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REVIEW

NLRP3 Inflammasome in Gynecologic Inflammatory Diseases: Mechanisms, Pathophysiology, and Therapeutic Strategies

TianHui Wang[1], Rui Zheng[1], YangFan Qu[1], Ping Shu[1], WenXia Ai[1], Jiao Zhao[1], Li Liu[1,2]

[1]Department of Obstetrics and Gynecology, Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China; [2]Department of Obstetrics and Gynecology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, People's Republic of China

Correspondence: Li Liu, Department of Obstetrics and Gynecology, First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Heping Road, Xiangfang District, Harbin, Heilongjiang, 150040, People's Republic of China, Tel +86 15045023666, Email liuliyouxiang2008@163.com

Abstract: The NOD-like receptor family containing pyridine domain 3 (NLRP3) inflammasome serves as a pivotal mediator of innate immune responses and a central driver of inflammatory processes. Upon detection of pathogenic or danger-associated signals, it assembles into a multiprotein complex that activates caspase-1, thereby promoting the maturation and release of the pro-inflammatory cytokine IL-1β and inducing pyroptotic cell death. NLRP3 inflammasome activation is regulated by highly diverse yet tightly controlled mechanisms, and its dysregulation has been implicated in various pathological conditions. Inflammatory gynecologic disorders [such as endometritis, pelvic inflammatory disease (PID), and endometriosis (EMS)] are typically characterized by chronicity, with persistent and recurrent symptoms that significantly compromise patients' quality of life. Although conventional anti-inflammatory drugs are widely used, their clinical efficacy is often limited. Emerging evidence has underscored the pivotal role of NLRP3 inflammasome in the pathogenesis of these conditions, highlighting its potential as a promising therapeutic target. This review summarized current knowledge on the mechanisms of NLRP3 inflammasome activation in gynecologic inflammatory diseases and explored possible therapeutic strategies targeting modulating NLRP3 inflammasome activation to alleviate disease progression.

Keywords: NLRP3, activation, inflammation, pelvic inflammation, endometritis, endometriosis

Introduction

The innate immune system is the most direct form of the body's immune defense against pathogenic infections, consisting of a barrier structure, a molecular structure, and innate immune cells.[1] Under certain stimuli, the innate immune system triggers an inflammatory response to combat infection, and an appropriate inflammatory response will facilitate the removal of damaged cells and promote tissue repair.[2] As has been evidenced previously, toll-like receptors (TLR) and NOD-like receptors (NLR) act as critical innate immune sensors, and abnormalities in the sensors can lead to excessive inflammatory responses, which have been implicated in inflammation in various diseases.[3] The NLR family includes NOD-like receptor family containing pyridine domain (NLRP)1, NLRP3, and NLRC4.[4] Additionally, other inflammatory vesicles such as NLRP2, NLRP6, NLRP7, NLRP12, and IFI16 have also been found to form an inflammasome in other systems.[5–8] In particular, NLRP3 plays a pivotal role in maintaining immune system homeostasis by inducing cellular death in response to microbial infections, endogenous signals, and environmental stimuli; additionally, aberrant activation of NLRP3 leads to a wide range of inflammatory diseases.[9]

Pyroptosis is tightly implicated in the pathophysiology of sepsis, contributing to injury in multiple organs and systems, including the lungs, kidneys, liver, and cardiovascular system. Gynecologic inflammatory diseases [such as endometritis, pelvic inflammatory disease (PID), vulvovaginitis, and endometriosis (EMS)] are prevalent conditions that can cause chronic pelvic pain (CPP) and infertility, along with reduced quality of life. Unlike acute gynecologic emergencies, these disorders are typically persistent and prone to recurrence, and current anti-inflammatory therapies often provide only partial and temporary relief, highlighting the need for targeted therapies. Recently, the NLRP3

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inflammasome has been reported as a central mediator of the inflammatory cascade in these conditions, and a promising target for innovative and more durable therapeutic approaches.[10]

This article summarized the NLRP3 inflammasome's activation mechanisms and its role in gynecologic inflammatory diseases, and explored potential therapeutic strategies targeting NLRP3. A comprehensive analysis of literature was conducted using PubMed, Web of Science, and Scopus from January 2000 to January 2025 with the keywords of "NLRP3 inflammasome", "gynecologic inflammatory diseases", "pyroptosis", and "therapeutic targets", and the reference lists of relevant articles were screened. This review aimed to provide a theoretical basis for developing preventive strategies and targeted therapies for gynecologic inflammatory diseases.

Structure and Activation of NLRP3

Structure of NLRP3

NLRP3 acts as a common node for inducing inflammatory responses by activating caspases and subsequently producing inflammatory mediators (such as IL-18 and IL-1β). It's well-established that the NLRP3 protein belongs to the NALP family and consists of three core components: the sensor (NLRP3), adapter [apoptosis-associated speck-like protein containing a caspase recruitment domain (CARD)] (ASC), and effector (Caspase-1 or −8).[11] As a sensor, NLRP3 is connected by an N-terminal pyrin-containing structural domain (PYD), a C-terminal leucine-rich repeat sequence (LRR), and a centrally located NACHT structural domain.[12] Moreover, the sensor NLRP3, also known as pattern recognition receptor (PRR), can specifically recognize exogenous pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs). This recognition pattern triggers the release of NLRP3 from its self-repressed state, undergoes oligomerization, and assembles to form a signaling complex via the N-terminus with an ASC adapter containing the CARD structural domain. In contrast, LRR's function is unclear, but a previous study has proposed that LRR can serve as a site of post-transcriptional regulation.[13] It has been evidenced that the subdomain nucleotide-binding structural domain (NBD) in the NACHT structural domain has the active ingredient ATPase required for NLRP3 oligomerization.[14] The ASC complex further recruits the effector protein caspase-1 for its proteolytic activity. Caspase-1 then activates and cleaves gasdermin D (GSDMD), which leads to cellular metastasis and mediates the release of pro-inflammatory cytokine from the IL-1 family, thereby triggering a programmed cell death process crucial for the immune defense mechanism.[15–17] Additionally, NLRP3 can play a biological role through PYD-mediated interactions with the CARD structural domain in the ASC.[18] Some PYPAF1 family members can participate in regulating inflammatory signaling activity and function.

Activation of NLRP3

Extensive studies have identified three known mechanisms of NLRP3 inflammasome activation: the classical pathway, the non-classical pathway, and the bypass alternative pathway.

Classical Pathway

First, the classical pathway requires two steps: initiation (signaling 1) and activation (signaling 2). Specifically, signal initiation is usually triggered by PRRs, such as TLR and tumor necrosis factor (TNF) signaling. TLR activation is dependent on the MyD88 receptor/IL-1 receptor-associated kinase pathway, which ultimately activates the nuclear transcription factor-κB (NF-κB) pathway.[19] It has been shown that NF-κB acts as a pro-inflammatory signal, with its activation regulating the expression of NLRP3, pro-IL-1β, and pro-IL-18, and exerting their respective biological functions.[20] However, the NLRP3 vesicle initiation process is complex, involving multiple mechanisms such as transcriptional and post-translational modifications, NLRP3 ubiquitination, phosphorylation, etc.[21] Additionally, Fas-related death domain proteins/caspase-8[22] and IKK complex,[23] as well as lipopolysaccharide (LPS) and other co-participants[24,25] can also promote NLRP3 signaling initiation via transcriptional or non-transcriptional pathways, facilitating a smooth activation.

The activation of NLRP3 requires the coordinated realization of several mechanisms. The first mechanism is ion migration and diffusion, of which K^+ efflux is the most important event, and the reduction of intracellular K^+ alone can sufficiently activate NLRP3 to produce an inflammatory response.[26] In addition, accumulating studies have reported Ca^{2+}

influx into cells under the influence of multiple NLRP3 stimulants (such as ATP, Nigerian mycobacteria, and particulate matter); increased cytoplasmic Ca^{2+} may trigger NLRP3 inflammatory vesicle activation.[27–29] Moreover, it has been shown that Na^{+} inward and Cl^{-} outward plasma transport events also occur during NLRP3 activation.[26,30,31] The second mechanism is that the entry of particulate irritants (MSU, alum, silica, asbestos, amyloid β-protein, cholesterol crystals, and calcium crystals) into the cell can affect lysosomal membrane permeability (LMP) and cause substantial lysosome rupture, thereby prompting the release of a large amount of proteinase B, Ca^{2+}, and K^{+} from the cytosol.[32] All these events are critical steps in the activation of inflammatory vesicles, and it can be assumed that lysosomal disruption is correlated with the activation of NLRP3.[33] In addition, it has been shown that K^{+} can be released from the GSDMD pore to activate NLRP3, further confirming the correlation between cellular pyroptosis and inflammatory vesicles.[34] The third mechanism is mitochondria undergoing LPS-induced dysfunction. It has been shown that NLRP3 activity is positively regulated by reactive oxygen species (ROS) and that inhibition of mitochondrial dysfunction-generated ROS (mtROS) could activate NLRP3.[35] Similarly, Nakahira et al have suggested that mitochondrial dysfunction produces mtDNA that is required for LPS and ATP in NLRP3 activation.[36] Moreover, Shimada et al have also reported that mtDNA released by ATP-induced mitochondrial dysfunction could bind to and activate NLRP3.[37] However, there is still controversy regarding the use of high concentrations of mtROS inhibitors in these studies and the lack of a certain degree of conviction in the experimental results.[38,39] Furthermore, Munoz-Planillo et al have also shown that mtROS production is nonessential upon NLRP3 activation.[26] Additionally, mitochondrial molecules are implicated in NLRP3 activation, including mitochondrial antiviral signaling protein (MAVS),[40], mitochondrial fusion protein 2,[41] and cardiolipin.[42] In summary, more future studies are needed to elucidate the mechanism of NLRP3 initiation and activation.

Non-Classical Pathway

It has been found that intracellular LPS can induce endotoxin shock via TLR4 and only responds to Gram-negative bacteria, which is referred to as the non-classical pathway.[43] The non-classical pathway of NLRP3 activation primarily relies on caspase-11 and its immediate homologue caspase-4/5 proteins.[44] Caspase-4/5 in humans and caspase-11 in mice have been shown to recognize LPS and mRNA, mediate NLRP3-ASC oligomerization, and enhance NLRP3 inflammasome activation.[45,46] Additionally, LPS has been recognized as an activator of the non-classical pathway of inflammatory vesicles.[47] Caspase-11 is a member of the caspase-1 subfamily of proteases. Unlike other caspases, caspase-11 activation requires the induction of inflammatory stimuli on the precursor substance procaspase-11; additionally, both TLR and interferon (IFN-β/IFN-γ) are required to process and cleave procaspase-11-induced expression of procaspase-11.[48] Activated caspase-11 cleaves GSDMD and releases the GSDMD-N-terminal structural domain (GSDMD-NTD), which promotes cell death, facilitates the secondary activation of NLRP3 vesicles, and induces the production of the inflammatory cytokine IL-1β.[49] Caspase-4, which exists in human macrophages, is required for the maturation of the inflammatory factor precursors (proIL-1β and proIL-18); additionally, it has been experimentally demonstrated that during NLRP3 vesicle activation, caspase-4 expression activates caspase-1, jointly releasing IL-1β and IL-18.[50] Regarding the primary function of caspase-5, it regulates the non-classical pathway and is modulated by LPS to induce inflammation during Gram-negative bacterial infections; hexanoylated lipid A in LPS binds to CARD in caspase-5, leading to oligomerization of caspase-5, and this binding mode activates NLRP3 vesicle formation in the non-classical pathway.[51] Although caspase-4/5 both functions similarly in the NLRP3 vesicle non-classical pathway, there is a clear divergence between the two, with caspase-4 being more proficient in targeting proIL-18 activation.[52] The necessity of caspase-5 is attenuated when LPS is isolated and transfected into cytoplasmic lysate, and its role is only enhanced during infection.[53]

Alternative Pathway

An alternative pathway for NLRP3 activation was also observed, which is different from both the classical and non-classical pathways. The specificity of this pathway lies in its dependence on the TLR4-TRIF-RIPK1-FADD-CASP8 signaling instead of K^{+} efflux and cellular pyroptosis formation.[39] This pathway exists in human peripheral blood mononuclear cells (PBMC) and can activate primary monocytes to secrete IL-1β upon LPS stimulation, without involving cellular pyroptosis and NLRP3 initiation during inflammatory vesicle activation. In addition, the catalytic

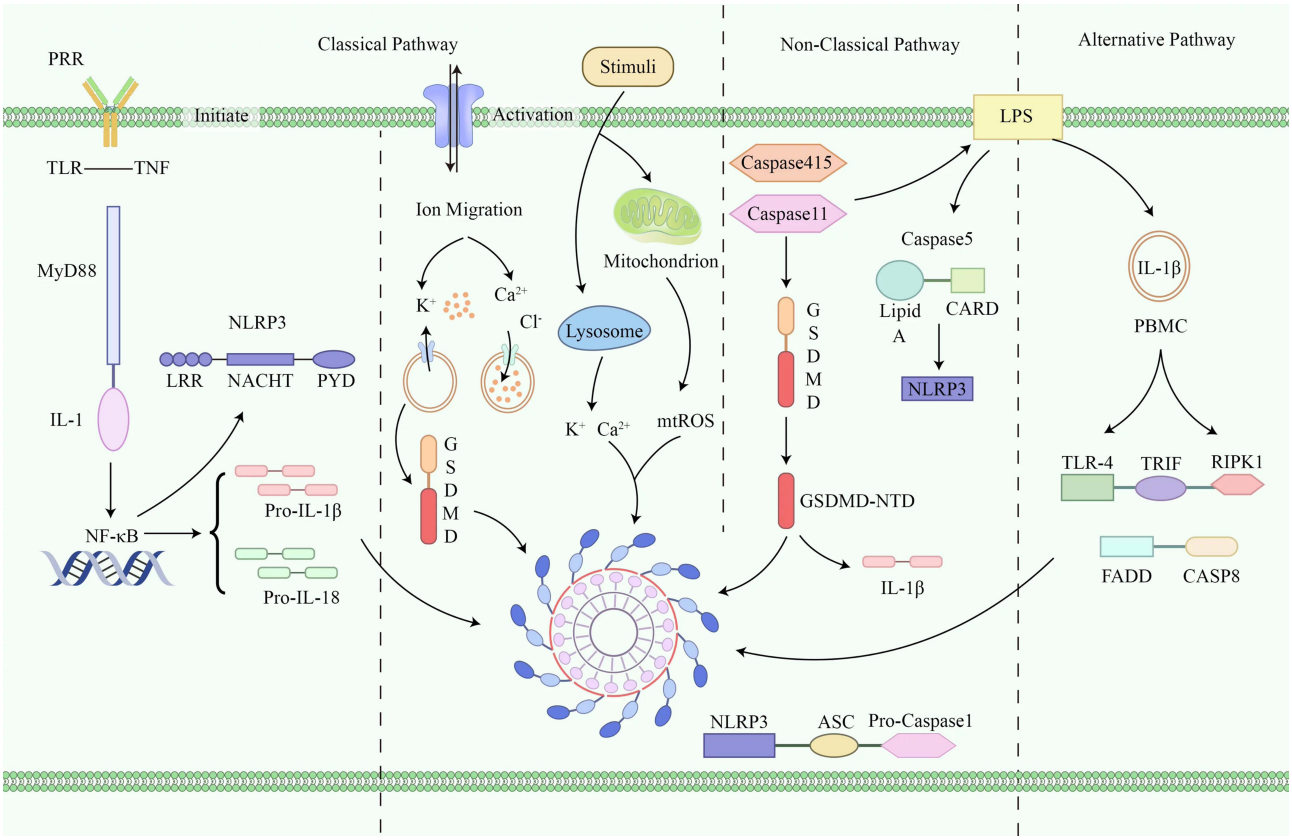

Figure 1 Three activation pathways of NLRP3. 1) The classical pathway: including initiation and activation signaling; the initiation signaling includes triggering NF-κB signaling to assist in the assembly of NLRP3 and release of IL-1β and IL-18 precursors; the activation signaling involves the activation of NLRP3 by cleavage of GSDMD to generate a pore through ion channels, mitochondrial barriers, etc. 2) The non-classical pathway: LPS prompts oligomerization of caspase 5 to generate NLRP3; or NLRP3 is directly activated by GSDMD-NTD cleavage. 3) Alternative pathway: NLRP3 is activated by LPS acting on intracellular IL-1β via TLR-4-TRIF-RIPK1-FADD-CASP8. Created in BioRender. Wang, T. (2025) https://BioRender.com/28ni9dl.

activity and auto-protein hydrolysis of caspase-8 have been shown to play a key role in the activation of the NLRP3 alternative pathway, and the superseding effect of caspase-8 upstream of the activation of the NLRP3 alternative pathway has been experimentally established[54] (Figure 1).

Role of NLRP3 Activation in Gynecologic Inflammatory Diseases

Gynecological inflammation may involve several internal and external genitalia, including the vulva, vagina, cervix, pelvis, uterus, and ovary. The activation mechanism of NLRP3, as the most important part of inflammatory vesicles, is also reflected in gynecological inflammation. In this review, we discussed the pathogenic mechanisms of different gynecologic inflammatory diseases through several clinical and experimental studies.

NLRP3 in External Genital Inflammation

Plasmacytosis Vulvovaginitis (PCV)

Inflammatory lesions of the skin or mucous membranes of the vulva are collectively referred to as vulvovaginitis, which is most commonly caused by pathogens invading the vulva or receiving undesirable stimuli. Among them, PCV is a relatively rare type.[55] NLRP3 vesicles play a key role in inflammatory diseases triggered by sterility or infection. Although the association between NLRP3 and PCV has not been reported, a previous study has illustrated the mechanism of inhibition of NLRP3 in attenuating plasma cell mastitis (PCM). Specifically, the inhibition of plasma cell infiltration in mammary tissues by the NLRP3 inhibitor MCC950 could significantly attenuate the release of inflammatory factors.[56] MCC950 is a class of selective NLRP3 vesicle small molecule inhibitors and can inhibit CARDs in the NLR family, thereby blocking NLRP3 signaling.[57] More research is needed to validate the involvement of NLRP3 and plasma cell

infiltration in vulvovaginitis, but this does not prevent us from maintaining a positive attitude towards the correlation between the two.

NLRP3 in Internal Genital Inflammation

Vaginitis

Vaginitis is one of the most frequent inflammatory conditions in women, caused by an immunopathologic response controlled by the host's innate immunity. Bacterial vulvovaginal candidiasis (VVC), trichomoniasis vaginalis (TV), and bacterial vaginosis (BV) are common and recurrent infections in vaginitis.[58] A previous study has revealed that IL-1β and IL-18 production in VVC mice contributes to vaginal mucosal recruitment of polymorphonuclear leukocytes (PMNs), while activated NLRP3 vesicles also facilitate inflammatory cell aggregation and injury in VVC.[59] In addition, the transcriptome sequencing results on VVC have also confirmed that the NLRP3 vesicle is a key factor contributing to VVC development.[60]

For TV, Trichomonas vaginalis can induce human vaginal epithelial cells (ECs) and macrophages to release inflammatory factors. It has been reported that human macrophages stimulated by Trichomonas vaginalis locally produce a certain amount of ATP and activate the macrophage P2X7 receptor, which activates the NLRP3 via the K^+ efflux pathway and then cleaves caspase-1, inducing macrophage cell pyroptosis.[61,62] Meanwhile, a recent study focusing on mice with and without symptomatic TV has found that NLRP3 and NLRP4 are highly expressed in the symptomatic mice, and TV also significantly increases caspase-1 and caspase-4 protein levels in vaginal tissues, releasing a large amount of IL-1β.[63]

Gardnerella vaginalis (GV) is a group of anaerobic vaginal bacteria that are important players in BV infection.[64,65] Xiang Nan et al have revealed a novel pathogenesis of BV. Specifically, GV promotes the production of inflammatory factors, THP-1 and ROS, and facilitates caspase-1 cleavage, which activates THP-1 monocytes in the NLRP3/ASC/caspase-1 pathway to mediate cellular death.[66] Additionally, a previous study has demonstrated that knocking out NLRP3 in BV mice is associated with reduced IL-1β secretion, corroborating the importance of NLRP3 in inducing inflammatory vesicle recruitment in BV.[67]

Cervicitis

Cervicitis is an inflammation of the cervical area, usually caused by infectious agents, typically including Chlamydia trachomatis and Neisseria gonorrhea.[68] There are also case studies showing that vaginal anaerobes may be the source of cervicitis infection.[69] Meanwhile, the correlation between cervicitis and BV is becoming clearer in several studies.[70–72] Cervical ECs form the first barrier against pathogens. When Mycoplasma genitalium invades the cervical ECs, it triggers the activation of the innate immune system through high expression of TLR2/6.[73] It has been shown that TLR2/6- NF-κB is a classical signaling initiation step of NLRP3 vesicles, which can induce reproductive tract mycoplasmas to act on the cervix and trigger inflammation.[74] In addition to Mycoplasma genitalium, the invasion of cervical EC for Chlamydia trachomatis has been explored. Chlamydial infection triggers K^+ efflux, leading to the production of large amounts of ROS in chlamydia-infected cells, which activate the NLRP3 vesicles and caspase-1 and then trigger cervicitis.[75] Neisseria gonorrhoeae (NG) often induces IL-1β and other inflammatory factors causing inflammation in the cervical region by IL-1β and other inflammatory factors.[76,77] Duncan et al have demonstrated that NG primarily relies on the activation of NLRP3/ASC signaling, which mediates NLRP3 vesicle activation and IL-1β release. However, data have also suggested a correlation between the ability of NG to cause disease and the virulence of its infection.[78] Moreover, it has also been proposed that NG infection provides the expression of the precursor substance IL-1β for NLRP3 vesicle activation, which is activated through P2X7 receptor-dependent K^+ efflux, lysosomal acidification, and mitochondrial dysfunction.[79] mtDNA mutations also highlight an important role in the classical NLRP3 pathway. Kara et al have investigated the correlation between 4977 bp deletion of mtDNA and cervicitis, and found that prolonged exposure to ROS could result in an increase in the frequency of 4977 bp deletion of mtDNA, which is positively correlated with cervicitis incidence.[80] Taken together, any of the classical or non-classical pathways could induce NLRP3 activation to stimulate cervical EC lesions and thus trigger inflammation, while providing corresponding potential molecular targets for the treatment of cervicitis.

Endometritis

Endometritis is defined as an inflammation caused by endometrial infection, resulting from retrograde infection by microorganisms from the vagina and cervix.[81] As the most common pathogenic microorganisms in acute endometritis, Chlamydia trachomatis and Neisseria gonorrhoeae activate inflammatory vesicles by affecting the link in the NLRP3 vesicle activation pathway, leading to the development of endometritis. The former triggers the TLR2/MyD88 signaling to activate NLRP3 vesicles, while the latter inhibits TLR2/TLR4, which slows down the progression of Neisseria gonorrhoeae-infected endometritis and reduces the expression of NLRP3 and other inflammatory factors.[82,83] However, the pathogenicity of both in chronic endometritis has not been demonstrated.[84] Mycoplasma genitalium infection is closely related to chronic endometritis. As has been revealed previously, triacylated lipoproteins in Mycoplasma genitalium induce NF-κB activation in a TLR1/TLR2 pathway-dependent way, which in turn activates NLRP3 vesicles.[85]

Pelvic Inflammation

PID is the most common gynecologic inflammatory disease among women of childbearing age, which is primarily caused by various novel microbial infections and complex pathologic mechanisms.[86] Recent research on PID has focused on macrophages and T cells.[87] It has been shown that M1-type macrophages located in the PID release various inflammatory factors during infection or inflammatory stimulation, while M2-type macrophages turn on the repair mode in the late stage of inflammation; the balance of M1/M2 is an important mechanism for maintaining immunity.[88] Inflammation serves as a major barrier against pathogen attack, and failure to resist can evolve into pathology that damages the organism. Chronic PID (CPID) is the result of prolonged polarized recruitment of M1-type macrophages, in which inflammatory cells not only stimulate NLRP3 vesicle activation but also stimulate M1 macrophage polarization and caspase-1 and IL-1β production, further promoting inflammatory progression.[89] Ma et al have shown that M1-type macrophages and NLRP3 are significantly upregulated in PID rats.[90] Additionally, autophagy is also involved in NLRP3 vesicle activation by removing aberrant proteins and organelles.[91] Moreover, PID can be triggered by cross-infection between various pathogens.[74,92,93] Both Neisseria gonorrhoeae and Chlamydia trachomatis activate inflammatory vesicles by stimulating a link in the NLRP3 vesicle activation pathway.[78,79,94] GV in bacterial vaginitis can also stimulate NLRP3 vesicle activation through retrograde infection, triggering PID.[67] Tubulitis is a type of PID, with chronic salpingitis (CS) being more common.[95] Infiltrating macrophages are critical in the remodeling and repair of inflamed tissues during CS. LIAO et al have concluded that the changes in macrophage function and the secretion of large amounts of IL-1β and caspase-1 proteins during Chlamydia trachomatis-induced CS facilitate the activation of NLRP3 vesicles.[96]

EMS

The etiology of EMS is complex, and it has been shown to be associated with inflammation.[97] Inflammation is also a major contributor to chronic pelvic pain (CPP) in EMS patients.[98] CPP induces neuronal alterations in key regions, generating pain signals through central sensitization and glial cell polarization, NLRP3 vesicle activation, and inflammatory factor overproduction.[99] In addition, it has also been shown that pro-inflammatory cytokines are extensively activated and released during the progression of EMS, and the most studied dangerous inflammatory vesicle is NLRP3.[100] As a key factor in the innate immune system, NLRP3 vesicles' activation can mediate the inflammatory response and subsequent exacerbation of EMS.[101] A prior study by Xu et al has demonstrated through bioinformatic prediction and assays that lnc-MALAT1 is essential for triggering NLRP3-mediated EMS cellular pyrokinesis via the sponge miR-141-3p; the use of the NLRP3 inhibitor MCC950 could significantly reduce the release of NLRP3 and inflammatory factors in EMS mice.[102] Moreover, in a recent clinical study, assays and tests of serum from EMS patients have revealed an association between NLRP3 vesicle inhibition and inhibition of LPS/ATP-induced endothelial cell tube formation, suggesting that NLRP3 inflammatory vesicle activation-mediated cellular pyroptosis can affect angiogenesis in EMS in a Notch1-dependent manner.[103] Additionally, EMS also serves as a class of hormone-dependent diseases, in which a hyperestrogenic state directly activates mast cells (MCs) in the immune system.[104] The relationship between sex hormone dysregulation and inflammatory vesicle activation needs further exploration. Hence, Guo et al have found that estrogen in EMS interacts with its nuclear receptor (ER-α) to promote NLRP3 expression in MCs and K^+ efflux

responsible for NLRP3 inflammatory vesicle activation, thus determining the molecular mechanism of hyperestrogenism and MC proinflammation in EMS; NLRP3 vesicles can act as a signaling pathway to maintain this inflammatory state.[105]

An Initiative to Target NLRP3 for the Treatment of Gynecologic Inflammatory Diseases

Aberrant activation of the NLRP3 inflammasome can lead to various inflammatory gynecological diseases, and pharmacological inhibition targeting the activation step of the NLRP3 vesicle is not an ineffective therapeutic strategy. This article introduced the targets and therapeutic potential of small molecule chemicals, biological agents, plant extracts, and Chinese medicine.

Small Molecule Substances

Small molecules play important roles in drug research. Bay 11–7082 is a synthetic compound that exerts anti-inflammatory effects by inhibiting the NF-κB pathway and the Pyrin structural domain of the NLR family containing the NLRP3/caspase-1 inflammatory factor.[106] It has been shown that treatment of Bay 11–7082 in the monocyte cell line Chlamydia trachomatis markedly inhibits IL-1β secretion and limits the activation of the inflammatory vesicle NLRP3.[107] In addition, Bay 11–7082 inhibits the ability of Trichomonas vaginalis to activate NLRP3 vesicles, thereby reducing IL-1β expression.[108] Moreover, a recent study has also found that NG can be eradicated by plasma-activated liquid (PAL). PAL is generated by the interaction between atmospheric pressure plasma and a liquid (saline). A previous study has evaluated the mechanism of sterilization of NG by PAL and found that PAL could kill large-scale frontal NG cells, and increasing PAL dose induces a trend of decreasing ROS, interfering with NLRP3 vesicle activation and the release of other inflammatory vesicles.[109] The antidiabetic sulfonylurea glibenclamide has been reported to partly alleviate inflammation through inhibition of NLRP3 inflammasome activation, although its primary effect in VVC models may involve decreasing pathogen burden. In a mouse model, the combined treatment of glibenclamide analog 16673-34-0 and the selective NLRP3 inhibitor MCC950 has been shown to reduce IL-1β secretion and NLRP3 expression, indicating that pathogen clearance combined with direct inflammasome inhibition could provide a complementary therapeutic approach for VVC.[110] Bile acids (BAs) not only play important roles in lipid uptake metabolism and anti-inflammation, but can also act as NLRP3 vesicle inhibitors by blocking NLRP3 vesicle activation through inhibition of NF-κB.[111] It has been found that treating endometritis in rats with BAs reduces LPS-induced up-regulation of NLRP3 vesicles, ASC, and caspase1; Bas exhibits anti-inflammatory properties, making it a novel agent for the treatment of endometritis.[112] Furthermore, a novel immunomodulatory peptide alloferon has also been identified during the exploration of endometritis. Alloferon can regulate the production of active factors by immune cells to exert anti-inflammatory effects.[113] Additionally, the experimental results by Chen et al have provided evidence for alloferon's ability to significantly alleviate endometrial tissue in endometritis rats by attenuating the NLRP3/CASP1/IL-1β/IL-18 signaling cascade to inhibit LPS-induced inflammation.[114] MCC950, a common NLRP3 inhibitor, has been shown to inhibit fibrosis induction by LPS + ATP within EMS and attenuate TGF-β1-mediated fibrosis.[101,102] It has been shown that C-Jun N-terminal kinase 1 (JNK1) can mediate NLRP3 vesicle activation.[115] Moreover, in a previous study focusing on intervention with the JNK1 inhibitor bentamapimod (AS602801) in an EMS mouse model, bentamapimod could mitigate disease progression by decreasing inflammatory vesicle activation responses and enhancing NK cell activity.[116,117] Another NLRP3 inhibitor CY-09 has been shown to inhibit EMS by reversing the Tripartite motif-containing 24 (TRIM24)-induced NLRP3/caspase-1/IL-1β cellular pyroptosis pathway.[118]

Biological Agents

Currently, there is a lack of definitive drugs targeting NG-mediated activation of NLRP3 vesicles, but research has reported that the angiotensin II receptor antagonist candesartan (CS) can affect macrophages in the NG.[119] Experiments have demonstrated that CS effectively inhibits caspase-1 activation, IL-1β secretion, and NLRP3 vesicle release in NG-infected macrophage infections; CS-induced autophagy exerts inhibitory effects on NLRP3 vesicles, which may provide evidence for the potential of CS as an anti-NG drug. Furthermore, in a mouse model of NG infection, it has been shown

that progesterone inhibits the phosphorylation level of NF-κB and attenuates NG-induced ROS generation, which is consistent with blocking the NLRP3 vesicle activation pathway.[120] Melatonin is a naturally occurring indoleamine with recognized antioxidant and anti-inflammatory properties, which attenuates NLRP3 inflammasome activation through multiple pathways.[121] For example, a previous study has revealed that intraperitoneal administration of melatonin at 20 mg/kg in a mouse model of LPS-induced endometritis significantly inhibits the thioredoxin-interacting protein (TXNIP)/NLRP3 signaling axis, suppresses NF-κB activation, and reduces ROS production.[122] Additionally, melatonin has been shown to activate adenosine monophosphate-activated protein kinase (AMPK), thereby restoring mitochondrial function and alleviating histopathological damage in uterine tissues. Previous studies have demonstrated that melatonin not only reduces the release of inflammatory cytokines (such as IL-1β and IL-18), but also promotes tissue repair by modulating oxidative stress and apoptosis pathways, making it a promising nutritional supplement for endometritis management with potential applicability to other gynecologic inflammatory conditions.

Most antibiotics can influence host cell functions during administration. For example, doxycycline is a tetracycline antibiotic that targets the ribosome, and its anti-inflammatory properties have been investigated. In both systemic inflammation and endometritis models, doxycycline could reduce NLRP3 inflammasome activation by inhibiting mitochondrial DNA synthesis, thereby reducing downstream IL-1β production and attenuating tissue injury.[123]

Additionally, studies have provided evidence that estrogen conductance leads to increased NLRP3 concentrations in a mouse model of EMS and that estrogen can act as a key substance for inflammatory activation of NLRP3 vesicles.[124,125] Denogestrel (DNG) is a common progesterone-based agent for EMS treatment. Clinical trial results have suggested that DNG utilizes progesterone's ability to regulate ROS levels to modulate NLRP3 levels in the serum of EMS patients, as a means of reducing inflammation and pain manifestations in patients.[126] Another trial has demonstrated that DNG can inhibit NLRP3 vesicle activation and inflammatory factor release by inducing autophagy.[127]

Plant Extracts

There are a large number of active ingredients in plants in nature, which exert anti-inflammatory pharmacological effects in various inflammatory diseases.[128] When studying the effects of Huperzol (a phenolic compound extracted from the Chinese herb Huperzia serrata) on macrophages in Neisseria gonorrhoeae, it has been found that Huperzol could effectively inhibit the activation of caspase-1, caspase-11, and GSDMD, reduce the release of extracellular speckled proteins containing ASCs from Neisseria gonorrhoeae-infected macrophages, prevent NLRP3 vesicle activation, and alleviate the manifestation of inflammation.[129] Diterpenoids extracted from the Chinese herb Naked Flower Violet Pearl have also been shown to effectively inhibit NLRP3 vesicles in an in-vitro model of cervicitis, highlighting their potential to modulate inflammatory factors in vitro.[130] Additionally, PU is an isoflavone compound extracted from the Chinese herb Pueraria Mirifica. A previous study has demonstrated that endometrial pro-inflammatory factors (such as TNF-α, IL-1β, and IL-6) are remarkably reduced in PU-treated endometritis mice, which activates the AMPK/SIRT1 signaling pathway to reduce LPS-induced inflammation, thereby inhibiting NLRP3 inflammasome-mediated cell apoptosis.[131] Fenrunculus, a traditional Chinese herb, has a long history of treating gynecological bleeding disorders; it contains flavonoids (TFC) that attenuate LPS-induced endometritis in vivo by inhibiting NLRP3 vesicle activation.[132] Moreover, rosmarinic acid (ROsA) is a naturally occurring phenolic acid extracted from the plant rosemary, which can combine with 10 mg/kg of exosomes to inhibit the TLR4-NLRP3 pathway to alleviate endometritis.[133] Di et al have also found that epigallocatechin gallate (EGCG) contained in green tea can block inflammatory responses via SIRT1/NLRP3, making it a promising candidate for endometritis treatment.[134]

Sarsaparilla is a commonly used herb for the treatment of PID, and its root extract flavonoids can notably reduce IL-1β and TNF-α levels in CPID rats, regulate the autophagy pathway of NLRP3 vesicles, and promote metabolic reprogramming of macrophages, thus alleviating CPID.[90] Tetramethylpyrazine (TMP) is a pyrazine alkaloid extracted from the traditional Chinese medicine (TCM) Ligusticum chuanxiong, which has been shown to notably improve the lesion size and reverse the elevated levels of inflammatory proteins, oxidative stress markers, NLRP3 inflammatory vesicles, and pyroptotic proteins when acted on EMS rats.[135] In addition, the natural polyphenol fexofenone, present in various vegetables and fruits, targets the MC-derived NLRP3 inflammatory vesicle pathway and oxidative stress acting on EMS.[136]

Principles and Practices of TCM

TCM has also contributed positively to the treatment of gynecologic inflammation. For example, Qianjin Gynecological Capsule (FKC) is a widely used patented formulation for gynecologic disorders, which is composed of multiple herbal ingredients, including *Radix Astragali* (Huangqi), *Radix Angelicae Sinensis* (Danggui), *Radix Codonopsis* (Dangshen), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Radix Paeoniae Alba* (Baishao), *Rhizoma Chuanxiong* (Chuanxiong), *Radix Glycyrrhizae* (Gancao), *Fructus Ligustri Lucidi* (Nvzhenzi), and *Fructus Schisandrae Chinensis* (Wuweizi). Xiong et al have demonstrated that FKC treatment effectively reverses the NLRP3 inflammasome activation and significantly reduces TLR4, p-P65, NLRP3, caspase-1, GSDMD, and IL-1β expression levels in uterine tissues of LPS-induced endometritis rats. These findings suggest that FKC exerts anti-inflammatory effects by modulating the TLR4/NF-κB/NLRP3 signaling pathways.[10] Additionally, the TCM JTY has been shown to notably downregulate the expression of inflammatory factors and NLRP3 vesicles in EMS patients, improving the inflammatory microenvironment of EMS.[137] Moreover, as has been evidenced previously in a prospective study, treatment of Tiaoqi Jiedu Gynecological Formula [composed of *Radix Bupleuri* (Chaihu), *Radix Angelicae Sinensis* (Danggui), *Radix Paeoniae Alba* (Baishao), Rhizoma Atractylodis Macrocephalae (Baizhu), Cortex Moutan (Mudanpi), Herba Taraxaci (Pugongying), and *Radix Glycyrrhizae* (Gancao)] could significantly inhibit the expression of NLRP3 and Caspase-1 and reduce the release of inflammatory factors in endometritis mice. These findings highlight the anti-inflammatory and anti-pyroptotic potential of this multi-herb formulation in endometritis treatment.[138]

Inflammatory pain remains a challenging symptom to manage in various inflammatory diseases, and the NLRP3 inflammasome has been identified as a critical mediator of chronic pain across various inflammatory conditions.[139] Electroacupuncture, as an emerging measure to alleviate inflammatory pain, has good analgesic effects and no side effects, making it a complementary and alternative medicine.[140] Xu et al have demonstrated that downregulation of the P2X7R/NLRP3 signaling pathway could significantly alleviate CPP symptoms by electroacupuncture intervention at different acupoints in rats.[141] In addition, acupuncture plays a pivotal role in the treatment of EMS by stimulating endogenous dopamine and subsequently modulating the inflammatory pathways in the body to control EMS lesions.[142] Moreover, a systematic evaluation has also assessed the content of acupuncture in delaying EMS pain. Specifically, it's concluded that although the overall efficacy of acupuncture in treating EMS is unclear, acupuncture maneuvers significantly improve patients' pain symptoms and quality of life[143] (Table 1).

Table 1 A Protocol for Targeting NLRP3 in the Treatment of Inflammatory Gynaecological Diseases

Small Molecule	Molecular Mechanism	Experimental Models	Reference
Bay 11–7082	Inhibition of Pyrin structural domain and IL-1β secretion	Chlamydia trachomatis Trichomonas vaginalis	[107,108]
BAs	Inhibits ROS and interferes with NLRP3 activation	NG	[109]
16,673-34-0	Inhibits IL-1βand NLRP3	VVC	[110]
Bile Acids	Inhibition of NF-κB reduces upregulation of NLRP3, ASC and Caspase1	Endometritis	[112]
Alloferon	Attenuated NLRP3/CASP1/IL-1β/IL-18 signaling	Endometritis	[114]
MCC950	NLRP3 inhibitor, inhibits fibrosis	Endometriosis	[101,102]
Bentamapimod (AS602801)	JNK1 inhibitor, reduces inflammatory vesicle activation response	Endometriosis	[116,117]
CY-09	Reversal of TRIM24-induced NLRP3/caspase-1/IL-1β cell pyroptosis	Endometriosis	[118]
Biological agents			
Candesartan	Induction of autophagy and inhibition of NLRP3, caspase-1 and IL-1β release	NG	[119]
Progesterone	Inhibits NF-κB and attenuates ROS generation	NG	[120]
Melatonin	Inhibition of TXNIP/ NLRP3 pathway, NF-κB activation and ROS production	Endometritis	[122]
Doxycycline	Blocking mtDNA synthesis	Endometritis	[123]
Dienogest	Regulates ROS levels and induces autophagy	Endometriosis	[126,127]

(*Continued*)

Table 1 (Continued).

Small Molecule	Molecular Mechanism		Experimental Models	Reference
Plant Extracts	Origins	Molecular Mechanism		
Honokiol	Houpoea officinalis.	Inhibition of caspase-1, caspase-11 and GSDMD activation	NG	[129]
Diterpene	Callicarpa nudiflora Hook.	Inhibits NLRP3	Cervicitis	[130]
PU	Pueraria montana.	Inhibits AMPK/SIRT1 pathway	Endometritis	[131]
TFC	Clinopodium chinense.	Inhibits NLRP3	Endometritis	[132]
ROsA	Salvia rosmarinus Spenn.	Inhibits TLR4-NLRP3 pathway	Endometritis	[133]
EGCG	Green tea	Blocking the inflammatory response via SIRT1/NLRP3	Endometritis	[134]
Flavonoids	Smilax china L.	Reduction of IL-1β, TNF-α levels and induction of macrophage metabolic reprogramming	CPID	[90]
TMP	Ligusticum sinense "Chuanxiong"	Improvement in EM lesion size, reversal of inflammatory proteins, oxidative stress markers, etc.	Endometritis	[135]
Fisetin	Vegetables and fruits	Targeting oxidative stress	Endometritis	[136]
Chinese Medical Treatment	Molecular Mechanism			
FKC	Regulation of the TLR4/NF-κB/NLRP3 pathway		Endometritis	[10]
JTY	Down-regulation of inflammatory factor expression to improve the inflammatory microenvironment		Endometriosis	[137]
Gynecological Tiao qi Jie du Formula	Inhibition of NLRP3 and Caspase-1		Endometritis	[138]
Electro-acupuncture	Down-regulation of the P2X7R/NLRP3 signalling pathway		CPID	[141]
Acupuncture	Suppression of inflammatory pain		Endometriosis	[142]

Although most studies on NLRP3-targeted interventions in gynecologic inflammatory diseases have been conducted in preclinical models, several agents described in this section have also been evaluated in clinical contexts. For example, in randomized clinical trials, the progesterone-based drug dienogest has been shown to reduce pelvic pain and improve the quality of life of EMS patients, potentially by modulating ROS and NLRP3-related pathways.[144] Similarly, it has been shown that clinical use of FKC is associated with relieved symptoms in patients with PID and endometritis,[145] which is consistent with the anti-inflammatory effects observed in animal models. Electroacupuncture has already been applied in clinical practice and has been shown to significantly reduce CPP scores in EMS women.[146] However, for many small molecules, plant extracts, and biological agents mentioned above (eg, MCC950, CY-09, melatonin, PU, EGCG), there is a lack of clinical trials, and their efficacy in improving patient-reported symptoms remains to be determined. Future translational studies should therefore focus on bridging the gap between mechanistic findings and actual clinical benefits (Table 1).

Discussion

NLRP3 is a class of complex proteins that trigger inflammatory responses, typically formed when cells are attacked by pathogens. Normal NLRP3 vesicles maintain immune homeostasis in vivo by regulating IL-1β. NLRP3 is stimulated by danger signals and triggers the immune defence process of cellular pyroptosis. Abnormally activated NLRP3 vesicles affect the development and regression of various diseases (such as cerebral ischaemia, gout, and neurological and atherosclerosis).[147–150] From the perspective of gynaecological diseases, there is a strong association between NLRP3

vesicles and gynaecological tumors, which can also affect reproduction-related diseases and modulate the pathogenesis of most inflammatory gynaecological diseases.[151] However, there are still a few inflammatory diseases (such as vulvovaginitis, salpingitis, and ovarian inflammation) whose correlation with NLRP3 has not been clarified. Based on the pathogenesis and characteristics of inflammatory diseases, an association between the disease and NLRP3 vehicles may be established through their commonalities. Additionally, we may find direct or indirect evidence from them by using different inflammatory cytokines and signalling pathways as mediators, and then verify the correlation between the two.

Based on the data searched in the available literature, we have summarized the mechanism of NLRP3 vesicle activation in gynaecological inflammation and identified therapeutic initiatives targeting NLRP3 vesicles, such as small molecule chemicals, biological agents, and plant extracts. The exploration of gynaecological inflammation and NLRP3 vesicles is still at the basic research level, and more clinical studies are needed in the future. The results of clinical studies can better provide evidence to support the correlation between gynaecological inflammation and NLRP3 vesicles. However, the progress of in-vitro and in-vivo experiments has provided us with confidence to continue exploring the specific mechanism of NLRP3 in gynaecological inflammatory diseases and to study and screen the target active drugs.

In addition, mechanistic evidence suggests that NLRP3 inflammasome activation in gynecologic inflammatory diseases not only drives local tissue inflammation through the release of IL-1β and IL-18, but also amplifies systemic immune dysregulation through pyroptosis-mediated cell death. Recent studies have demonstrated that pharmacologic inhibition or genetic silencing of NLRP3 could reduce inflammatory cytokine levels, limit tissue damage, and improve reproductive outcomes in experimental models. These findings are consistent with our synthesis of the literature and reinforce the potential of NLRP3 as a pivotal therapeutic target. Nevertheless, conflicting data (such as the different roles of mitochondrial ROS in NLRP3 activation) highlight the need for further mechanistic clarification.

Conclusion

This review summarizes the current knowledge about the structure, activation mechanisms, and pathogenic roles of NLRP3 inflammasome in gynecologic inflammatory diseases. Existing evidence underscores that NLRP3 is a central driver and a promising therapeutic target for chronic inflammation, along with potential interventions such as small-molecule inhibitors, plant-derived compounds, and biologics. Although preclinical findings are encouraging, robust clinical studies are needed to validate these strategies, assess long-term safety, and determine their impact on reproductive health. Future work should also focus on identifying the most likely patient subgroups to benefit and on developing targeted delivery systems to maximize therapeutic efficacy while minimizing off-target effects.

Data Sharing Statement

Data will be made available upon request to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interest or personal relationship that could have appeared to influence the work reported in this paper.

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