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## EDITED BY

Dan Jane-wit,  
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## REVIEWED BY

Xin Hu,  
National Center for Child Health and  
Development (NCCHD), Japan  
Ling Yin,  
Hefei Comprehensive National Science Center  
Data Space Research Institute, China

## \*CORRESPONDENCE

Hong-tao Jiang  
✉ jht20032003@163.com

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# Research advances on NLRP3 inflammasomes in organ transplantation

Kun Wang<sup>1</sup>, Hong Luo<sup>1</sup>, Xiao-jie Ma<sup>2</sup>, Yu Zhang<sup>1</sup>,  
Yu-xiang Chen<sup>1</sup>, Tao Li<sup>1</sup>, Yi Wang<sup>1</sup> and Hong-tao Jiang<sup>1\*</sup>

<sup>1</sup>Department of Renal Transplantation, The Second Affiliated Hospital of Hainan Medical University, Haikou, China, <sup>2</sup>Department of Rehabilitation Therapy, The Second Affiliated Hospital of Hainan Medical University, Haikou, China

Organ transplantation is a life-saving therapy for end-organ failure; however, long-term outcomes are limited by complications such as ischemia-reperfusion injury (IRI), allograft rejection, and infection. The NLRP3 inflammasome, a key innate immune signaling platform, plays a central role in driving inflammation in these settings. Its activation follows a two-signal paradigm and contributes critically to tissue damage during IRI, bridges innate and adaptive immunity in acute and chronic rejection, and exerts context-dependent roles, either protective or detrimental, during infection. Although targeting NLRP3 through genetic, pharmacological, or cellular approaches shows therapeutic promise in preclinical studies, clinical translation remains challenging. Future efforts should focus on refining these strategies and elucidating its interplay within broader immune networks to improve transplant outcomes.

## KEYWORDS

**caspase-1, damage-associated molecules, ischemia-reperfusion injury, NLRP3 inflammasome, organ transplantation**

## 1 Introduction

Organ transplantation, a revolutionary breakthrough in modern medicine, has become a core therapeutic approach for saving lives in patients with end-stage failure of vital organs such as the heart, liver, and kidneys. Since the first successful kidney transplant, advancements in surgical techniques, iterations of immunosuppressive agents, and optimized perioperative management have significantly improved short-term survival rates and quality of life for transplant recipients (1). According to global organ transplant registry data, the 1-year survival rate for kidney transplant recipients now exceeds 95% (2), while the 5-year survival rate for liver transplant recipients remains stable above 70% (3). This medical achievement has brought renewed hope to countless patients facing terminal illness.

However, the three core postoperative complications, ischemic reperfusion injury (IRI), acute/chronic rejection, and secondary microbial infection, remain critical bottlenecks constraining graft long-term survival and recipient prognosis (4–6). Ischemia-reperfusion injury, an unavoidable pathological event during transplantation, can cause early graft

dysfunction. Its incidence is particularly pronounced in liver transplantation, with severe cases directly leading to primary graft failure (7, 8). Rejection, representing the immune system's recognition and attack of the "foreign organ," occurs in a small proportion of recipients within the first year post-surgery despite potent immunosuppressive therapy. The immunosuppression required for long-term organ preservation compromises immune function, exposing recipients to a higher risk of infection than the general population. With expanding age restrictions and inclusion of more severely ill patients, the indications for organ transplantation continue to broaden (9), further increasing the incidence of post-transplant infectious complications.

In-depth studies reveal that the development of these complications is closely linked to uncontrolled inflammatory responses. As a vital component of innate immunity, inflammation initiates tissue repair mechanisms during the early post-transplant phase (10). However, excessive activation triggers an "inflammatory storm" (11), leading to graft tissue structural damage, vascular endothelial injury, and disruption of immune tolerance (10). Within this intricate inflammatory regulatory network, inflammasomes, multiprotein complexes assembled by intracellular pattern recognition receptors, serve as central regulators (12). By sensing danger signals in the transplant microenvironment, such as ATP released from damaged cells or transplant-associated oxidative stress products, it activates caspase-1, thereby promoting the maturation and release of proinflammatory cytokines IL-1 $\beta$  and IL-18, triggering a cascade of inflammatory responses (13). Among the more than ten inflammasomes identified, NLRP3 has emerged as a research hotspot in organ transplantation due to its diverse activation mechanisms (responding to metabolic disturbances, oxidative stress, pathogen invasion, and other stimuli) and high expression in multiple transplant-related disease models. Numerous animal studies confirm that inhibiting NLRP3 inflammasome activity significantly reduces IRI severity after heart transplantation (14), diminishes inflammatory responses and apoptosis in kidney transplantation (15), and decreases infection complications following lung transplantation. These findings provide novel insights into the molecular mechanisms of transplant complications and lay a theoretical foundation for developing novel inflammasome-targeted therapeutic strategies.

Therefore, systematically elucidating the mechanisms of NLRP3 inflammasome in organ transplantation and clarifying its regulatory networks in IRI, rejection, and infection holds significant theoretical value and clinical translational implications for overcoming current therapeutic bottlenecks and achieving long-term graft survival.

## 2 Structure and activation mechanism of the NLRP3 inflammasome

### 2.1 Structural features and molecular assembly mechanism of the NLRP3 inflammasome

As one of the most extensively studied members of the NOD-like receptor (NLR) family, the NLRP3 inflammasome serves as a

key molecular platform regulating innate immune responses and inflammatory reactions (Figure 1). Its core structure comprises the NLRP3 protein, apoptosis-related spot-like protein (ASC), and caspase-1 (Caspase-1). These three components form a functional complex through precise domain interactions, playing an irreplaceable role in recognizing danger signals and initiating inflammatory cascades.

#### 2.1.1 Domain composition and functional characteristics of NLRP3 protein

As the core recognition unit of the inflammasome, the NLRP3 protein exhibits a typical three-domain molecular structure, with each domain performing specific functions in signal sensing and complex assembly.

The N-terminal pyrophosphorylated domain (PYD) belongs to the death domain superfamily, comprising a conserved folding structure of six  $\alpha$ -helices. This domain forms a stable heterodimer through homodimeric interactions with the PYD domain of ASC protein via a conserved hydrophobic interface, constituting the initial molecular event in inflammasome assembly (16, 17). Studies indicate that mutations in key amino acid residues within the  $\alpha$ 2 and  $\alpha$ 3 helical regions of the PYD domain significantly inhibit NLRP3-ASC binding efficiency, thereby blocking downstream signaling (18).

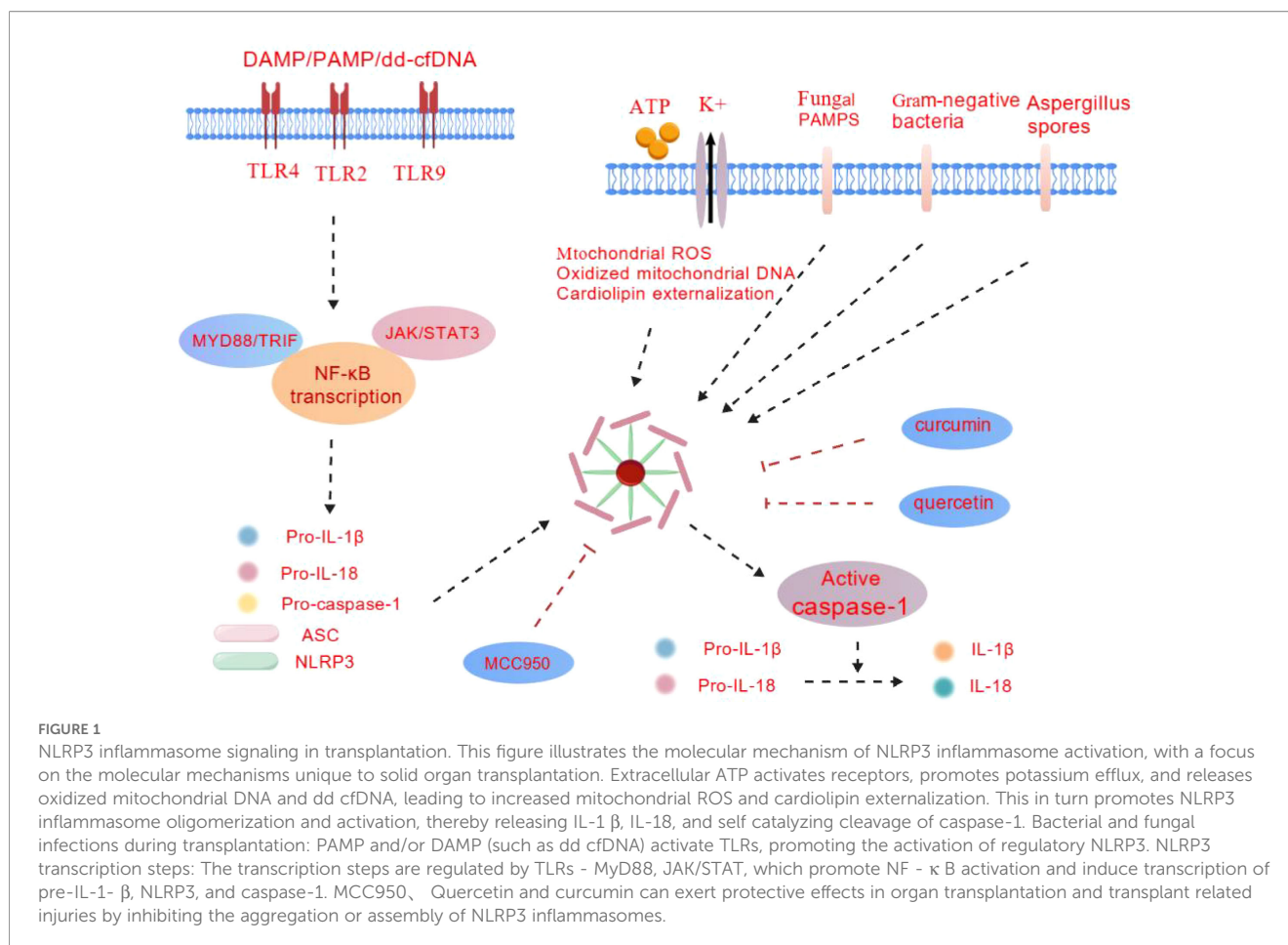
The intermediate nucleotide-binding and oligomerization domain (NACHT) is a hallmark domain of the NLR family, containing conserved Walker A and Walker B motifs and possessing ATPase activity (19). In the resting state, the NACHT domain maintains an autoinhibitory conformation through intramolecular interactions with the LRR domain. Upon activation by signals, its ATPase activity is triggered. The binding and hydrolysis of ATP drive NLRP3 to undergo conformational rearrangement, releasing the autoinhibition and mediating protein oligomerization to form a functional polymeric scaffold (20). Recent cryo-EM studies confirm that activated NLRP3 forms oligomers with hexagonal symmetry, providing a spatial platform for subsequent recruitment of adaptor proteins.

The C-terminal leucine-rich repeat (LRR) domain comprises multiple leucine repeat units, forming a curved horseshoe structure. As the core region for pattern recognition, this domain identifies various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through conformational changes (21). Notably, the LRR domain not only participates in danger signal recognition but also regulates the activation threshold of NLRP3 through dynamic interactions with the NACHT domain. This self-regulatory mechanism constitutes a crucial molecular basis for maintaining immune homeostasis.

#### 2.1.2 The bridging function and structural basis of ASC

Apoptosis-related spot-like protein (ASC), a key signaling adaptor molecule, mediates functional coupling between NLRP3 and Caspase-1 through a molecular bridging action facilitated by its dual domains (22).

The ASC molecule comprises an N-terminal PYD domain and a C-terminal caspase recruitment domain (CARD), connected by a



flexible linker. This structural feature enables simultaneous recognition and binding of upstream sensors and downstream effector molecules (23). Its PYD domain forms a stable complex with the PYD domain of NLRP3 through a specific hydrogen bond network, while the C-terminal CARD domain undergoes homodimeric interaction with the CARD domain of Caspase-1, establishing a continuous signaling pathway (24).

During inflammasome assembly, ASC not only serves as a linker but also forms fibrillar aggregates via the aggregation properties of its own PYD domain. This “speckle-like” supramolecular structure significantly increases local protein concentration, promoting the oligomerization and activation of Caspase-1. Recent studies reveal that ASC fibers exhibit a core-shell structure: the core consists of a fiber scaffold formed by PYD-PYD interactions, while the shell comprises an ordered arrangement of CARD domains. This structural arrangement efficiently mediates effector molecule activation (25).

### 2.1.3 Activation mechanism and substrate specificity of caspase-1

As an effector molecule of inflammasomes, Caspase-1 belongs to the cysteine protease family. Its activation process involves precise conformational changes and proteolytic events (26).

In its inactive state, Caspase-1 exists as a pro-enzyme (pro-Caspase-1), comprising an N-terminal CARD domain, a large subunit (p20), and a small subunit (p10) (27). Upon forming a complex with ASC and NLRP3, pro-Caspase-1 undergoes oligomerization through CARD domain interactions, inducing intramolecular proteolysis and releasing the catalytically active p20/p10 heterodimer. Activated Caspase-1 specifically cleaves substrate proteins at aspartic acid residues through nucleophilic attack on cysteine residues (28). Its primary physiological substrates include pro-IL-1 $\beta$  and pro-IL-18; cleavage by Caspase-1 removes the N-terminal precursor peptide, yielding mature IL-1 $\beta$  and IL-18 (29). These active cytokines are released extracellularly via non-classical secretory pathways, initiating downstream inflammatory cascades that recruit and activate immune cells, thereby enhancing local immune responses (30). Notably, Caspase-1 activation is also closely associated with pyroptosis. By cleaving substrate molecules such as gasdermin D, it mediates inflammatory cell death, a process crucial for clearing intracellular pathogens (31).

### 2.1.4 Assembly kinetics and structural regulation of the inflammasome

The assembly of the NLRP3 inflammasome is a highly ordered dynamic process involving multiple structural transitions and molecular recognition events to form a complete signaling pathway.

During the initiation phase, LRR domain recognition of danger signals triggers NLRP3 conformational rearrangement, activating the ATPase activity of the NACHT domain. This drives protein oligomerization to form a primary complex. Subsequently, oligomerized NLRP3 recruits ASC molecules via PYD-PYD interactions, forming an intermediate complex. ASC molecules self-assemble into fibrillar structures while recruiting pro-Caspase-1 via their CARD domains, ultimately forming the mature inflammasome complex (Figure 1). Within this complex, pro-Caspase-1 undergoes self-cleavage activation, initiating the maturation and release of downstream inflammatory cytokines (32).

This assembly process undergoes multi-level regulation influenced by factors including post-translational modifications (phosphorylation, ubiquitination, etc.), ion concentration changes, and cellular metabolic states. Elucidating the structural characteristics and assembly mechanisms of the NLRP3 inflammasome not only advances our understanding of the molecular basis of innate immunity but also provides critical structural biology insights for targeted therapies in inflammation-related diseases.

## 2.2 Activation mechanism and regulatory network of the NLRP3 inflammasome

The activation of the NLRP3 inflammasome is a finely regulated multistep process, characterized by a “dual-signal activation model” (33). This model employs hierarchical signal regulation to ensure rapid inflammatory responses to danger signals while maintaining strict activation thresholds to prevent tissue damage from excessive inflammation. In recent years, the molecular details of this activation mechanism have been progressively revealed through techniques such as single-molecule imaging and cryo-electron microscopy.

### 2.2.1 Signal 1: molecular conduction pathway of initiating signals

Signal 1 serves as the preparatory step for inflammasome activation, primarily initiating the transcriptional expression of relevant molecules through pattern recognition receptor-mediated signaling pathways, thereby laying the material foundation for subsequent activation.

The Toll-like receptor (TLR) family serves as the primary receptor for transmitting the initiation signal. Specifically, TLR4 recognizes lipopolysaccharide (LPS), TLR3 detects viral double-stranded RNA, TLR2 identifies bacterial peptidoglycan, and other pathogen-associated molecular patterns (PAMPs), while TLR9 recognizes damage-associated molecular patterns (DAMPs) such as endogenous DNA (34). Upon ligand binding, these receptors initiate downstream signaling cascades by recruiting intracellular adaptor proteins MyD88 or TRIF: MyD88 recruits IRAK4 and IRAK1 to form a signaling complex, activating TAK1 kinase, which subsequently phosphorylates the IKK complex (IKK $\alpha$ / $\beta$ / $\gamma$ ). This leads to the phosphorylation and degradation of the NF- $\kappa$ B

inhibitor I $\kappa$ B $\alpha$ , releasing the NF- $\kappa$ B dimer (p65/p50) for translocation to the nucleus, where it initiates target gene transcription (35).

This transcriptional regulation primarily promotes the expression of three types of molecules: NLRP3 protein itself, pro-inflammatory cytokine precursors pro-IL-1 $\beta$  and pro-IL-18, and certain inflammasome regulatory molecules. Notably, gene expression profiles induced by different activation signals exhibit distinct patterns: bacterial PAMPs predominantly upregulate NLRP3 and pro-IL-1 $\beta$  expression, whereas viral infection more significantly promotes pro-IL-18 transcription. This selective regulation may correlate with distinct pathogen immune evasion strategies (36, 37). Recent studies reveal that Signal 1 also modulates chromatin accessibility in the NLRP3 promoter region via epigenetic modifications, enabling fine-tuned regulation of its expression levels (38).

### 2.2.2 Signal 2: molecular trigger mechanism of activation signals

Signal 2 serves as the “trigger signal” for NLRP3 inflammasome assembly, initiating the formation of functional inflammasome complexes by inducing NLRP3 conformational rearrangement and oligomerization (39). Multiple intracellular environmental changes have been confirmed as potential Signal 2s, converging on NLRP3 activation pathways through distinct molecular mechanisms.

Ion homeostasis disruption stands as one of the most well-established activation signals. Among these, potassium efflux is considered the most conserved activation mechanism: when cells are stimulated by ATP (via P2X7 receptors), nigericin, or similar agents, the opening of ion channels in the cell membrane leads to changes in intracellular potassium concentration. This directly disrupts the self-inhibitory interaction between NLRP3 and its LRR domains, promoting conformational rearrangement (40). Recent cryo-EM structures reveal that hypokalemic conditions induce exposure of the ATP-binding site within the NACHT domain of NLRP3, establishing the structural foundation for subsequent oligomerization (41). Additionally, calcium influx participates in NLRP3 activation regulation by activating calmodulin-dependent kinase II (CaMKII), though its precise molecular targets require further elucidation (42).

Reactive oxygen species (ROS) accumulation represents another critical activation signal, primarily originating from mitochondrial respiratory chain dysfunction or NADPH oxidase activation. Mitochondrial ROS can alter NLRP3's conformation by oxidizing key cysteine residues while promoting mitochondrial DNA (mtDNA) release into the cytoplasm. Released mtDNA directly enhances NLRP3 activation by binding to its LRR domain (43). Studies confirm that the antioxidant N-acetylcysteine (NAC) significantly inhibits urate crystal-induced NLRP3 activation, providing experimental evidence for the critical role of ROS (44).

Lysosomal damage-mediated activation signals are primarily associated with crystalloid substances (e.g., uric acid crystals, asbestos fibers). Upon entering cells via endocytosis, these substances physically disrupt lysosomal membrane integrity, leading to the release of lysosomal proteases (e.g., cathepsin B)

into the cytoplasm (45). Cathepsin B releases NLRP3 from its autoinhibited state by cleaving specific sites on NLRP3 or degrading its inhibitory proteins (46).

Mitochondrial dysfunction contributes to activation through multiple mechanisms: beyond releasing ROS and mtDNA, cardiolipin released from damaged mitochondria directly binds to NLRP3, while inhibition of mitophagy leads to accumulation of damaged mitochondria, further amplifying the activation signal (47). Recent studies reveal that the formation of the mitochondria-endoplasmic reticulum contact site (MAM) can recruit NLRP3 and associated signaling molecules, creating localized activation microdomains (48).

### 2.2.3 Synergistic regulation and spatiotemporal coupling of dual signals

Activation of the NLRP3 inflammasome is not a simple summation of two signals but involves precise spatiotemporal coordination. NLRP3 protein synthesis induced by Signal 1 must reach a threshold concentration to respond to Signal 2. This “dose-dependent” characteristic prevents accidental activation of NLRP3 at low expression levels.

Temporally, Signal 1 typically precedes Signal 2, providing sufficient protein reserves for inflammasome assembly. The duration of Signal 2 determines inflammatory response intensity, brief stimulation triggers localized activation, while sustained stimulation leads to systemic cytokine release.

Spatially, NLRP3 activation occurs within specific intracellular microdomains: at endoplasmic reticulum-mitochondrial contact sites, NLRP3 interacts with the adaptor protein ASC via their PYD domains to form an initial complex, followed by the recruitment and activation of Caspase-1 (49–51). This spatial confinement ensures controlled transmission of inflammatory signals, preventing disruption to core cellular functional zones.

### 2.2.4 Post-activation regulatory network

Following NLRP3 inflammasome activation, multi-level negative feedback regulation persists to prevent excessive inflammation-induced tissue damage. At the transcriptional level, IL-1 $\beta$  downregulates NLRP3 expression by activating IL-1 receptors. At the post-translational modification level, ubiquitination (e.g., K48-linked ubiquitination mediated by TRIM31) and phosphorylation (e.g., Ser295 phosphorylation mediated by AMPK) promote NLRP3 degradation or inhibit its oligomerization (52, 53). Furthermore, autophagy constitutes a crucial negative feedback loop by selectively degrading activated inflammasome complexes (54).

These intricate regulatory mechanisms collectively maintain the activation equilibrium of the NLRP3 inflammasome, whose dysregulation is closely associated with various inflammatory diseases (e.g., gout, Alzheimer’s disease, atherosclerosis). Elucidating its molecular activation mechanisms provides a critical theoretical foundation for developing specific anti-inflammatory drugs targeting NLRP3.

## 3 Role of NLRP3 inflammasome in organ transplantation-related complications

### 3.1 NLRP3 inflammasome and ischemia-reperfusion injury

The NLRP3 inflammasome plays a pivotal role in IRI-mediated inflammation (55). Ischemia-reperfusion injury (IRI) is a common and severe early complication following organ transplantation, adversely affecting graft functional recovery and long-term survival. During IRI, the ischemic phase induces tissue hypoxia, impaired energy metabolism, disrupted intracellular homeostasis, impaired mitochondrial function, and increased reactive oxygen species (ROS) production. Reperfusion then floods tissues with oxygen molecules, further exacerbating oxidative stress while activating the innate immune system and triggering inflammatory responses (56–59). When donor organs undergo ischemia-reperfusion, factors such as mitochondrial damage and lysosomal leakage stimulate cells to produce abundant DAMPs, including heat shock proteins, mtDNA, and ATP, which activate the NLRP3 inflammasome (60, 61). The activated NLRP3 inflammasome promotes the cleavage of pro-Caspase-1 into active Caspase-1, which cleaves pro-IL-1 $\beta$  and pro-IL-18, leading to their maturation and release into the extracellular space. This triggers downstream inflammatory cascades, resulting in tissue injury and organ dysfunction (62–64).

In kidney transplantation, IRI causes damage to renal tubular epithelial cells, microvascular dysfunction, and inflammatory cell infiltration in the renal interstitium. Studies indicate that inhibiting NLRP3 inflammasome activity can mitigate renal IRI injury and improve renal function (65, 66). For instance, in a mouse kidney transplantation model treated with the NLRP3-specific inhibitor MCC950, significant reductions were observed in renal tissue expression of NLRP3, ASC, and Caspase-1. This treatment also decreased IL-1 $\beta$  and IL-18 release, mitigated tubular injury and interstitial inflammation, and improved graft survival (67). In liver transplantation, IRI similarly activates the NLRP3 inflammasome, triggering inflammatory responses that lead to hepatocyte apoptosis and impaired liver function. Inhibiting the NLRP3 inflammasome mitigates hepatic IRI injury and promotes liver function recovery (68). Related studies indicate that knockout of the NLRP3 gene in mice using gene knockout technology significantly reduces inflammatory injury in the liver and markedly improves liver function indicators in a liver transplantation IRI model.

In heart transplantation, IRI can lead to myocardial cell necrosis, myocardial interstitial edema, and arrhythmia. NLRP3 inflammasome is rapidly activated in myocardial IRI, and the released IL-1 $\beta$  can exacerbate myocarditis infiltration. Inhibiting NLRP3 activity can significantly reduce myocarditis and improve the contractile function of the transplanted heart (69). In lung transplantation, IRI leads to a significant release of intracellular ATP and its conversion into extracellular ATP (eATP), which activates the purinergic receptor P2X7 to initiate NLRP3

inflammasome assembly; After activation, the inflammasome mediates the mature release of IL-1  $\beta$  and IL-18, inducing neutrophil infiltration on one hand, and triggering apoptosis of alveolar epithelial cells and downregulating the expression of tight junction proteins such as Claudin-5 and Occludin on the other hand, ultimately leading to alveolar barrier disruption and pulmonary edema (70).

### 3.2 NLRP3 inflammasome and rejection reactions

Rejection, representing the immune system's "recognition-attack" response to the graft post-transplantation, is categorized into three major types based on timing, immune mechanisms, and pathological features: hyperacute rejection, acute rejection, and chronic rejection. As a key cross-linking molecule between innate and adaptive immunity, the NLRP3 inflammasome plays a crucial role in the initiation, amplification, and maintenance of various rejection responses. Its activation mechanisms and pathological effects exhibit distinct stage-specificity (71).

Hyperacute rejection, a severe immune response occurring within minutes to hours after transplantation, is primarily triggered by the binding of recipient pre-existing antibodies (such as anti-HLA antibodies and ABO blood group antibodies) to antigens on the surface of graft vascular endothelial cells. This process is accompanied by rapid activation of the complement system and thrombosis. Recent studies reveal that the NLRP3 inflammasome exacerbates tissue injury through the "complement-NLRP3 axis": C5a fragments generated by complement activation directly bind to C5aR on neutrophil surfaces, triggering intracellular potassium efflux and reactive oxygen species bursts (71, 72), thereby activating the NLRP3 inflammasome. The latter, by releasing IL-1 $\beta$  and IL-18, further recruits neutrophil infiltration and enhances the procoagulant activity of vascular endothelial cells, forming a vicious cycle of "complement activation - inflammasome activation - thrombosis" (73–76). Studies indicate that inhibiting the NLRP3 inflammasome delays the onset of hyperacute rejection and reduces intravascular thrombus area in grafts, suggesting it may serve as a potential target for blocking hyperacute rejection in xenotransplantation.

Acute rejection typically occurs within days to months post-transplantation, characterized by T cell-mediated immune attacks accompanied by extensive inflammatory cell infiltration and graft parenchymal injury. NLRP3 inflammasome exerts a "dual priming effect" during this phase: On one hand, residual damage-associated molecular patterns (DAMPs) in the graft (e.g., heat shock proteins, ATP) directly activate NLRP3 inflammasomes within resident macrophages and dendritic cells (DCs). The released IL-1 $\beta$  promotes T cell activation by upregulating DC surface co-stimulatory molecules (CD80/CD86) (77). On the other hand, IFN- $\gamma$  secreted by activated Th1 cells enhances NLRP3 inflammasome assembly efficiency in macrophages, forming a cascade reaction of "innate immune initiation - adaptive immune amplification" (77). The NLRP3 inflammasome connects innate

and adaptive immunity through the maturation of IL-1 $\beta$  and IL-18; IL-1 $\beta$  promotes Th17 cell differentiation (associated with IL-17 production) and recruits CD4<sup>+</sup>T and CD8<sup>+</sup>T cells to the graft site. In heart transplantation, inflammasome activation has been described as a key driver of "sterile inflammation," participating in the initiation of the adaptive immune response.

Chronic rejection, a major barrier to long-term graft survival, is characterized by chronic graft fibrosis and occlusive vascular lesions, with disease progression spanning years to decades. The NLRP3 inflammasome participates in this pathological process through a "low-level persistent activation" model: on one hand, gut microbiota dysbiosis induced by long-term immunosuppressive therapy can persistently activate the NLRP3 inflammasome via metabolic byproducts (e.g., reduced short-chain fatty acids, translocated lipopolysaccharides), promoting macrophage polarization toward a pro-fibrotic phenotype (78, 79); On the other hand, continuous stimulation of vascular endothelial cells by oxidized LDL and mechanical stress activates NLRP3 inflammasomes, which promote smooth muscle cell proliferation and migration via the IL-1 $\beta$ /IL-18 signaling axis, accelerating the progression of chronic allograft nephropathy (CAN) in kidney transplantation and cardiovascular allograft disease (CAV) in heart transplantation (80). Studies indicate that serum levels of NLRP3 inflammasome-associated markers (e.g., caspase-1 active fragment, IL-1 $\beta$ ) in models of chronic rejection post-kidney transplantation are elevated compared to stable-phase recipients and positively correlate with glomerular sclerosis severity, suggesting its potential as an early warning indicator and intervention target for chronic rejection (81, 82). In the process of fibrosis, NLRP3 can exert its effects through three specific pathways. Firstly, through the IL-1  $\beta$ /MyD88/TGF -  $\beta$ /Smad axis, it activates downstream complexes and initiates TGF -  $\beta$  1 transcription and secretion by binding to IL-1  $\beta$  receptors, thereby activating the Smad pathway to induce ECM related gene expression. This triggers EMT and IF/TA in renal tubular epithelial cells during kidney transplantation, and activates hepatic stellate cells during liver transplantation, leading to liver parenchymal fibrosis (83). Secondly, through the IL-18/JAK/STAT3/CTGF axis, IL-18 activates the JAK/STAT3 pathway to upregulate CTGF, amplify ECM synthesis, and inhibit its degradation (84); In terms of vascular occlusive lesions, NLRP3 mainly induces high expression of Jagged1 in vascular endothelium and activates the Notch pathway of VSMC through the IL-1  $\beta$ /IL-18/Notch/Jagged1 axis, promoting phenotype transformation and proliferation migration, leading to thickening of vascular endothelium (85); Through the IL-1  $\beta$ /PI3K/Akt/mTOR axis, PI3K/Akt is activated and mTORC1 and FoxO3a are regulated, promoting VSMC proliferation and inhibiting cell autophagy, especially leading to stenosis of renal transplant artery anastomosis. EndMT can also be induced through multiple pathways, disrupting the endothelial barrier and anticoagulant function, accelerating thrombus formation and intimal hyperplasia (86).

In summary, the NLRP3 inflammasome participates in the pathological processes of three types of rejection through distinct molecular mechanisms. Its specific regulation holds promise for providing novel strategies for the precise prevention and treatment of transplant rejection and prolonging graft survival.

### 3.3 NLRP3 inflammasome and microbial infection

As a crucial sensor in innate immunity, the NLRP3 inflammasome plays a dual role in the anti-infective immunity of organ transplant recipients: on one hand, it recognizes invading pathogens such as viruses and bacteria, initiating inflammatory responses to eliminate pathogens; on the other hand, under immunosuppressed conditions, its excessive activation or dysregulation may exacerbate infection-related tissue damage and even induce systemic inflammatory response syndrome (87, 88). This complex mechanism renders it a key target in post-transplant infection prevention research.

#### 3.3.1 Role in viral infections

Organ transplant recipients exhibit significantly heightened susceptibility to viruses due to long-term immunosuppressive therapy, with cytomegalovirus (CMV), herpes simplex virus (HSV), and influenza virus being common pathogens. The NLRP3 inflammasome activates immune responses by recognizing viral nucleic acids or replication products. For example, during CMV infection, the release of intracellular mitochondrial DNA triggers NLRP3 inflammasome assembly, activating caspase-1 and releasing IL-1 $\beta$  and IL-18 (89), which in turn recruit natural killer cells and T cells to eliminate infected cells. Studies indicate that in CMV-positive kidney transplant recipients, peripheral blood monocyte NLRP3 expression correlates positively with viral load (90), suggesting its role in monitoring antiviral immunity.

However, viruses have evolved escape mechanisms to interfere with NLRP3 function. For instance, the influenza virus non-structural protein NS1 directly binds NLRP3 to inhibit its oligomerization, resulting in weakened inflammatory responses and delayed viral clearance. This “host-virus” game creates a regulatory dilemma for NLRP3 inflammasomes: overactivation may trigger a “cytokine storm” (e.g., acute respiratory distress syndrome following influenza infection), while underactivation fails to effectively control viral replication.

#### 3.3.2 Role in bacterial infections

Bacterial infections are the most common post-transplant infections. Both Gram-negative bacteria (e.g., *Escherichia coli*, *Klebsiella pneumoniae*) and Gram-positive bacteria (e.g., *Staphylococcus aureus*, *Enterococcus*) activate the NLRP3 inflammasome through distinct mechanisms. For Gram-negative bacteria, their cell wall component lipopolysaccharide (LPS) first induces pro-inflammatory factor precursor (pro-IL-1 $\beta$ ) expression via the TLR4 signaling pathway. Subsequently, bacterial exotoxins (e.g., Shiga toxin) or ion disruption (e.g., potassium ion efflux) trigger NLRP3 inflammasome activation, forming a “two-step activation model” (91, 92). In contrast, peptidoglycan fragments and toxins released by Gram-positive bacteria directly damage cell membranes, activating the NLRP3 pathway through reactive oxygen species accumulation or lysosomal rupture.

In transplant recipients, this activation mechanism has dual effects: on one hand, NLRP3-mediated inflammation enhances neutrophil phagocytosis, controlling early bacterial spread (e.g., in *Klebsiella pneumoniae* urinary tract infections); on the other hand, prolonged immunosuppression may lead to NLRP3 overactivation (93). For instance, during *Staphylococcus aureus* infections, the phenol-soluble regulatory protein it produces can continuously stimulate NLRP3 to release IL-1 $\beta$ , exacerbating tissue and cellular damage and even inducing sepsis (94, 95). Clinical studies reveal elevated serum IL-1 $\beta$  levels in patients with bacterial infections compared to non-septic individuals, with NLRP3 gene polymorphisms significantly correlated with sepsis susceptibility. Research demonstrates that *Acinetobacter baumannii* powerfully activates the NLRP3 inflammasome’s nucleotide-binding and oligodomain-containing receptor family pyrin domain through Dectin-1/Syk-dependent signaling and the cytoplasmic scaffold protein p62/SQSTM1 (p62) in human macrophages, thereby initiating inflammatory responses (96).

#### 3.3.3 Role in fungal infections

Fungal infections carry high mortality rates in organ transplant recipients, where NLRP3 inflammasomes primarily function by recognizing fungal cell wall components such as  $\beta$ -glucan and mannose. *Candida* hyphae activate the NLRP3-ASC complex via the Syk kinase pathway, while *Aspergillus fumigatus* conidia activate NLRP3 through ROS-dependent mechanisms within phagocytes, inducing IL-1 $\beta$  release to recruit inflammatory cells (97).

However, NLRP3 inflammasome activation may be constrained under immunosuppressed conditions: for instance, prolonged glucocorticoid use affects NF- $\kappa$ B expression, thereby suppressing NLRP3 expression and diminishing fungal clearance capacity. This contributes to the progression of post-transplant *Aspergillus* infection to invasive pulmonary aspergillosis (98). Furthermore, NLRP3 overactivation triggered by fungal infection may exacerbate graft injury. For instance, in kidney transplant recipients with concurrent candidemia, NLRP3-mediated inflammation can induce acute tubular necrosis, causing abrupt decline in graft function (99). In *Candida* infection, morphological transformation of hyphae is a necessary condition for activating NLRP3. Candidalysin secreted by hyphae can activate NLRP3 by inducing potassium ion efflux and ROS production. At the same time, Dectin-1 recognizes  $\beta$ -glucan to initiate NLRP3 pre activation. Activated NLRP3 can recruit pro-inflammatory factors to activate immune cells and enhance antifungal defense (100); In *Aspergillus* infection, the galactomannan and hypoxanthine of *Aspergillus fumigatus* can activate NLRP3 through multiple pathways. Its ROS Syk axis, potassium ion efflux, lysosome disruption, and other pathways promote inflammasome assembly (101). At the same time, NLRP3 can also form a “safety redundancy system” with AIM2, jointly forming a collaborative protection network against *Aspergillus* (102).

In summary, NLRP3 inflammasomes participate in anti-infective immunity by recognizing specific components of different microorganisms. However, their regulation in transplant recipients requires precise balance, maintaining sufficient immune

responses to clear pathogens while avoiding tissue damage caused by excessive activation. Deepening our understanding of its interaction mechanisms with microorganisms may provide a theoretical foundation for developing anti-infective therapeutic strategies targeting NLRP3.

## 4 Regulatory strategies for the NLRP3 inflammasome and its application prospects in organ transplantation

### 4.1 Genetic regulation

Genetic regulation represents a key intervention strategy for the NLRP3 inflammasome. Gene editing technologies, such as the CRISPR/Cas9 system, can block NLRP3 inflammasome activation by knocking out or silencing upstream NLRP3 genes. In relevant experiments, CRISPR/Cas9-mediated knockout of the upstream gene TXNIP in mice resulted in significantly reduced inflammatory responses and improved renal ischemia-reperfusion injury in an IRI model. However, gene editing technologies face numerous challenges in clinical application, including off-target effects, immunogenicity, and ethical concerns, limiting their widespread use. Additionally, RNA interference (RNAi) technology can be employed to silence NLRP3 gene expression. By designing small interfering RNA (siRNA) or short hairpin RNA (shRNA) targeting NLRP3 mRNA, NLRP3 expression levels can be specifically reduced, thereby inhibiting NLRP3 inflammasome activation. In both cellular experiments and animal models, RNAi technology has been demonstrated to effectively suppress NLRP3 inflammasome-related inflammatory responses (103). However, RNAi technology also presents challenges such as low transfection efficiency, poor *in vivo* stability, and potential immune stimulation, necessitating further optimization and refinement.

### 4.2 Pharmacological intervention

Drug intervention is currently the most extensively studied strategy for regulating the NLRP3 inflammasome. Multiple small-molecule compounds have been identified that can inhibit NLRP3 inflammasome activation. MCC950 is a specific NLRP3 inhibitor that binds to the NACHT domain of NLRP3, blocking its oligomerization and activation, thereby suppressing the production of downstream inflammatory cytokines. In organ transplantation-related animal models, MCC950 has demonstrated promising therapeutic effects. For instance, in a renal transplantation ischemia-reperfusion injury (IRI) model, MCC950 treatment significantly reduced renal tissue damage and improved renal function (104). In diabetic nephropathy models, MCC950 also reduced inflammatory responses (105). At present, MCC950 has entered phase I/II clinical trials for some inflammatory diseases, and clinical trials for transplant related diseases are still in the preliminary exploration stage. The core challenges it faces

include: how to suppress NLRP3 inflammation while avoiding weakening the anti-infective immunity of transplant recipients; How to combine with existing immunosuppressants to avoid drug interactions and reduce low toxicity and side effects; And how to achieve targeted delivery of transplanted organs and increase local drug concentration. Beyond MCC950, other compounds such as glibenclamide, quercetin, and curcumin have also been reported to inhibit NLRP3 inflammasome activity, but they typically lack specificity, and their effects may stem from a wide range of anti-inflammatory and antioxidant properties. Glibenclamide inhibits NLRP3 activation by blocking K<sup>+</sup> efflux pathways (106); quercetin and curcumin possess antioxidant and anti-inflammatory properties that suppress NLRP3 inflammasome activation through multiple mechanisms (107, 108). These drugs are mostly in the preclinical research stage, and their effectiveness and safety in transplant patients still need to be further validated through large-scale clinical trials. Some drugs have low bioavailability and non-specific targets, and their clinical application value needs to be improved through drug molecular modification.

### 4.3 Cell therapy

As an emerging therapeutic approach, cell therapy also shows potential applications in regulating the NLRP3 inflammasome. Bone marrow-derived mesenchymal stem cells (BMSCs) are among the most extensively studied stem cell types for cell therapy. BMSCs possess multiple functions, including immunomodulation, anti-inflammation, and tissue repair. Studies indicate that BMSCs exert therapeutic effects on organ transplant-related complications by inhibiting NLRP3 inflammasome activation (109). In the field of organ transplantation, BMSC therapy may also function through similar mechanisms. For instance, in transplant ischemia-reperfusion injury (IRI) models, transplanted BMSCs reduce tissue expression of NLRP3, ASC, and Caspase-1, thereby mitigating inflammatory damage and improving organ function (110, 111). Additionally, other cell types such as regulatory T cells (Tregs) mediate immunosuppression through adenosine production via CD39/CD73 expression. Adenosine has been demonstrated to inhibit NLRP3 inflammasome activation by blocking ATP-P2X7 signaling (112). Tregs suppress effector T cell activation and proliferation, reducing inflammatory cytokine production and thereby mitigating inflammatory responses (113). In transplant rejection, adoptive transfer of Tregs has been shown to prolong graft survival, with a potential mechanism involving inhibition of NLRP3 inflammasome-related inflammatory responses (114).

## 5 Conclusions and outlook

The NLRP3 inflammasome plays a key role in complications such as ischemia-reperfusion injury (IRI), rejection, and microbial infections after organ transplantation, and its activation mediated inflammatory response is the core mechanism causing graft injury and functional impairment. In IRI, NLRP3 exacerbates early tissue

damage in multiple organ transplantation; In rejection reactions, it can promote the fibrosis and vascular occlusion process of chronic rejection through multiple specific signaling pathways; In infections, the dual effects of immune defense and pathological damage against *Candida* and *Aspergillus* are particularly prominent in transplant recipients with immune suppression.

NLRP3 and its downstream cytokines (such as IL-1  $\beta$  and caspase-1 active fragments) have great potential as biomarkers for predicting or monitoring transplant complications. For example, the levels of relevant biomarkers in the serum of chronic kidney transplant rejection patients are positively correlated with the degree of glomerulosclerosis, and the expression of NLRP3 in peripheral blood mononuclear cells of CMV positive kidney transplant recipients is positively correlated with viral load. In the future, standardized detection systems can be established to achieve early warning of transplant complications.

At present, the regulatory strategies for NLRP3 inflammasome, including gene regulation, drug intervention, and cell therapy, have achieved promising results in animal research. The clinical translation of inhibitors such as MCC950 has entered the preliminary exploration stage, but clinical translation faces significant challenges: gene editing technology has safety and ethical controversies; Drugs need to balance efficacy and toxic side effects, while addressing compatibility issues with existing immunosuppressants; Cell therapy requires the establishment of a standardized preparation and quality control system. To promote the clinical translation of NLRP3 targeted therapy into organ transplantation in the future, priority should be given to optimizing existing regulatory strategies: developing precise gene delivery systems to reduce off target effects; Modify drug molecules to enhance specificity and reduce toxicity, while conducting multicenter, randomized controlled clinical trials to validate their safety and efficacy in transplant patients; Establish a large-scale preparation system for cell therapy. In addition, it is necessary to thoroughly analyze the cross regulatory mechanisms of NLRP3 with immune pathways such as TLR4 and NF -  $\kappa$  B, and construct a multi-target joint regulatory scheme. Meanwhile, emerging technologies such as single-cell RNA sequencing and spatial transcriptomics can help elucidate the cell type specific function of NLRP3 in the transplantation microenvironment, such as distinguishing the differential role of NLRP3 in macrophages, endothelial cells, and fibroblasts, providing more detailed theoretical support for precise targeting. With the continuous deepening of research, the NLRP3 targeted therapy strategy is expected to bring new hope to organ transplant patients, helping to achieve the goal of long-term survival of transplants and improved patient prognosis.

## Author contributions

KW: Writing – original draft. HL: Writing – review & editing. XM: Writing – review & editing. YZ: Writing – review & editing. YC: Writing – review & editing. TL: Writing – review & editing. YW: Writing – review & editing. HJ: Writing – review & editing.

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## Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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