

Review article

The role of the NLRP3 inflammasome in preeclampsia and implantation failure: A molecular review

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Abstract

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome is a critical molecular sensor for danger signals within the innate immune system. While its role in general inflammatory disorders is well-documented, its specific contribution to reproductive failures remains a critical knowledge gap in maternal-fetal medicine. Preeclampsia and implantation failure represent significant clinical challenges characterized by maladaptive sterile inflammation. This review synthesizes the molecular architecture of NLRP3 and its dual role in health and disease. We specifically examine how NLRP3 dysregulation disrupts the delicate immunological balance at the maternal-fetal interface. By analyzing the mechanisms of hyper-activation and failure within the uterine microenvironment, we highlight potential therapeutic strategies, such as small-molecule inhibitors, to improve obstetric outcomes.

Keywords: Implantation failure, NLRP3 inflammasome, preeclampsia, reproductive immunology, sterile inflammation.

The innate immune system serves as the body's first line of defense, orchestrating rapid responses to cellular stress and pathogenic invasion. Central to this system are inflammasomes, which are large intracellular multiprotein complexes responsible for activating inflammatory processes.^(1,2) Among these, the NLRP3 inflammasome has emerged as a “double-edged sword” in reproductive biology. Successful pregnancy requires a precise, transient inflammatory state for embryo implantation and placentation; however, a breakdown in this regulation is a hallmark of preeclampsia and implantation failure. While general NLRP3 biology is extensively studied, there is a pressing need to connect these fundamental mechanisms directly to the pathophysiological pathways of specific pregnancy complications. This review aims to address this gap by focusing on the molecular triggers and therapeutic targets relevant to PE and IF.⁽³⁾ The NLRP3 inflammasome is often

described as a “double-edged sword”: its activation is essential for host defense and maintaining tissue homeostasis, yet its dysregulation is implicated in the pathophysiology of numerous inflammatory and autoimmune diseases.^(2,4)

Molecularly, the assembly of the canonical NLRP3 inflammasome is a tightly regulated, two-step process. The first step, known as priming, is typically initiated by signals from receptors like toll-like receptors (TLRs), leading to the transcriptional upregulation of key inflammasome components, including *NLRP3* itself and pro-interleukin (IL)-1 β .⁽⁵⁾ The second step, activation, is triggered by a diverse range of stimuli such as ATP efflux, lysosomal rupture, or crystalline structures. This leads to the conformational change and oligomerization of the NLRP3 sensor protein, which then recruits the apoptosis-associated speck-like protein containing a CARD (ASC) adaptor. ASC, in turn, recruits procaspase-1, facilitating its proximity-induced auto-cleavage and activation. Active caspase-1 then cleaves the pro-inflammatory cytokines pro-IL-1 β and pro-IL-18 into their mature, biologically active forms, which are subsequently secreted to mount an inflammatory response.^(1,6)

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The term “NLRP3 inflammasome dysregulation” encapsulates a spectrum of functional imbalances, not limited to one direction. It includes both hyper-activation, an excessive and uncontrolled inflammatory response contributing to chronic diseases like neurodegenerative disorders, cardiovascular diseases, and metabolic syndromes^(4, 7, 8) and hypo-activation, an insufficient or failed response that can impair pathogen clearance and compromise tissue repair. This precise regulation is critical, especially in unique immunological contexts such as pregnancy. Processes like embryo implantation and placentation require a delicate and transient inflammatory balance. Dysregulation of this balance, potentially driven by NLRP3 inflammasome malfunction, is increasingly implicated in devastating pregnancy complications, including implantation failure and preeclampsia, which are characterized by sterile inflammation and immune maladaptation.

While the role of NLRP3 in canonical inflammatory diseases is extensively studied, its specific molecular contributions to reproductive failures remain a fragmented and rapidly evolving field of research. There is a pressing need to synthesize the current molecular evidence to provide a clearer understanding of how NLRP3 inflammasome dysregulation contributes to the pathogenesis of these specific conditions. A critical gap exists in the literature for a comprehensive review that connects the fundamental molecular mechanisms of NLRP3 activation and failure directly to the distinct pathophysiological pathways of implantation failure and preeclampsia.

Therefore, this review aims to address this gap by providing a concise overview of the NLRP3 inflammasome’s molecular architecture and activation; critically analyzing the evidence linking its dysregulation to the pathophysiology of implantation failure; elucidating its mechanistic role in the development of preeclampsia; and discussing emerging therapeutic strategies that target this pathway as potential interventions for these severe pregnancy-related disorders.

Methods

A systematic literature search was conducted across PubMed, Scopus, and Google Scholar databases to identify relevant molecular studies. Primary search terms included “NLRP3 inflammasome,” “preeclampsia,” “implantation failure,” and “maternal-

fetal interface”. We prioritized recent molecular reviews and primary research articles (2015–2025) that specifically discussed NLRP3 in the context of sterile inflammation and reproductive pathology. Data were organized to contrast canonical NLRP3 activation with its specific dysregulation in the uterine microenvironment during early and late gestation

Molecular mechanisms of NLRP3 inflammasome dysregulation

The activity of the NLRP3 inflammasome is exquisitely controlled at multiple molecular checkpoints, and its dysregulation is a multi-faceted process that can originate from genetic predispositions, dynamic protein modifications, and failures in cellular homeostasis. At the most fundamental level, the integrity of the *NLRP3* gene itself is paramount. Gain-of-function mutations, such as those identified in Cryopyrin-Associated Periodic Syndromes (CAPS), create a protein with a lower activation threshold, leading to constitutive inflammasome assembly and excessive IL-1 β secretion from minimal stimuli.⁽⁹⁻¹¹⁾ Beyond these fixed genetic errors, the NLRP3 protein is subject to a complex network of post-translational modifications (PTMs) that act as dynamic “accelerators” and “brakes”. For instance, phosphorylation by kinases like MINK1 can prime the inflammasome for activation, while ubiquitination serves a dual role: K48-linked ubiquitination targets NLRP3 for degradation to terminate the signal, whereas K63-linked ubiquitination can enhance its assembly.^(12, 13) Similarly, SUMOylation and deSUMOylation by enzymes like TRIM28 and SENP3, respectively, toggle the stability of the NLRP3 protein, thereby fine-tuning the potential for an inflammatory response.^(14, 15)

The activation of the NLRP3 inflammasome is intimately tied to the health of cellular organelles, which serve as sentinel platforms for detecting danger. Mitochondrial dysfunction is a primary trigger, releasing potent activating signals like mitochondrial reactive oxygen species (mROS) and oxidized mitochondrial DNA (mtDNA) into the cytosol.^(16, 17) In parallel, lysosomal damage, often caused by crystalline substances or pathogens, leads to the release of cathepsins, which also initiate inflammasome assembly.^(18, 19) While these events are normal responses to acute stress, pathological dysregulation occurs when the cell’s quality control systems fail. A critical homeostatic process is autophagy (specifically mitophagy), which is responsible for clearing damaged

mitochondria. The failure of autophagy leads to an accumulation of dysfunctional mitochondria, creating a persistent source of activating signals that drive chronic, sterile inflammation.⁽¹⁷⁾ Likewise, inefficient lysosomal repair mechanisms can result in sustained inflammasome activation, transforming a protective response into a detrimental one.⁽²⁰⁾

Ultimately, the final output of the NLRP3 inflammasome is governed by a complex interplay of its core components with a host of accessory regulatory proteins. These proteins determine the threshold and magnitude of the response. The kinase NEK7, for example, is an essential positive regulator that directly binds NLRP3 to facilitate its oligomerization, acting as a critical checkpoint for activation.⁽²¹⁾ Conversely, proteins such as CARD9 can function as negative regulators, reining in the response to prevent excessive inflammation.⁽²²⁾ Therefore, NLRP3 dysregulation should be viewed not just as a failure of a single molecule, but as a network collapse. A breakdown at any point whether from a genetic mutation, an imbalance in PTMs, chronic organellar stress, or the malfunction of a key regulatory protein can tip the scales towards either pathological hyper activation, contributing to inflammatory diseases, or insufficient activation (hypo-activation), leading to compromised host defense.

Consequences of NLRP3 hyper-activation: A molecular cascade of damage

While essential for acute host defense, the persistent and excessive activation or hyper-activation of the NLRP3 inflammasome is a central pathological mechanism driving a diverse range of non-communicable chronic inflammatory diseases. This dysregulation can stem from intrinsic genetic defects, sustained metabolic stress, or the accumulation of pathological protein aggregates. Understanding these distinct activation contexts reveals how NLRP3 converts varied danger signals into sustained, tissue-damaging inflammation.

The clearest example of intrinsic NLRP3 hyper-activation is observed in Cryopyrin-Associated Periodic Syndromes (CAPS), a group of autoinflammatory diseases caused by gain-of-function mutations in the *NLRP3* gene. These mutations result in a constitutively active inflammasome that operates independently of canonical activation signals, leading to the relentless processing and secretion of IL-1 β and IL-18.^(23, 24) Molecularly, this occurs as mutated

NLRP3 proteins spontaneously form cryo-sensitive aggregates that serve as scaffolds for inflammasome assembly, a process further enhanced by cold exposure and dependent on calcium influx.⁽²⁵⁾ This constant inflammasome activity, fueled by enhanced caspase-1 cleavage, not only drives systemic cytokine production but also induces pyroptosis, a pro-inflammatory form of cell death that amplifies tissue damage and perpetuates the inflammatory cycle.^(26, 27)

Beyond rare genetic disorders, NLRP3 hyper-activation is a critical sensor of metabolic dysregulation, linking metabolic stress to chronic inflammation in prevalent conditions like atherosclerosis, gout, and type 2 diabetes. In these diseases, endogenous metabolic danger signals act as potent inflammasome triggers. For instance, cholesterol crystals within atherosclerotic plaques, monosodium urate (MSU) crystals in gouty joints, and high glucose or excess fatty acids in diabetes all converge on NLRP3 activation.⁽²⁸⁻³⁰⁾ The underlying molecular pathways are often shared and involve organellar stress. These metabolic triggers frequently induce mitochondrial dysfunction, leading to the overproduction of reactive oxygen species (ROS), which activates the NF- κ B pathway and subsequent transcription of inflammasome components.^(31, 32) Concurrently, triggers like cholesterol or MSU crystals can cause lysosomal damage upon phagocytosis, while disturbances in cellular ionic fluxes, particularly potassium efflux, provide a common downstream signal for inflammasome assembly.^(33, 34) This chronic, low-grade activation of NLRP3 in metabolic tissues contributes directly to disease pathology, promoting plaque formation in arteries, joint inflammation in gout, and insulin resistance in diabetes.⁽³⁵⁾

In the context of the central nervous system, the NLRP3 inflammasome in microglial cells functions as a key sensor of proteotoxic stress, driving neuroinflammation in neurodegenerative diseases. Pathological protein aggregates, such as amyloid-beta (A β) in Alzheimer's disease and alpha-synuclein (α -syn) in Parkinson's disease, are recognized by microglia and trigger potent NLRP3 activation. This activation can be initiated through receptor-mediated pathways, such as the P2X7 receptor for A β or Toll-like receptors for α -syn, or via lysosomal damage following the phagocytosis and failed degradation of these protein fibrils.^(36, 37) Once activated, the microglial inflammasome unleashes a cascade of

downstream events detrimental to neuronal health. The sustained release of IL-1 β and IL-18 fosters a chronic neuroinflammatory environment, while the activation of caspase-1 can also induce neuronal pyroptosis, a lytic form of cell death that contributes directly to neurodegeneration.^(38, 39) This persistent, inflammasome-driven neuroinflammation is a critical factor in synaptic dysfunction, cognitive decline, and the overall progression of these debilitating diseases.

Pathophysiological consequences of NLRP3 inflammasome failure and dysregulation

While NLRP3 hyper-activation is a known driver of many chronic inflammatory diseases, the failure of the inflammasome to activate when required a state of hypo-activation or immune evasion poses a significant threat to host defense. A primary physiological role of the NLRP3 inflammasome is to detect and respond to invading pathogens. Consequently, its failure compromises the immune system's ability to control specific infections. Many pathogens have evolved sophisticated molecular strategies to actively inhibit or evade detection by the NLRP3 inflammasome. For example, *Pseudomonas aeruginosa* produces the pigment pyocyanin, which generates intracellular reactive oxygen and nitrogen species that post-translationally inhibit NLRP3 speck formation and caspase-1 maturation.⁽⁴⁰⁾ Similarly, intracellular pathogens like *Brucella abortus* modulate nitric oxide signaling to regulate IL-1 β secretion, while the parasite *Leishmania donovani* directly inhibits caspase-1 activation, effectively preventing the maturation of pro-inflammatory cytokines and evading the host inflammatory response.^(41, 42) Viruses also employ a wide array of complex strategies to target and modulate inflammasome components, underscoring the critical role of NLRP3 as a central hub in antiviral immunity.^(43, 44)

The role of the NLRP3 inflammasome in cancer is notably dichotomous, where both its failure and its chronic activation can have profound, albeit opposing, effects on tumor progression. A failure of NLRP3 activation within the tumor microenvironment (TME) can significantly impede an effective anti-tumor response. The acute, regulated activation of the NLRP3 inflammasome is crucial for secreting IL-1 β and IL-18, cytokines that promote the recruitment and activation of cytotoxic CD8⁺ T cells and dendritic cells, which are essential for tumor clearance.⁽⁴⁵⁾ Therefore, an inability to activate NLRP3 can lead to

a “cold” or non-inflamed TME that is permissive to tumor growth.⁽⁴⁶⁾ Conversely, chronic and persistent NLRP3 activation can paradoxically promote tumorigenesis. The sustained release of IL-1 β can foster a pro-tumorigenic niche that supports tumor growth, angiogenesis, and metastasis.^(47, 48) This has been demonstrated in breast and colorectal cancers, where NLRP3-driven IL-1 β promotes epithelial-mesenchymal transition (EMT) and metastatic potential.⁽⁴⁹⁻⁵¹⁾ Furthermore, in contexts like pancreatic cancer, chronic NLRP3 signaling can drive the expansion of immunosuppressive cells, such as regulatory T cells, which actively suppress anti-tumor immunity.⁽⁵²⁾

Beyond its role in fighting infections and cancer, controlled and transient NLRP3 activation is fundamental to maintaining tissue homeostasis, particularly in processes like the clearance of apoptotic cells (efferocytosis) and the initiation of tissue repair. Proper inflammasome function helps facilitate the resolution of inflammation following injury or stress. A failure in this finely tuned regulatory function can lead to the accumulation of apoptotic debris, which undergoes secondary necrosis and releases damage-associated molecular patterns (DAMPs). This accumulation of DAMPs can trigger a secondary, uncontrolled inflammatory response that the system fails to resolve. This state of unresolved inflammation is a key contributor to the pathogenesis of numerous chronic diseases and can lead to maladaptive tissue repair. Instead of regeneration, the persistent inflammatory environment promotes the activation of fibroblasts and excessive deposition of extracellular matrix, culminating in pathological fibrosis, a hallmark of chronic organ damage.

Therapeutic strategies targeting the NLRP3 inflammasome pathway

The central role of the NLRP3 inflammasome in numerous inflammatory diseases has made it a highly attractive target for therapeutic intervention. The most advanced strategy involves the development of small-molecule inhibitors that directly target the NLRP3 protein to prevent its activation and the subsequent inflammatory cascade. A diverse array of chemical scaffolds has been explored, including tertiary sulfonamide compounds, 4-oxo-2-thioxo-thiazolidinone derivatives, and sulfonamide-based molecules.⁽⁵³⁻⁵⁵⁾ The diarylsulfonamide MCC950 is the most extensively studied benchmark inhibitor, demonstrating

significant efficacy in a wide range of preclinical inflammatory disease models.^(56 - 58) These direct inhibitors employ varied molecular mechanisms of action; some, like BOT-4-one, alkylate NLRP3 to inhibit its critical ATPase activity, while others prevent the homo-oligomerization of the pyrin domain (PYD) required for inflammasome assembly [59][60]. MCC950 itself is understood to block the crucial interaction between NLRP3 and the kinase NEK7, a necessary step for inflammasome activation.⁽⁵⁸⁾ While many of these compounds remain in preclinical development, the progress of MCC950 and its derivatives into clinical trials represents a significant milestone in the field.

Beyond direct inhibition of the NLRP3 protein, the therapeutic landscape includes strategies that target the pathway at both upstream and downstream points. Targeting downstream effector molecules is a clinically validated approach, with the anti-IL-1 β monoclonal antibody Canakinumab being a prime example. Clinical trials have demonstrated its efficacy in reducing the recurrence of ischemic events in cardiovascular disease, showcasing the therapeutic benefit of blocking a key product of inflammasome activation.^(61, 62) However, this approach is limited to neutralizing IL-1 β and does not affect the secretion of IL-18 or the induction of pyroptosis, both of which are also NLRP3-dependent. Furthermore, anti-IL-1 therapies are associated with an increased risk of infections, highlighting a potential safety liability.⁽⁶²⁾ In contrast, direct NLRP3 inhibitors offer a more comprehensive blockade of all downstream consequences and have shown promising preclinical safety profiles.⁽⁶³⁾ An alternative strategy involves targeting upstream triggering signals, such as mitochondrial dysfunction or post-translational modifications like acetylation, which are required for full NLRP3 activation.^(32, 64) Intervening at this level could prevent the initial activation signal, offering a prophylactic approach to dampening pathological inflammation.

In stark contrast to inhibition, an emerging and highly experimental therapeutic strategy involves the controlled activation of the NLRP3 inflammasome. The rationale for this approach is to harness the potent pro-inflammatory power of the inflammasome to enhance immune responses in contexts where they are suboptimal, such as in cancer immunotherapy or

during certain infections. Investigational approaches include the development of synthetic NLRP3 agonists, the use of PAMPs, or the deployment of nanoparticle-based systems to deliver activating signals directly to target immune cells. However, this strategy is fraught with significant molecular challenges and safety risks. Achieving specific, transient, and localized activation of NLRP3 without causing systemic, off-target inflammation is a major hurdle. The primary safety concern is the potential for inducing excessive inflammation or a “cytokine storm,” which can be life-threatening. Furthermore, chronic or repeated activation carries the theoretical risk of promoting autoimmunity or fostering an inflammatory environment conducive to other pathologies. Therefore, while therapeutically intriguing, the development of NLRP3 agonists requires a deep understanding of its regulatory mechanisms to ensure a controlled and beneficial immune response.

Conclusion

The NLRP3 inflammasome stands as a pivotal, yet profoundly volatile, component of the innate immune system. As this review has articulated, its capacity to function as both a guardian against a myriad of danger signals and a potent driver of pathology underscores its characterization as a molecular “double-edged sword”. The evidence synthesized herein strongly implicates the dysregulation of the NLRP3 inflammasome as a central mechanistic contributor to the sterile inflammation underpinning implantation failure and preeclampsia. An imbalance, whether manifesting as sustained hyper-activation within the uteroplacental interface or a systemic failure to resolve inflammation, disrupts the delicate immunological equilibrium required for a successful pregnancy.

The NLRP3 inflammasome is a pivotal driver of the sterile inflammation underpinning implantation failure and preeclampsia. Future research must move beyond general biology to define the precise triggers whether metabolic or stress-related that activate this pathway at different stages of gestation. Understanding the context-specific roles of hyper- versus hypo-activation will be critical for developing safe, targeted interventions to improve maternal and fetal outcomes.

Author contributions

ABS served as the lead author, conceptualized the study, and developed the core ideas for this manuscript. MTD served as the second author and assisted the lead author in writing and preparing the manuscript. LS served as the supervisor, providing guidance, mentorship, and critical review throughout the writing process to improve the quality of the manuscript.

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Conflict of interest statement

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

Data sharing statement

The present review is based on the references cited. All data generated or analyzed during the present study are included in this published article and the citations herein. Further details, opinions, and interpretation are available from the corresponding author on reasonable request.

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