid (FFA) and high-mobility group box 1 (HMGB1), molecules that serve as danger signals to activate the inflammasome pathway, especially the NLRP3 inflammasome pathway.[28]

During the development of PCOS, follicular dysfunction and anovulation are closely linked to ovarian fibrosis. Thus, affected patients manifest with increased cystic follicles, a thickened thecal cell layer, loose arrangements

of GCs, and reduced corpus luteum formation, which has also been replicated in animal models of PCOS.[29,30] Activation of the NLRP3 inflammasome accelerates ovarian fibrosis in mice with PCOS. Thus, the NLRP3 inflammasome is implicated as a potential target in the prevention of ovarian fibrosis. When GCs were treated with INF39, a specific inhibitor of NLRP3, the ovarian fibrosis indexes such as the levels of alpha smooth muscle actin (α-SMA), connective tissue growth factor (CTGF), TGF-β were suppressed and ovarian interstitial fibrosis was remarkably reduced.[27]

Activation of the NLRP3 inflammasome results in activation of caspase-1, which in turn promotes the production of mature IL-1β and IL-18 from pro-IL-1β and pro-IL-18, respectively. Such cytokines play important roles in regulating ovarian steroidogenesis, maturation of ovarian follicles, and other reproductive processes, and the expression of IL-18 was significantly increased in patients with PCOS.[31] In addition, IL-1β is involved in the development of obesity-related insulin resistance and macrophage adipocyte crosstalk. IL-1β impairs the insulin sensitivity of adipose tissue by inhibiting insulin signaling, so blocking its activity or production might enhance insulin signaling.[32] In addition, IL-1β stimulates lipolysis and increases body weight by inhibiting the expression of fatty acid translocases and fatty acid transporters.[33] These studies have suggested that IL-1β might be protectively involved in the onset and progression of weight gain. In addition, Guo *et al*[34] found that the pioglitazone metformin complex preparation could reduce inflammation, inhibit activation of the NLRP3 inflammasome, and reduce the release of IL-1β in the treatment of PCOS.

However, further experiments are still needed to clarify the exact role of NLRP3 inflammasomes in PCOS, and such studies may lead to new treatments and managements for this disease.

NLRP3 and RSA

The causes of RSA are very complex. Many factors including anatomy, endocrine, genes, immunity and infection are considered to be involved.[35,36] Only about 30% of cases of RSA have a clear cause, and many unrecognized cases are believed to be related to abnormal immune and inflammatory responses.[37,38]

RSA is considered to reflect an allogeneic transplantation process. The balance of anti- and pro-inflammatory factors at the maternal-fetal interface plays an important role in maintaining pregnancy, and most inflammation requires the participation of inflammasomes. A significantly increased expression of the endometrial NLRP3 inflammasome, and of caspase-1-dependent secretion of IL-1β and IL-18 were demonstrated in endometrial tissues obtained from women with RSA compared with a control group (fertile women).[39,40] Thus, the NLRP3 inflammasome might represent a novel family of marker proteins of endometrial receptivity. Abnormal inflammasome activation, might be one of the molecular mechanisms involved in establishing an unreceptive endometrium, which potentially leads to early fetal loss. Tersigni *et al*[41] also found that the intestinal permeability of patients with RSA was increased abnormally, and that the expression levels of caspase-1, IL-1β, and NLRP3 in endometrial tissue were increased significantly. They speculated that women with RSA might have a leaky gut, which could induce an endometrial immune response, and lead to recurrent miscarriage. *In vitro* cell experiments showed that administration of palmitic acid or antiphospholipid antibodies activated NLRP3 inflammasomes in normal early gestational trophoblast cells, and increased the expression of IL-1β,[42,43] indicating that the abnormal inflammatory reaction caused by NLRP3 inflammasomes might be linked to RSA. As is well known, regulatory T (Treg) and Th17 cells play important roles in the pathogenesis of RSA,[44-46] and Lu *et al*[47] reported that activated NLRP3 inflammasomes participate in the pathogenesis of RSA by regulating the balance of Th17 and Treg cells.

Because NLRP3 is involved in several inflammatory diseases, there is significant interest in the discovery of beneficial therapeutics that could selectively inhibit its activation. MCC950 is a selective, potent, small-molecule inhibitor of the NLRP3 inflammasome. It inhibits NLRP3-induced ASC oligomerization in mouse and human macrophages.[48] Beta-hydroxybutyrate is another inflammasome inhibitor, that can reduce caspase-1 activation and IL-1β secretion in mouse models of NLRP3-mediated diseases.[49] Micro RNAs (miRs) such as miR 223[50] and miR 9[51] are both reported to inhibit activation of the NLRP3 inflammasome. Furthermore, several herbal extracts and their bioactive constituents are effective in mediating the inflammatory response caused by activation of the NLRP3 inflammasome, such as resveratrol,[52] arglabin,[53] and extracts from *Morus bombycis*.[54]

However, efficacious inflammasome inhibitors for use in clinical studies are still at an early stage of development and high-quality studies are needed to evaluate the effectiveness and safety of these drugs for unexplained RSA.

NLRP3 and preterm birth

Human childbirth is a complex process and its initiation remains unclear. Preterm birth is one of the most common, yet detrimental, obstetric syndromes. Approximately 70% of all preterm births are preceded by spontaneous preterm labor.[55] Of all the putative causes associated with spontaneous preterm labor, only intraamniotic inflammation/infection has been linked causally to preterm birth.[56-58] Pregnancy-related tissues such as uterine muscle, fetal membranes, and placenta all express NLRP3 inflammasomes.[59] Gomez-Lopez *et al*[60] found that women with spontaneous preterm labor and acute chorioamnionitis had activated NLRP3 inflammasomes in chorionic tissues and significantly increased levels of the active form of caspase-1 and mature forms of IL-1β and IL-18, indicating that abnormal activation of NLRP3 in spontaneous preterm labor was caused by acute chorioamnionitis. The expressions of inflammasome-related genes (*eg,* those encoding NLRP3, caspase-1, and IL-1β) were upregulated in the chorioamnionitis membranes of

women who underwent spontaneous preterm labor compared with women who delivered preterm without this placental lesion.[60] In an animal model of lipopolysaccharide-induced intra-amniotic inflammation, NLRP3 was activated in the fetal membrane before premature delivery, and higher IL-1β protein levels were released in the base of the fetal membrane, the decidual membranes and amniotic fluid.[61]

Many recent studies found that pro-inflammatory cytokines, such as IL-1β, the main products of NLRP3 activation, promote the production of prostaglandin synthetase-2 (PGHS-2), as well as the secretion of more prostaglandins via the effect of PGHS-2. Prostaglandins are important regulators of cervical ripening and increase significantly during delivery. One study found that the expression levels of IL-β, IL-6, IL-8, and TNF-α were all significantly increased in the chorionic and amniotic membranes of women undergoing preterm labor.[62] IL-1β, IL-6 and TNF-α mRNA and protein levels were significantly elevated in uterine muscle during labor,[63] and these cytokines stimulate the synthesis of interstitial metalloproteinases in the endometrium and amniotic sac.

Importantly, the NLRP3 inflammasome might be a therapeutic target for preventing preterm birth. The study found that the intra-amniotic administration of the alarmin S100B could activate the NLRP3 inflammasome in fetal membranes, increase the levels of the NLRP3 sensor molecule, active caspase-1, and mature IL-1β, then induce preterm labor/birth with adverse neonatal outcomes.[64] Inhibition of the NLRP3 inflammasome via the specific inhibitor MCC950 prevented preterm labor/birth and reduced neonatal mortality.[61,64] Faro *et al*[61] reported that the use of MCC950 could extend gestational length and not only reduce the rate of intra-amniotic inflammation-induced preterm birth by 30%, but can significantly improve neonatal survival as well in mouse. Moreover, a preliminary study provided evidence that MCC950 could be safe for clinical use in humans.[65] However, the inhibition of the NLRP3 inflammasome at term does not obstruct the physiological process of parturition.

Therefore, we suggest that targeting NLRP3 activation might provide one avenue to reduce the incidence of preterm birth and improve neonatal outcomes.

NLRP3 and PE

PE is a pregnancy-specific syndrome characterized by elevated blood pressure, proteinuria and fetal intrauterine growth restriction. Pathophysiological changes in PE include inflammation and immune cell activation.[66-68] The placenta clearly plays a central role in the pathogenesis of PE as demonstrated by the rapid disappearance of disease symptoms after delivery. Thus, placenta-derived circulating factors might induce excessive inflammation and endothelial defects, which leads to PE.[69] Mulla *et al*[70] and Xie *et al*[71] were the first to demonstrate that activation of the NLRP3 inflammasome in trophoblasts and peripheral blood was implicated in the pathogenesis of PE. Since then, there has been a rapid increase in reports that the NLRP3 inflammasome is involved in the pathogenesis of PE.[72-76] Thus, there was significantly higher expression of NLRP3 and related mediators such as caspase-1, IL-1β, and IL-18 in samples from women with PE compared with controls.[73] Moreover, Xu *et al*[77] and Pontillo *et al*[78] reported that specific NLRP3 gene polymorphisms are associated with a significantly higher risk of PE. Omi *et al*[79] examined 1911 patients (987 with hypertension and 924 controls) and found that homozygotes carriers of high activity NLRP3 alleles that produce more chemokines after stimulation, had a greater risk of developing hypertension compared with both heterozygote and homozygote carrier of low activity NLRP3 alleles. These results suggest that the placentas of pregnant women with PE show higher expression of NLRP3 inflammasomes, which may be related to the significantly upregulated inflammation state in PE. Thus, NLRP3 inflammasome activity has an important role in the development of PE.

Are there some specific triggers during activation of NLRP3 in PE? In affected patients, many endogenous danger/damage-associated molecular patterns (DAMPs), such as, cholesterol, uric acid crystals, extracellular DNA, HMGB1 proteins, extracellular cell debris, free fatty acids, and advanced glycation end-products, have been detected at higher levels in the peripheral blood and placenta and act as NLRP3 inflammasome activators.[80-99] These DAMPs induced the cytosolic leakage of cathepsin B via lysosomal rupture.[100] Leakage of cathepsin B also leads to potassium efflux and mitochondrial damage. Potassium efflux and reduced intracellular potassium concentrations result in activation of the NLRP3 inflammasome.[101]

In an *in vitro* human placental explant experiment, treatment with cholesterol crystals significantly increased the release of IL-1β, and was suppressed by treatment with MCC950, a specific inhibitor of the NLRP3 inflammasome.[102] Allopurinol is a xanthine oxidase inhibitor that inhibits uric acid and reactive oxygen species (ROS) production. Negi *et al*[103] reported that allopurinol could significantly inhibit trophoblast secretion of inflammatory IL-1β and caspase-1 activity. Thus, allopurinol could be a candidate medication to prevent placental dysfunction and adverse pregnancy outcomes, such as PE. Moreover, Park *et al*[104] found that antioxidants such as resveratrol and N-acetylcysteine could inhibit the expression of NLRP3 protein and caspase-1 activation in trophoblast cells. They might represent suitable therapeutic options for the treatment of inflammation-associated pregnancy complications.

The above findings suggest that the NLRP3 inflammasome plays a crucial role in the development of PE, so inhibitors could be very effective treatments. However, more detailed research is still needed to confirm this possibility in the prevention and treatment of PE by targeting NLRP3.

NLRP3 and GDM

GDM is a metabolic disorder in pregnant women characterized by glucose intolerance during the second or third trimester of pregnancy.[105] GDM can harm

pregnancy outcomes and the long-term health and wellbeing of offspring.[106] Under all hyperglycemic conditions, maternal plasma and placental levels of inflammatory factors (IL-1β, IL-6, and monocyte chemoattractant protein-1) increased, and ASC, caspase-1, NLRP1, and NLRP3 were upregulated in all hyperglycemic groups.[107] Chronic proinflammatory cytokines are considered to be pathologic mediators of diabetogenic metabolic disorders, associated with insulin resistance and pancreatic islet cell death.[108-111] In patients with GDM, studies have proved a connection between activation of the NLRP3 inflammasome and insulin resistance.[112] High glucose levels increase NLRP3 activation compared with those induced by normal and low glucose levels.[113] It is known that hyperglycemia or diabetes during pregnancy can induce activation of the NLRP3 inflammasome and the secretion of many inflammatory cytokines, which results in severely adverse pregnancy complications.

Therefore, how to inhibit activated inflammasomes could be an important consideration when managing hyperglycemia and preventing adverse pregnancy outcomes. Glombik *et al*[114] observed that maternal diabetes causes the activation of NLRP3 inflammasome signaling by increasing the level of the NLRP3 protein subunit, and glyburide, as a NLRP3 inflammasome inhibitor, diminishes the level of NLRP3 protein and caspase-1 subunits, and has particular therapeutic value in anti- metabolic-related inflammation. Zhang *et al*[115] found that astragaloside IV (AS-IV) treatment was an effective therapy for GDM in a mouse model through the inhibition of NLRP3 inflammasome in the pancreas. Negi *et al*[116] reported allopurinol significantly inhibited NLRP3 activation, inhibited trophoblast secretion of inflammatory IL-1β; caspase-1 activity, reduced additional pro-inflammatory and anti-angiogenic responses to excess glucose, prevent placental dysfunction and adverse pregnancy outcomes in patients with GDM. Therefore, this inflammasome represent a useful therapeutic target in the treatment of GDM.

Conclusions

In summary, the NLRP3 inflammasome plays an important role in high-risk reproductive disorders, and can cause infertility, miscarriage and many pregnancy complications. 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. Thus, NLRP3 inflammatory complex inhibitors have certain therapeutic options for treating related diseases.[117] However, we still need more research to understand the pathogenesis and to develop the mechanism-specific and safe treatments for reproductive disorders.

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Conflicts of interest

None.

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