



The NLRP3 inflammasome: a pivotal orchestrator of multisystem diseases—from molecular mechanisms to therapeutic innovation

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Abstract

The NLRP3 inflammasome, a key regulatory component in the innate immune system, bridges pathogen recognition to chronic disease pathogenesis by modulating pyroptosis, inflammatory factor release, and metabolic homeostasis. Its central role in inflammatory cascades has positioned it as a prime therapeutic target. This review delineates the NLRP3 inflammasome's pathological contributions to multisystem disorders—spanning neurological, cardiovascular, respiratory, gastrointestinal, urological, endocrine, and rheumatological immune diseases—while systematically evaluating associated therapeutic strategies. Furthermore, we consolidate the classical activation pathways of this molecular complex and discuss targeted inhibition approaches against both the NLRP3 inflammasome and its downstream effectors. Collectively, this work establishes a critical framework for understanding disease mechanisms and advancing translational interventions.

Keywords NLRP3 inflammasome · Pyroptosis · Multisystem diseases · Inflammatory signaling pathways · Herapeutic inhibitors

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Introduction

Inflammasomes are multiprotein complexes comprising pattern recognition receptors (PRRs) that orchestrate innate immune responses. They are activated by NOD-like receptors (NLRs), which detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [1, 2]. Among NLRs, the NLRP3 inflammasome is particularly notable due to its broad implications in infectious diseases [3], metabolic disorders [4], and neurodegenerative diseases [5]. Structurally, the NLRP3 inflammasome includes three core components: (1) the receptor protein, NLRP3, which has a pyrin domain at the N-terminus for protein interactions, a central NACHT domain for ATPase activity, and a leucine-rich repeat at the C-terminus for ligand recognition and autoinhibition; (2) the adaptor protein, ASC, which links NLRP3 to effector proteins via its PYD and caspase activation and recruitment domain (CARD); (3) the effector protease, caspase-1, which upon activation, cleaves gasdermin D (GSDMD: a substrate of inflammatory caspases whose N-terminal fragment oligomerizes to form membrane pores) to induce pyroptotic cell demise and promote the maturation and release of pro-inflammatory cytokines such as IL-1 β and IL-18 [6–8]. In

recent cryo-electron microscopy studies, the NEK7 kinase is further identified as a critical NLRP3 regulator [9].

Although the NLRP3 inflammasome activation mechanism remains incompletely understood, known triggers include potassium (K^+) efflux, lysosomal disruption, mitochondrial dysfunction, production of reactive oxygen species (ROS) production, and purinergic receptor signaling. While controlled NLRP3 inflammasome activation aids pathogen defense and homeostasis, its dysregulation is strongly linked to inflammatory and metabolic disorders [3, 10], including Alzheimer's disease, arthritis, atherosclerosis, type 2 diabetes, inflammatory bowel disease, and immune-related adverse events. This review systematically examines NLRP3 inflammasome regulatory mechanisms, activation pathways, and its pathogenic position in multi-system diseases.

The classical pathway of NLRP3 inflammasome activation and its regulatory network

Activation of the NLRP3 inflammasome

The activation of the NLRP3 inflammasome occurs in two stages [11] (Fig. 1). Stage 1 is known as the initiation stage. This is triggered by the activation of pattern-recognition receptors (PRRs) or tumor necrosis factor receptors (TNFRs) and begins with the recognition of PAMPs and DAMPs by PRRs. During this phase, PRRs recognize various stressors and activate the nuclear factor- κ B (NF- κ B) signaling pathway, leading to the upregulation of precursor proteins such as NLRP3, pro-IL-1 β , and pro-IL-18 [12, 13]. The NLRP3 inflammasome is induced by a wide range of bacterial and viral pathogens, including group B *Streptococcus* [14], *Bacillus cereus* [15], influenza virus [16], and human respiratory syncytial virus [17]. Additionally, NLRP3 can

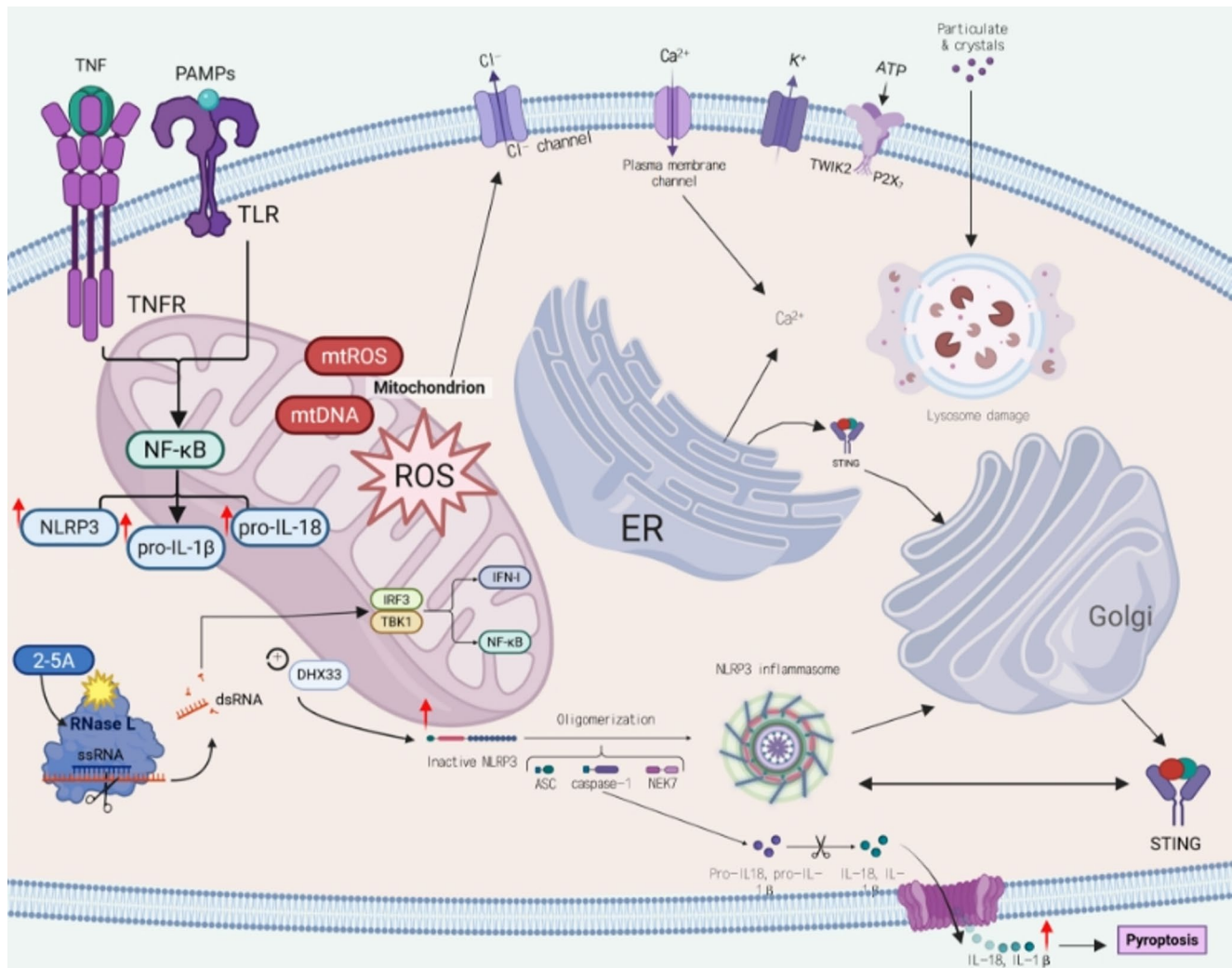


Fig. 1 The classical pathway of NLRP3 inflammasome activation

perceive certain PAMPs with the assistance of other receptors. For example, RNase L is activated during viral infection by binding to a 2',5'-linked oligoadenylate (2–5 A), which in turn dimerises and exerts catalytic activity. In order to produce RNA fragments containing double-stranded regions, activated RNase L cleaves single-stranded RNA (ssRNA) from viruses and cells. DHX33, the DExD/H-box RNA deconjugating enzyme, binds to these double-stranded RNAs (dsRNAs) and forms a complex with NLRP3 and ASC, activating the NLRP3 inflammasome [18, 19].

Next, the NLRP3 inflammasome activates in its effector phase, when it is fully activated, usually after being stimulated by infections, tissue damage, or metabolic imbalances. In addition to ion fluxes (e.g., K^+ efflux), extracellular ATP, mitochondrial dysfunction, ROS production, lysosomal damage, tissue proteinase B, cholesterol crystals, uric acid, and others, there are also other factors involved. ASC binds to NLRP3 to form the core structure of the NLRP3 inflammasome and activates caspase-1 as a result of these signals, resulting in conformational changes and self-aggregation of NLRP3. As a result, inflammatory factors mature and are secreted, and a severe inflammatory response occurs [13, 20].

In the upstream environment, K^+ efflux is one of the most significant and widespread phenomena in the activation of NLRP3 inflammasome and is closely synergised with multiple other signalling pathways [21]. K^+ efflux is not only induced by ATP via $P_2 \times 7$ receptors in concert with TWIK2 channels, but is also required for the activation of NLRP3 by a variety of particulate stimuli (e.g., alum, silica, and uric acid crystals) and membrane attack complexes. There is also a significant synergistic relationship between K^+ efflux and calcium ion flux (Ca^{2+} influx), where K^+ efflux facilitates Ca^{2+} release from the endoplasmic reticulum and opens Ca^{2+} channels at the plasma membrane, allowing Ca^{2+} to flow into the cytoplasm. And ATP also induces Ca^{2+} inward and K^+ outward currents via $P_2 \times 7$ receptors to synergistically trigger NLRP3 [22]. Similarly, chloride efflux (Cl^- efflux) has been shown to play an irreplaceable role in NLRP3 inflammasome assembly, which occurs in dependence on the membrane translocation of Chloride Intracellular Channel (CLIC) proteins following mitochondrial reactive oxygen species (mtROS) release and downstream regulation of ASC polymerisation, complementing the K^+ efflux-driven NLRP3 polymerisation process [23]. In addition, K^+ efflux and Ca^{2+} influx induced by lysosomal rupture constitute the core pathway for granule-mediated NLRP3 activation, suggesting that different types of cellular stress signals may ultimately converge on the K^+ -regulated pathway. In terms of mitochondrial dysfunction, mtROS and oxidised mtDNA can replace K^+ efflux to independently activate NLRP3 under certain circumstances,

however whether this pathway is fully decoupled from K^+ signalling remains controversial [13]. Notably, K^+ efflux has also been found to be essential for the recruitment of NLRP3 to the Golgi, and Golgi remodelling is one of the key nodes for NLRP3 aggregation and inflammasome assembly.

In addition, recent studies have shown that there is a complex interaction between interferon gene stimulating protein (STING) and NLRP3. STING, as a core molecule of the cytoplasmic DNA-sensing pathway, mainly responds to exogenous or endogenous DNA (e.g., viral DNA or mitochondrial DNA) in the cytoplasm. When activated, STING induces type I interferon through the TBK1-IRF3 axis (IFN-I) production and can activate the NF- κ B signalling pathway to promote the expression of multiple inflammatory factors. Moreover, STING signalling not only upregulates NLRP3 expression at the transcriptional level, but also induces mitochondrial damage and ROS generation, which provides a key initiating signal for the activation of NLRP3 inflammasome [24, 25]. STING signaling may also be feedback-regulated by NLRP3 inflammasome activation. Its downstream effector molecules, IL-1 β and IL-18, may further enhance STING-mediated immune-inflammatory responses. Meanwhile, the assembly process of inflammasome may indirectly regulate STING activity by affecting intracellular ion permeability, mitochondrial function or ROS levels. The interaction between the two is important in antiviral immunity, autoimmune diseases and inflammatory diseases. Future studies could further explore the specific molecular mechanisms of STING-NLRP3 interactions and provide a new theoretical basis for the treatment of related diseases [26].

Regulatory mechanisms of NLRP3 inflammasome

Activation of NLRP3 inflammasome is closely related to cellular pyroptosis, a pro-inflammatory type of programmed cell death in which activated caspase-1 triggers the cleavage of precursor inflammatory factors, releasing GSDMD as well. This fragment can be inserted into the cell membrane to form a pore, leading to the leakage of cellular contents and triggering cellular pyroptosis. GSDMD, as a key effector molecule in the NLRP3 inflammasome signalling pathway, mediates the release of inflammatory factors and cell lysis, and regulates the process of pyroptosis. Therefore, blocking GSDMD can effectively alleviate chronic inflammation [10]. Cellular pyroptosis mediated by NLRP3 inflammasome is shown to play a crucial role in various diseases. In Alzheimer's disease (AD), A β protein activates NLRP3 inflammasome, induces IL-1 β and IL-18 secretion, and triggers neuronal pyroptosis, thereby exacerbating the pathological process of AD. In contrast, it has been shown that the bisphenol A (BPA) reduces A β oligomers and plaques,

inhibits NLRP3 inflammasome activation, and reduces IL-1 β levels, thereby slowing down AD progression [27]. In atherosclerosis, macrophage phagocytosis of cholesterol crystals or oxidised low-density lipoprotein (ox-LDL) activates NLRP3 inflammasome which promotes caspase-1 activation and IL-1 β production, inducing inflammation, while interfering with cholesterol efflux and promoting foam cell formation [28]. In diabetic retinopathy (DR), however, signals such as ROS and ATP trigger cellular pyroptosis by activating NLRP3 inflammasome. The process of pyroptosis is accompanied by cell rupture and inflammatory factor release, accelerating DR progression [29]. Furthermore, STING induces hepatocyte cellular pyroptosis in mice by activating the NLRP3 inflammasome, whereas hepatocyte-specific deletion of NLRP3 or knockdown of the GSDMD gene significantly attenuates hepatocyte pyroptosis, inflammation, and fibrosis [30]. Therefore, blocking GSDMD becomes a novel strategy to inhibit chronic inflammation downstream of NLRP3 inflammasome. Related compounds (e.g., direct inhibition of NLRP3 inflammasome or blocking GSDMD-induced cellular pyroptosis) are being developed as potential anti-inflammatory therapies. It is noteworthy that the activation of the NLRP3 inflammasome not only leads to pyroptosis, but may also lead to other forms of cell death, including necroptosis, ferroptosis, and apoptosis [31]. The complex relationship between NLRP3 inflammasome and cell death provides a promising prospect for future studies.

PANoptosis is also a complex programmed cell death controlled by the PANoptosome complex, which integrates pyroptosis, apoptosis, and necroptosis pathways [32]. It has been shown that NLRP3 inflammasome has a bidirectional regulatory relationship with PANoptosis. In positive regulation, NLRP3 inflammasome can initiate PANoptosis through multiple mechanisms: firstly, it can activate caspase-1 to cleave the GSDMD through inflammasome, inducing pyroptosis; it can also activate caspase-8, triggering apoptosis (e.g., NLRP3-caspase-8 interactions observed in a bacterial infection model); and secondly, it can activate GSDMD by inducing K⁺ efflux indirectly activates the RIPK1/RIPK3/MLKL pathway and promotes necroptosis. In terms of reverse regulation, PANoptosis key molecules can also enhance NLRP3 inflammasome activity, e.g., during influenza virus infection, ZBP1 not only induces PANoptosis, but also the assembly of NLRP3 inflammasome, forming a positive feedback regulatory loop [33]. Notably, under the stimulation of tumor necrosis factor- α (TNF- α) and interferon- γ (IFN- γ), NLRP3 inflammasome can co-assemble PANoptosome with ZBP1 and FADD, integrate multiple death signals, release DAMPs (e.g., HMGB1, ATP) and re-activate NLRP3, forming a positive feedback loop of inflammation-cell death and participating in pathological

processes such as sepsis and severe COVID-19 [34]. In addition, NLRP3 inflammasome and PANoptosome exhibit synergistic effects in anti-infective immunity, autoimmune diseases and tumour microenvironment regulation. At the mechanistic level, the two construct a regulatory network through (1) dynamic assembly of molecular complexes such as PANoptosome; (2) signalling crossover of key molecules such as caspase-1/-8 and RIPK3; and (3) positive feedback regulation of inflammatory mediators [35]. This network plays a dual role between maintaining immune homeostasis and triggering pathological damage. However, its spatio-temporal regulatory mechanisms still need to be thoroughly investigated.

There has been significant progress in studying the mechanism of NLRP3 inflammasome activation, but a lot of unexplored territory remains. The in-depth study of these mechanisms will contribute to a comprehensive understanding of the function of NLRP3 inflammasome as well as provide theoretical support for its precise regulation.

NLRP3 inflammasome and multisystem diseases

NLRP3 inflammasome is a prominent regulator of intrinsic immunity, and their aberrant activation is closely associated with a variety of systemic diseases (Fig. 2; Table 1). In neurodegenerative diseases, cardiovascular diseases, pulmonary fibrosis, inflammatory bowel disease, diabetic nephropathy, metabolic diseases, and autoimmune diseases, NLRP3 inflammasome exacerbates pathological injury by promoting inflammatory factor release, cellular pyroptosis, and fibrosis, among other mechanisms. Researchers have shown that inhibiting the NLRP3 inflammasome pathway improves disease progression, but the dual nature of its function (host defence and pathological damage) requires precise modulation of therapeutic strategies. Future studies need to further elucidate its tissue-specific mechanisms to develop more effective interventions.

Nervous system

AD is a degenerative disorder of the central nervous system (CNS) that primarily affects the elderly or individuals in the presenile stage. It is characterized by progressive cognitive dysfunction and behavioral impairment [36, 37]. Abnormal phosphorylation and aggregation of Tau proteins are hallmark pathological features of AD and related Tau proteinopathies. Pathological Tau proteins exhibit prion-like propagation properties and can mediate neurodegeneration. A Tau transgenic mouse model and AD patients with increased NLRP3 acetylation and inflammasome activity

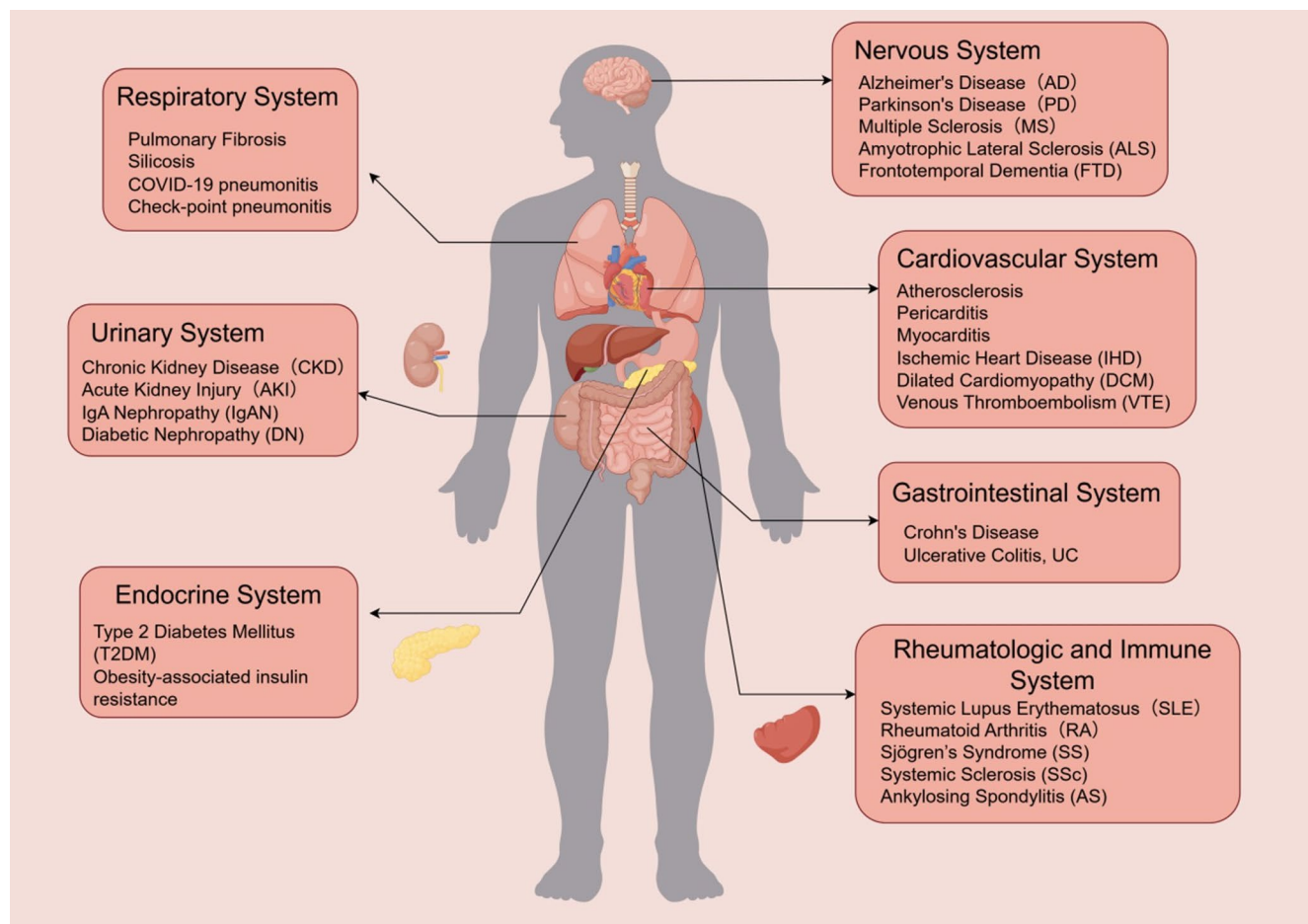


Fig. 2 NLRP3 inflammasome in multisystem diseases

have been found. Tau promotes NLRP3 acetylation via its K18 acetyltransferase active domain and directly acetylates the K21, K22, and K24 residues within the NLRP3-PYD domain in vitro. Tau-NLRP3-binding blocking (TNB) peptides inhibit microglial cellular interactions by competitively binding to and blocking the Tau-NLRP3 interaction. As a result, NLRP3 acetylation was suppressed, and downstream inflammasome activation was reduced in microglia, improving mice's cognition [38]. Microglia play a significant detrimental role in the progression of AD. On one hand, microglia phagocytose β -amyloid deposits in the brain and transport them to lysosomes, resulting in lysosomal swelling and instability. cathepsin B released from lysosomes activates the NLRP3 inflammasome and caspase-1, thereby promoting the secretion of mature IL-1 β [27]. IL-1 β induces the production of nitric oxide (NO) and TNF- α triggering neurotoxicity. Microglia that are also activated by inflammasomes undergo a metabolic shift from oxidative phosphorylation to glycolysis and are polarized toward a pro-inflammatory M1 phenotype, ultimately contributing to neuroinflammation and neurodegeneration [39]. Additionally, white matter loss resulting from oligodendrocyte

dysfunction or death is an early pathological feature of AD [40]. In a mouse model, hyperactivation of dynamin-related protein 1 (Drp1), a mitochondrial fission guanosine triphosphatase, induces glycolysis defects in oligodendrocytes, triggering NLRP3 inflammasome assembly and leading to oligodendrocyte pyroptosis [41]. Inflammasomes like the NLRP3 play a vital role not just in AD, but also in other neurodegenerative diseases, including Parkinson's disease (PD) [42], multiple sclerosis (MS) [43], amyotrophic lateral sclerosis (ALS) [44], and frontotemporal dementia (FTD) [45]. However, the specific mechanisms underlying these roles remain largely unknown.

Respiratory system

A devastating lung disease, pulmonary fibrosis is characterized by excessive inflammation and extracellular matrix accumulation. It has been shown in a number of studies that pulmonary fibrosis is directly related to the activation of NLRP3 inflammasomes. A dysfunctional NLRP3 inflammasome in the lung microenvironment may exacerbate inflammation and contribute to fibrosis [46]. However, the specific

Table 1 NLRP3 inflammasome in multisystem diseases

System	Diseases associated with NLRP3 inflammasome	
Nervous System	Alzheimer's Disease (AD)	DOI: https://doi.org/10.1039/d1sc06071f
	Parkinson's Disease (PD)	DOI: https://doi.org/10.3389/fimmu.2021.719807
	Multiple Sclerosis (MS)	DOI: https://doi.org/10.1073/pnas.1722041115
	Amyotrophic Lateral Sclerosis (ALS)	DOI: https://doi.org/10.1002/glia.23728
	Frontotemporal Dementia (FTD)	DOI: https://doi.org/10.1038/s41598-023-35945-4
Respiratory System	Pulmonary Fibrosis	DOI: https://doi.org/10.1007/s10787-023-01389-5
	Silicosis	DOI: https://doi.org/10.7150/ijbs.80605
	COVID-19 pneumonitis	DOI: https://doi.org/10.1016/j.cytogfr.2021.06.002
Cardiovascular System	Atherosclerosis	DOI: https://doi.org/10.1016/j.ebiom.2020.102985
	Pericarditis	DOI: https://doi.org/10.1038/s41569-023-00946-3
	Myocarditis	DOI: https://doi.org/10.1007/s00395-022-00948-1
	Ischemic Heart Disease (IHD)	DOI: https://doi.org/10.3390/antiox12071396
	Dilated Cardiomyopathy (DCM)	DOI: https://doi.org/10.1016/j.redox.2020.101523
	Venous Thromboembolism (VTE)	DOI: https://doi.org/10.1016/j.jacbts.2023.03.017
		DOI: https://doi.org/10.1016/j.molcel.2018.11.018
Gastrointestinal System	Crohn's Disease	DOI: https://doi.org/10.1016/j.apsb.2021.03.011
	Ulcerative Colitis (UC)	DOI: https://doi.org/10.1016/j.bbrep.2022.101417
Urinary System	Chronic Kidney Disease (CKD)	DOI: https://doi.org/10.1080/15548627.2020.1848971
	Acute Kidney Injury (AKI)	DOI: https://doi.org/10.3390/medicina59010082
	IgA Nephropathy (IgAN)	DOI: https://doi.org/10.3389/fphys.2022.907504
	Diabetic Nephropathy (DN)	DOI: https://doi.org/10.1186/s13287-017-0668-1
Endocrine System	Type 2 Diabetes Mellitus (T2DM)	DOI: https://doi.org/10.1038/nature04516
	Gout	DOI: https://doi.org/10.2340/actadv.102.2293
Rheumatologic & Immune System	Systemic Lupus Erythematosus (SLE)	DOI: https://doi.org/10.3389/fimmu.2022.931690
	Rheumatoid Arthritis (RA)	DOI: https://doi.org/10.1016/j.intimp.2024.112815
	Sjögren's Syndrome (SS)	DOI: https://doi.org/10.1186/s13075-022-02889-5
	Systemic Sclerosis (SSc)	DOI: https://doi.org/10.1186/s13018-023-04200-x
	Ankylosing Spondylitis (AS)	

mechanisms by which the NLRP3 inflammasome triggers a pro-fibrotic response remain incompletely understood. In a mouse model of bleomycin-induced pulmonary fibrosis, the NLRP3 inflammasome was overactivated in lung fibroblasts [47]. The claim that pharmacological inhibitors of NLRP3 inflammasomes effectively prevent lung fibrosis progression has been proven, which suggests that targeting the NLRP3 signaling pathway in fibroblasts may represent an effective antifibrotic treatment [48, 49]. Silicosis is a common occupational disease primarily caused by silica-induced lung epithelial damage and fibrosis. A mouse lung stem/progenitor cell-derived organotypic system was investigated [50] (which included two-dimensional air-liquid interfaces and three-dimensional organoids). Activating the NLRP3 inflammasome by silica disrupted epithelial structure and impaired mucosal ciliary clearance in 2D cultures, while inhibiting organoid development in 3D cultures.

Cardiovascular system

Ample cardiovascular diseases are associated with the activation of the NLRP3 inflammasome, such as atherosclerosis, ischemic heart disease, dilated cardiomyopathy, myocarditis, cardiac nodal disease, pericarditis, and venous

thromboembolism [51]. Atherosclerosis has been extensively investigated in relation to the NLRP3 inflammasome. It is a chronic inflammatory disease characterized by macrophage infiltration into the vessel wall. In atherosclerotic plaques, the abundant presence of cholesterol crystals [52] and oxLDL [53] activates the NLRP3 inflammasome. The mechanisms by which cholesterol crystals and oxLDL activate the inflammasome are different. Following the phagocytosis of cholesterol crystals by macrophages, their accumulation in lysosomes leads to lysosomal membrane rupture and the release of cathepsin B into the cytoplasm, directly activating NLRP3. Additionally, the leakage of lysosomal contents triggers K⁺ efflux, promoting NLRP3 inflammasome assembly [54]. In contrast, oxLDL is endocytosed via a receptor that resembles a lectin, called LOX-1 or CD36, activating NADPH oxidase (NOX2). This generates ROS, leading to a decrease in mitochondrial membrane potential and DNA damage, which subsequently activates the NLRP3 inflammasome [55, 56]. There is a synergistic effect between cholesterol and ox-LDL: ox-LDL induces macrophage foaming, increasing intracellular free cholesterol and promoting crystal formation. By contrary, cholesterol crystal-induced inflammatory responses upregulate the expression of the LOX-1 receptor, enhancing the uptake

of ox-LDL and its toxicity. Recent studies have demonstrated that high-density lipoprotein (HDL) inhibits inflammasome activity in atherosclerosis, highlighting its novel anti-inflammatory properties [57]. HDL inhibits cholesterol crystal formation by promoting reverse cholesterol transport and reducing the accumulation of free cholesterol in macrophages. Additionally, its antioxidant components, such as apolipoprotein A-I (ApoA-I) and paraoxonase, reduce ROS production, a significant signal for NLRP3 inflammasome activation. Furthermore, HDL inhibits NF- κ B nuclear translocation by activating the sphingosine kinase-1 (SphK1) pathway, thereby reducing the transcription of NLRP3 and pro-IL-1 β . It also promotes NLRP3 protein deacetylation through the upregulation of SIRT1 expression, inhibiting its oligomerization and inflammasome assembly. However, in diabetes or chronic inflammatory states, HDL may become oxidized or glycosylated (forming ox-HDL or glycated HDL), lose its anti-inflammatory capacity, and even activate NLRP3 through the LOX-1 receptor [58]. Notably, smoking is a significant risk factor for heart disease on its own [59]. Nicotine, a major component of cigarettes, has been shown to impair lysosomal function. Dysfunctional lysosomes activate the NLRP3 inflammasome through cathepsin B in vascular smooth muscle cells (VSMCs), further exacerbating atherosclerosis and contributing to plaque instability [60].

Digestive tract system

The NLRP3 inflammasome has a two-fold role in gastrointestinal (GI) diseases: it mediates host defense and drives pathological inflammatory processes. It activates the immune response by recognizing pathogens, such as *Salmonella*, *Clostridioides difficile* (*C. difficile*), and *Giardia*, to clear infections [61, 62]. Studies have demonstrated that NLRP3-deficient mice are more susceptible to intestinal infections, as indicated by reduced bacterial clearance and attenuated inflammatory responses. As part of the pathological processes of inflammatory bowel disease (IBD), aberrant activation of the NLRP3 inflammasome has also been implicated [63]. IBD, especially ulcerative colitis and Crohn's disease, is a chronic disease in which the gastrointestinal tract is inflamed recurrently and often during a period of time [64]. Despite the lack of elucidation of the etiology and pathogenesis of IBD, studies have clearly demonstrated that inflammatory reactions resulting from abnormal immune responses play a critical role in the disease [65]. In clinical studies, NLRP3 expression has been demonstrated to be significantly upregulated in colonic tissues of patients with inflammatory bowel disease, along with cell death-related proteins, such as activated caspase-1 and GSDMD [66]. This indicates that moderate activation of the NLRP3 inflammasome is essential for maintaining mucosal

immune homeostasis, whereas persistent activation may contribute to pathological conditions [67]. Notably, NLRP3 gene polymorphisms may enhance genetic susceptibility to IBD. Although targeting the NLRP3 pathway offers a novel direction for the treatment of GI diseases, the dual nature of its function (defense versus pathogenicity) and the potential side effects of interventions require further in-depth exploration. For instance, complete inhibition of the NLRP3 inflammasome may compromise the host's ability to combat infections, while excessive activation exacerbates tissue damage, necessitating precise regulation of therapeutic strategies.

Urinary system

A number of renal diseases, including acute kidney injury (AKI), chronic kidney disease (CKD), diabetic nephropathy (DN), and IgA nephropathy (IgAN), are linked to NLRP3 inflammasome. Its activation drives the renal inflammatory response and fibrotic processes [68]. In diabetic nephropathy, for instance, hyperglycemia-induced overproduction of ROS exacerbates renal injury by activating the NLRP3 inflammasome, which promotes the maturation and secretion of IL-1 β and IL-18 [69]. Mechanistically, the NLRP3 inflammasome triggers renal tubular epithelial and podocyte pyroptosis through a caspase-1-dependent pathway, leading to renal structural and functional damage. As an additional effect, it accelerates renal interstitial fibrosis by upregulating the expression of transforming growth factor- β 1 (TGF- β 1) and connective tissue growth factor (CTGF), as well as activating Smad3 signaling. Animal experiments have demonstrated that NLRP3 knockdown or the use of specific inhibitors, such as MCC950, significantly improves renal function in diabetic model mice. In CKD, the expression level of NLRP3 is positively correlated with disease progression. NLRP3 gene-deficient mice exhibit reduced tubular injury, decreased inflammatory cell infiltration, and diminished fibrosis in a CKD model [70]. Notably, although the pathological roles of the NLRP3 inflammasome in AKI, CKD, DN, and IgAN have been confirmed, its specific regulatory mechanisms and interaction networks in different renal diseases require further investigation. Through integrated multi-omics analyses, it remains to be determined whether the NLRP3 inflammasome contributes to the heterogeneous phenotypes of these diseases.

Endocrine system

Recent studies have shown that NLRP3 inflammasome contributes to the development of obesity-associated insulin resistance and type 2 diabetes mellitus (T2DM). In an obese mouse model, elevated levels of NLRP3 expression

in adipose tissue were significantly and positively correlated with insulin resistance, whereas improvement in insulin sensitivity induced by caloric restriction interventions was accompanied by a simultaneous decrease in NLRP3 inflammasome activity and IL-1 β expression [71]. Particularly, one of the pathological features of T2DM is a systemic chronic inflammatory state manifested by persistently elevated levels of circulating pro-inflammatory factors (e.g., TNF α , IL-6, IL-2, or IL-1 β) [72]. Animal experiments have confirmed that pharmacological inhibition of the NLRP3/caspase-1/IL-1 β signalling pathway significantly ameliorates insulin resistance and restores pancreatic β -cell function [73]. In the metabolic disease spectrum, NLRP3 inflammasome are similarly involved in the pathological process of gout. The essence of the disease is the pathological deposition of monosodium urate (MSU) crystals in the joints and surrounding tissues. Hyperuricaemia is a central risk factor for the development of gout, and MSU crystals trigger IL-1 β release through activation of NLRP3 inflammasome, a central mechanism for gouty attacks [76]. Genetic studies have shown that mouse macrophages deficient in caspase-1, ASC, or NLRP3 genes cannot effectively activate IL-1 β in response to crystal stimulation. This confirms the necessity of this inflammasome in gout [75]. The above evidence suggests that the NLRP3 inflammasome plays a dual role in the pathophysiology of endocrine metabolic diseases by modulating the inflammatory response network: as an important regulator of metabolic homeostasis and as a driver of pathological inflammation. There may be new targets for treating related diseases if this pathway is precisely regulated, but tissue-specific effects and away-from-target risks must be investigated thoroughly.

Rheumatological immune system

An important component of the intrinsic immune system, the NLRP3 inflammasome contributes significantly to the pathology of several autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis (SSc), and ankylosing spondylitis (AS) [76]. In patients with RA, the expression level of this inflammasome is markedly upregulated in the monocyte-macrophage system, dendritic cells (DCs), and synovial tissues, and it is thereby responsible for amplifying the inflammatory response to the joints and tissue destruction by enhancing the secretion of IL-1 β and IL-18 [77]. Given its central regulatory position in the pathogenesis of RA, NLRP3 inflammasome has emerged as therapeutic targets with significant research value [78]. The results of preclinical studies indicate that specific inhibition of NLRP3 inflammasome activation not only effectively alleviates the inflammatory response, but also significantly

ameliorates structural injuries such as bone erosion, providing a novel intervention strategy for RA treatment [79, 80]. In SLE disease models, T follicular helper cells (Tfh) present an aberrant activation phenotype of NLRP3 inflammasome. This pathological state contributes to the overproduction of IL-1 β and IL-18 by Tfh cells, which ultimately leads to the worsening of the systemic autoimmune response through the activation of B cell-mediated antibody-dependent immune responses [81]. Notably, the degree of NLRP3 inflammasome production was significantly and positively correlated with the disease activity index (SLEDAI) in SLE patients, and its specific inhibitors were effective in reducing auto-antibody titres and improving clinical prognosis [82]. Although the molecular mechanisms of SS and SSc have not been fully elucidated, clinical observations have shown that the mRNA expression levels of NLRP3, IL-1 β , and IL-18 were significantly elevated in the peripheral blood and lesion tissues of patients, and the intensity of their expression showed a clear positive association with the severity of the disease [83, 84]. In addition, in the study of AS pathogenesis, although the specific pathways of NLRP3 inflammasome still need to be deeply resolved, preliminary evidence has shown that its activation status is significantly associated with disc inflammatory response and bone remodelling abnormalities [85].

Inhibitors of NLRP3 inflammasome

As a core molecular target of inflammation regulation, functional inhibition of NLRP3 inflammasome has become an important strategy for the treatment of related diseases (Table 2). Pharmacological strategies targeting the NLRP3 inflammasome are categorized into three mechanistic tiers: (i) direct inhibitors binding the NLRP3 protein with high specificity; (ii) indirect modulators targeting upstream cellular events essential for NLRP3 activation, such as ion flux and ROS generation; and (iii) downstream blockers neutralizing effector cytokines (e.g., IL-1 β) or inhibiting enzymes (e.g., caspase-1) immediately downstream of the inflammasome complex. Diaryl sulfonylureas, typified by MCC950, exert potent inhibition by blocking ATP hydrolysis via binding to the Walker B motif within the NACHT domain [86]. However, hepatic and renal toxicity has prompted development of safer alternatives, among which Dapansutril has garnered attention for specific NLRP3 targeting. This compound inhibits oligomerization by disrupting NLRP3-ASC and NLRP3-caspase-1 interactions; in vitro experiments confirm its reduction of recombinant ATPase activity, suggesting a direct mechanism [87, 88]. Oridonin, a natural NLRP3 inhibitor, covalently modifies the Cys279 residue to block NLRP3-NEK7 interaction,

Table 2 Different inhibitors of NLRP3 inflammasome

	Name of inhibitor	Mechanism of action	Characteristic	Modelling of the main indications
Direct suppression	MCC950 (also known as CRID3 or CP-456,773)	Binds to the NACHT structural domain, inhibits ATPase activity and prevents inflammasome assembly	High specificity, extensive preclinical studies	AD, PD, T2DM, atherosclerosis, EAE, stroke, liver disease, enteritis, etc.
	CY-09	Binds to Walker A site and inhibits ATPase activity	Good selectivity but slight inhibition of P450 enzymes	Diabetes, stroke, heart attack, NAFLD, gout, etc.
	Danpansutrine (formerly known as OLT1177)	Inhibits ATPase activity by an unspecified mechanism	Can be taken orally and is in clinical trials	AD, IBD, arthritis, asthma, acute kidney injury, etc.
	Oridonin	Covalent modification of Cys279 to block NLRP3-NEK7 binding	Natural product, multi-targeted action, antioxidant and anti-inflammatory broadly	Liver fibrosis, gout, brain damage, lung damage, T2DM, etc.
	Tranilast	Inhibits of NLRP3 oligomerisation and blocks of its protein-protein interactions	Old drugs, new uses, mild action, lower side effects	NASH, T2DM, heart attack, brain toxicity, colitis, etc.
	MNS	Covalent binding to the NACHT domain of NLRP3 protein to inhibit its oligomerisation and activation	Also acts on targets such as Syk and p97	Burn repair, airway inflammation
	HS-203,873	Covalently targets the Cys279 site of NLRP3, stabilising its inactive state	Limited research, predominantly in vitro data	No definitive animal model is available
	KN3014	Inhibits NLRP3 interaction with ASC	High specificity, well-defined mechanism	Gout, AD, PD, diabetes, atherosclerosis, multiple sclerosis, Sepsis
Indirect suppression	Glyburide	Inhibition of NLRP3 inflammasome assembly (K^+ ATP channel)	Non-selective, multipotent	Cutaneous leishmaniasis
	NAC	Reduces ROS levels and indirectly inhibits the ROS/NLRP3 signalling pathway	Non-specific targeting, high safety profile, multipotency	Renal inflammation, liver injury, neurodegenerative diseases
	Colchicine	Disrupts microtubule dynamics, impairing ASC speck formation (indirect)	Disrupts microtubule dynamics, impairing ASC speck formation (indirect)	Gout, familial Mediterranean fever, pericarditis
	Mefenamic acid (fenamates)	Inhibits NLRP3 via volume-regulated anion channels (VRACs) (indirect and system-dependent)	NSAID; multiple actions	Pain, inflammation; investigational for NLRP3-related conditions
	P2 $\times$ 7 antagonists (e.g., A438079, AZD9056, JNJ-47965567)	Antagonize P2 $\times$ 7 receptor, preventing ATP-induced NLRP3 activation	A438079 (tool compound); AZD9056 (failed phase II RA); JNJ-47,965,567 (phase I)	Investigational for inflammatory diseases
Targeting downstream signals	Cytokine signaling	Canakinumab	Neutralisation of IL-1 β and indirect inhibition of inflammasome activation	Atherosclerosis, CAPS
		Anakinra	IL-1R antagonist	RA, adult-onset Still's disease, COVID-19
		Rilonacept	IL-1 trap	Recurrent pericarditis, CAPS
	Effector molecules	VX-765 (Belnacasan)	Inhibition of caspase-1 activity and indirect inhibition of inflammasome activation	Silicosis, IPF, ALI, RA, Inflammatory Bowel Disease, AD
		Disulfiram	Covalent modification of GSDMD at Cys191/192, blocking pyroptosis	Investigational for inflammatory conditions
		Necrosulfonamide	Inhibits MLKL (necroptosis) and GSDMD (pyroptosis)	Research use

suppressing inflammasome assembly. Although demonstrating multi-targeted anti-inflammatory and antioxidant activities in diabetes, liver fibrosis, and gout models, its irreversible covalent modification and pharmacokinetic limitations—including < 2% oral bioavailability and off-target toxicity—severely constrain clinical translatability [89]. Small-molecule inhibitors like CY-09 (targeting NACHT ATPase) display high selectivity but insufficient blood-brain barrier penetration [90, 91]. Other direct inhibitors including MNS [92], HS-203,873, and KN3014 [93] represent a new generation of selective agents with neurodegenerative and metabolic syndrome potential, though clinical translation hurdles persist. Among indirect modulators, colchicine disrupts microtubule-dependent ASC trafficking to inhibit inflammasome assembly and is clinically used for gout/pericarditis, despite a narrow therapeutic window necessitating cautious dosing [94]. Its repurposing strategy holds promise for NLRP3-driven conditions. $P2 \times 7$ antagonists [95–97]—such as tool compound A438079 and clinical-stage JNJ-47,965,567—block the ATP- $P2 \times 7$ -NLRP3 axis. Notably, while JNJ-47,965,567 advances in Phase I RA trials, AZD9056's Phase II failure underscores target complexity. Fenamates (e.g., mefenamic acid) indirectly suppress NLRP3 via volume-regulated anion channels (VRACs) [98]; their NSAID background may accelerate translation, but system-dependent effects require disease-specific evaluation. Within downstream blockers, cytokine inhibitors include: Canakinumab (anti-IL-1 β mAb), approved for CAPS/atherosclerosis though limited by cost [99]; Anakinra [100] (IL-1R antagonist), indicated for DIRA/COVID-19 cytokine storms but requiring daily injections for acute use; and Rilonacept [101] (IL-1 trap), demonstrating efficacy in recurrent pericarditis with weekly dosing yet necessitating infection monitoring. Among effector inhibitors, repurposed agent Disulfiram [102] covalently modifies GSDMD to block pyroptosis—cost-effective but requiring dose optimization. Although clinically discontinued, VX-765 [103] (caspase-1 inhibitor) provided pyroptosis-targeting proof-of-concept. Necrosulfonamide serves as a research tool inhibiting both MLKL (necroptosis) and GSDMD (human-specific pyroptosis), highlighting multimodal cell death intervention potential [104]. Consequently, these agents are indicated for palliative symptom management rather than mechanistic disease intervention. This has driven the emergence of metabotropic inhibitors as a research hotspot, which selectively modulate NLRP3 inflammasome activation based on the maintenance of physiological immunity by binding to NACHT or LRR structural domain metabotropic sites (confirmed by cryo-electron microscopy and crystallography) [95]. Compared with traditional ATP-competitive inhibitors, these drugs have the advantages of

precise targeting and controlled toxicity, providing a new paradigm for the treatment of inflammatory diseases.

Prospects and outlook

Despite significant advances in the study of NLRP3 inflammasomes, their activation mechanisms and pathological functions remain unclear. First, the activation mechanism of NLRP3 inflammasome has not been fully elucidated, especially in different disease contexts, and its triggers and specific regulation of signalling pathways remain unclear. Future studies need to further reveal the activation mechanism of NLRP3 inflammasome, especially the molecular details of how different stimuli regulate its oligomerisation and its assembly. Second, the role of NLRP3 inflammasome in disease is dual. In inflammatory and metabolic diseases, NLRP3 inflammasome usually exerts deleterious effects, but may have protective effects in certain infectious diseases and cancers. For example, in cancer, NLRP3 inflammasome exhibits dual pro-inflammatory and anti-tumour functions, and its mechanism of action is complex and highly dependent on the microenvironment. Specifically, NLRP3 inflammasome activation accelerates cancer progression by mediating the maturation and release of IL-1 β and IL-18 via caspase-1, driving chronic inflammatory responses, and promoting tumour cell proliferation, angiogenesis, and the formation of an immunosuppressive microenvironment. In addition, over-activation of NLRP3 inflammasome induces GSDMD-dependent epithelial cellular pyroptosis, leading to abnormal mucosal barrier damage and repair and increasing the risk of carcinogenesis. However, NLRP3-mediated cell death can also release tumour antigens and DAMPs, which activate dendritic cells and enhance the immune response of T cells, thereby inhibiting tumour growth. It was also found that abhydrolase domain containing 8 (ABHD8) degrades NLRP3 through the molecular chaperone-mediated autophagy pathway, limiting excessive inflammatory responses and potentially inhibiting the malignant transformation of tumour-associated chronic inflammation [105]. In summary, NLRP3 inflammasome is both a pro-oncogenic factor (driven through inflammation) and a potential immunomodulatory target (through activation of anti-tumour immunity) in cancer, and its balanced regulation may provide new strategies for cancer therapy.

Conclusion

As a key regulator of the intrinsic immune system, NLRP3 inflammasome plays a pivotal role in connecting pathogen recognition, inflammatory amplification and programmed

cell death in a variety of systemic diseases. Its aberrant activation is closely related to pathological processes such as infection, metabolic disorders, neurodegeneration, and immune imbalance, and constitutes a complex inflammatory regulatory network through interactions with STING pathway, PANoptosis, and other signalling axes. More and more studies have confirmed that NLRP3 inflammasome is not only the driving core of inflammatory response, but also may have immunoprotective function under certain pathological conditions, showing a dual role of 'defence-injury'. Currently, several NLRP3 inflammasome inhibitors have shown good therapeutic potential, but still face challenges such as poor targeting selectivity, side effect risks, and barriers to clinical translation. Therefore, future research should focus on the following directions: first, to reveal the spatiotemporal regulation mechanism of NLRP3 inflammasome activation and its fine interactions with other immune pathways; second, to develop targeted regulatory molecules with high selectivity and low toxicity, and to explore their application strategies in specific tissues or disease states; and third, to facilitate the clinical translation of NLRP3-targeted therapies and systematically assess their long-term safety and efficacy in chronic diseases. In conclusion, NLRP3 inflammasome as a common inflammatory node in many diseases, has important research and clinical value. The precise regulation of NLRP3 inflammasome is anticipated to be a new breakthrough in the treatment of inflammatory diseases in the future, and provide a new paradigm of cross-disease and mechanism-oriented treatment for multisystem diseases.

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Declarations

Competing interests The authors declare no competing interests.

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