



REVIEW ARTICLE

Novel insights into NOD-like receptors in renal diseases

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Nucleotide-binding oligomerization domain-like receptors (NLRs), including NLRAs, NLRBs (also known as NAIPs), NLRCs, and NLRPs, are a major subfamily of pattern recognition receptors (PRRs). Owing to a recent surge in research, NLRs have gained considerable attention due to their involvement in mediating the innate immune response and perpetuating inflammatory pathways, which is a central phenomenon in the pathogenesis of multiple diseases, including renal diseases. NLRs are expressed in different renal tissues during pathological conditions, which suggest that these receptors play roles in acute kidney injury, obstructive nephropathy, diabetic nephropathy, IgA nephropathy, lupus nephritis, crystal nephropathy, uric acid nephropathy, and renal cell carcinoma, among others. This review summarises recent progress on the functions of NLRs and their mechanisms in the pathophysiological processes of different types of renal diseases to help us better understand the role of NLRs in the kidney and provide a theoretical basis for NLR-targeted therapy for renal diseases.

Keywords: NOD-like receptors; innate immunity; inflammasome; renal disease

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INTRODUCTION

Compared to the adaptive immune system, the innate immune system exerts a rapid response to pathogens or tissue injury and is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs) [1, 2]. DAMPs include intracellular components released during different types of cell death and molecules resulting from the enzymatic degradation of quiescent extracellular matrix (ECM) during ECM remodelling. In addition, these factors can originate in the kidney and can include crystals and uromodulin [3].

PRRs are a group of germline-encoded receptors that mediate the initial innate immune response to cellular injury and stress [4]. PRRs can be classified into five subfamilies according to their different structural domains: Toll-like receptors (TLRs), retinoic acid-inducible gene-1-like receptors, C-type lectin receptors, absent in melanoma 2 (AIM2)-like receptors, and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) [5]. NLRs are intracellular receptors located mainly in the cytoplasm, although some are also found in mitochondria. A total of 22 and 35 NLR genes have been identified in humans and mice, respectively [6, 7]. The structure of NLRs includes a C-terminal leucine-rich repeat domain that functions as a ligand sensor, a conserved nucleotide-binding (NACHT) domain that is required for nucleotide binding and oligomerization, and an N-terminal effector domain that mediates downstream protein–protein interactions, such as an acidic transactivation domain, caspase recruitment domain (CARD), pyrin domain (PYD), and baculoviral

inhibitory repeat (BIR)-like domain [7, 8]. Based on their N-terminal domains, NLRs can be subdivided into four different subfamilies: NLRAs, NLRBs (also known as NAIPs), NLRCs, and NLRPs.

The NLRA subfamily, which contains an acidic transactivating domain (AA), consists of only one member: CIITA. The NLRB subfamily contains an N-terminal BIR-like domain, and BIR consists of NAIP in humans and NAIP1–7 in mice. The NLRC subfamily includes NOD1, NOD2, and NLRC3–5, in which a CARD domain is present. NLRX1, which is located in the mitochondrial matrix and is mediated by an N-terminal addressing sequence, belongs to the NLRC subfamily. The NLRP subfamily consists of 14 members named NLRP1–14, each of which contains a PYD domain. All members also contain the NACHT and LRR domains, except for NLRP10, which lacks an LRR domain. NAIPs and NLRC4 can pair with each other to form inflammasomes in animals [9, 10].

Most NLRs function in (1) antigen presentation; (2) pathogen/damage sensing; (3) inflammasome activation; and (4) inflammatory signalling inhibition (Fig. 1). However, several NLRs play definitive roles in embryonic development [11]. These findings suggest alternative functions for some NLRs in different cell types and multiple activation mechanisms with separate downstream effects for other NLRs. Although an increasing number of studies have shown links between NLRs and renal diseases, the results have been inconclusive. In this review, we summarise recent progress on the functions of NLRs and discuss whether these receptors could serve as therapeutic targets in renal diseases.

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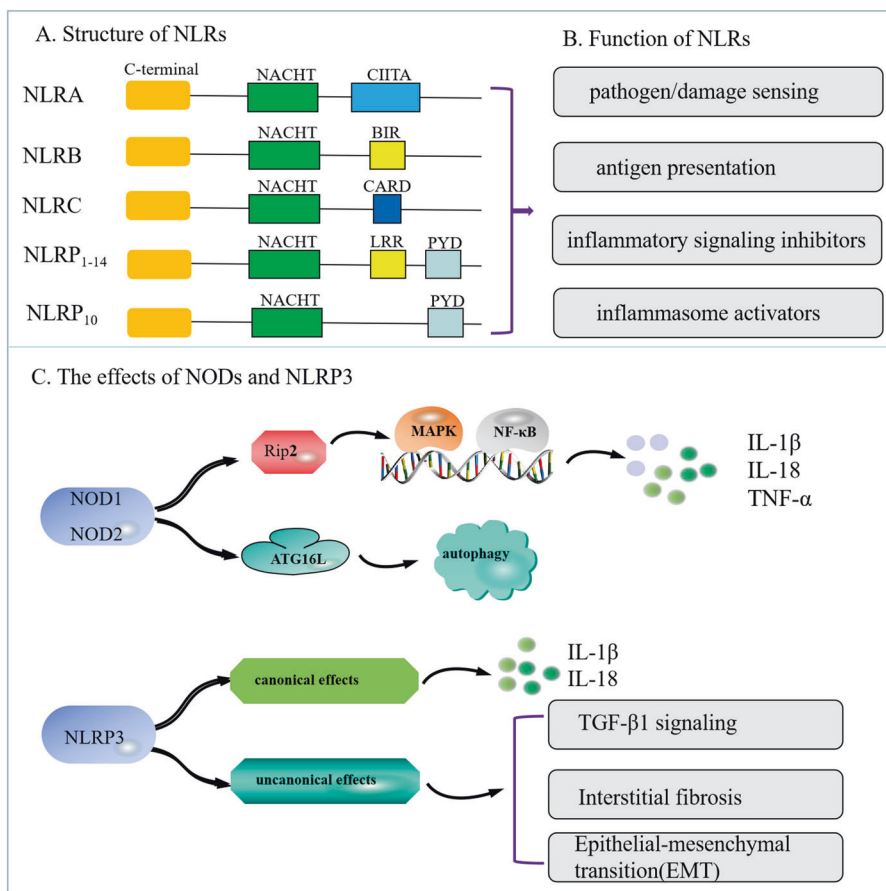


Fig. 1 Characteristics of NLRs. **A** Structure of NLRs. Based on their N-terminal domains, NLRs can be subdivided into four different subfamilies: NLRAs, NLRBs (also known as NAIPs), NLRCs and NLRPs. **B** Function of NLRs. Multiple NLRs serve as antigen presentation, pathogen/damage sensing, inflammasome activators, inflammatory signalling inhibitors. **C** The effects of NODs and NLRP3. NOD1 and NOD2 can both interact with the receptor-interacting protein 2 (Rip2) kinase and recruit the Rip2s through the CARD-CARD binding which will lead to the activation of NF-κB or MAPK pathway, resulting in the secretion of proinflammatory cytokines, such as IL-6, IL-1β and TNF-α. Additionally, NOD1 and NOD2 interact with ATG16L to mediate autophagy. NLRP3 can work in a canonical (inflammasome dependent) or a noncanonical manner (inflammasome independent). Canonical inflammasomes convert procaspase-1 into its mature form caspase-1, whereas noncanonical inflammasome activate procaspase-11.

CHARACTERISTICS OF NLRs IN BIOLOGICAL PROCESSES

NLRs in pathogen/damage sensing

NOD1 is expressed in tubular epithelial cells (TECs) in the kidneys of humans and mice, as well as in many other cells and organs. The expression of NOD2 can be detected in TECs and glomerular endothelial cells in humans and in podocytes, mesangial cells, and TECs in mice [12]. NOD1 can recognise γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP), which is the degradation product of gram-negative bacteria and certain gram-positive bacteria, while NOD2 can recognise muramyl dipeptide (MDP), which is the degradation product of gram-negative and gram-positive bacteria [13–15]. Binding with the corresponding ligand results in the rapid self-oligomerization of NOD1 or NOD2. Although the ligands identified by NOD1 and NOD2 are different, they can interact with the downstream protein receptor-interacting protein 2 (Rip2) kinase and recruit Rip2 through CARD-CARD binding, which leads to activation of the NF-κB or MAPK pathway, resulting in the secretion of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α [16]. Additionally, NOD1 and NOD2 interact with ATG16L to mediate autophagy [17]. Furthermore, NOD1 and NOD2 can participate in the recognition of DAMPs derived from cell damage [10].

Exogenously derived PAMPs and DAMPs convert NLRs from inactive monomers to activated oligomers [18]. The NLR family plays a critical role in sensing PAMPs and DAMPs in the cytosol

[19]. The primary DAMPs associated with inflammatory diseases are ATP, hyaluronan, uric acid, monosodium urate (MSU) crystals, cholesterol crystals and β amyloid (Aβ) [20, 21]. Recent studies have demonstrated that the NLRP3 inflammasome can recognise pathogen- and danger-associated molecular patterns [22, 23]. Uric acid and MSU crystals directly induce insulin resistance, insulin signalling impairment, CKD and gouty arthritis by inducing NLRP3 inflammasome activation [23–26]. Extracellular ATP is released by necrotic or apoptotic cells and sensed by P2X7 receptors to activate innate immune responses, including the NLRP3 inflammasome [27, 28]. In addition, the NLRP3 inflammasome is also activated by cholesterol crystals [29, 30]. Prxs are ubiquitously expressed peroxidases that are released from cells in response to various stress conditions. These factors function as DAMPs. A recent study showed that NLRP3 inflammasome activation induced Prx2 secretion, which induced C1q-mediated classic complement pathway activation [31]. Furthermore, NOD1 and NOD2 can also participate in the recognition of DAMPs derived from cell damage [10]. The recognised bacterial peptidoglycan derivatives iE-DAP and MDP undergo conformational alterations and ATP-dependent self-oligomerization of the NACHT domain followed by downstream signalling [18, 32].

PAMPs include lipopolysaccharides (LPS), flagellin, single-stranded RNA, and unmethylated CpG DNA [33]. NOD2 variants in Crohn's disease share a signalling defect in response to LPS [34].

NLRC4, which is activated by bacterial flagellin or the rod complex, plays a role in pathogen sensing [35–37]. NAIP proteins are receptors of bacterial ligands, while NLRC4 is a downstream adaptor that multimerizes with NAIPs to form an inflammasome with adaptor apoptosis-associated speck-like protein (ASC) and caspase-1, resulting in the release of IL-1 β and IL-18 [11, 37].

In summary, these studies show that the NLR family contains cytosolic PRRs that play important roles in innate immune signalling.

NLRs in antigen presentation

NLRC5 has a CARD-like N-terminal domains, is predominantly expressed in cells of the myeloid and lymphoid lineages and is induced by IFN- γ , LPS, and polyinosinic:polycytidylic acid [38]. NLRC5 is not only an essential factor for MHC class I gene expression and type I interferon responses but also mediates the activation of CD8⁺ T cells and CD4⁺ T cells [39, 40]. Furthermore, NLRC5 plays a role not only in immune regulation but also in cancer immunity [41].

CIITA, which has an N-terminal CARD and acid transactivation domain, displays features similar to those of NLRC5. CIITA acts as a transcriptional coactivator and is involved in the regulation of MHC class II expression [42, 43]. Both NLRC5 and CIITA shuttle between the cytosol and the nucleus in a CrmA-dependent manner [38].

NLRs in inflammation regulation

Recent studies have demonstrated that multiple NLRs play essential roles in regulating inflammation. The role of different NLRs in regulating inflammation may be different. NLRC3, NLRC5, NLRX1 and NLRP6 may serve as negative modulators of inflammation, while NLRP3, NLRP1, NLRP2, NLRP6, and NLRP7 are able to form inflammasomes and promote the inflammatory response.

NLRs as inhibitory regulators of inflammation. A recent study showed that LPS administration increased hypothermia and enhanced macrophage infiltration and IL-6 production in *NLRC3*^{-/-}

mice. NF- κ B, a key downstream transcription factor of TLR signalling, is activated in *NLRC3*^{-/-} macrophages [44]. Mechanistically, NLRC3 inhibits NF- κ B activation by decreasing the K63-linked ubiquitination of TRAF6 [45]. Thus, NLRC3 functions as a negative modulator of inflammatory pathways [46].

Similar to NLRC3, NLRC5 has been proposed to function as a negative modulator of inflammatory pathways. NLRC5 overexpression inhibits NF- κ B-dependent signalling [38]. NLRP6 also inhibits NF- κ B activation. NLRP6 has been shown to impede NF- κ B activation during bacterial pathogen infection, and in the absence of NLRP6, bacteria are cleared more rapidly, indicating that NLRP6 may serve as a negative modulator of inflammation [47].

The lack of pyrin and caspase domains, which are essential for caspase-1 activation and recruitment, as well as the unique localisation of NLRX1 in the mitochondrial matrix, are the main causes of the specific effects of NLRX1. NLRX1 plays a significant role in suppressing the NF- κ B pathway, negatively regulates antiviral immune responses, and prevents apoptosis [48]. Additionally, NLRX1 interacts with some mitochondrial proteins, such as dynamin-related protein 1, to increase mitochondrial fission and ubiquinol cytochrome *c* reductase core protein II, which is a subunit of complex III, to induce the generation of reactive oxygen species (ROS) [49, 50].

NLRs as positive regulators of inflammation. NLRP3 is the most well-understood NLR in kidney diseases [51]. Activation of the NLRP3 inflammasome requires two signals: the priming signal and the activation signal (Fig. 2). The first signal is related to the expression of NLRP3 and pro-IL-1 β and is mediated by the NF- κ B signalling pathway. IL-6 or TNF- α can also stimulate the NLRP3 inflammasome as the first signal [52]. The second signal is the activation of NLRP3 by copious amounts of priming signals, such as ROS, ATP, amyloid-beta, biglycan, crystals of MSU, hyaluronan, uric acid, and pathogens [53–57]. Soluble biglycan, a macromolecule in the ECM, induces the activation of NLRP3/ASC inflammasomes by signalling through TLR2/4, as well as purinergic P2X7 receptors, and activates the inflammasome in an ROS-dependent manner, releasing caspase-1 and IL-1 β for the subsequent inflammatory response. A lack of ASC has been

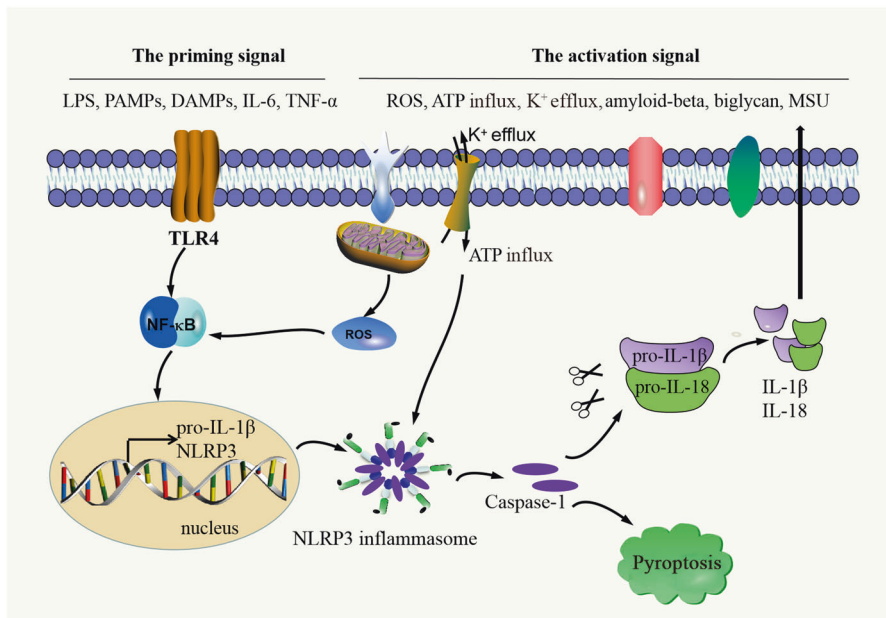


Fig. 2 The activation of NLRP3 inflammasome needs two signals, the priming signal and the activation signal. LPS, PAMPs, DAMPs, IL-6, TNF- α could also stimulate NLRP3 inflammasome as the first signal. The second signal is that the activation of NLRP3 can be initiated by copious amount of activation signals, such as, reactive oxygen species (ROS), ATP, K⁺ efflux, amyloid-beta, biglycan, crystals of monosodium urate (MSU), hyaluronan, uric acid, pathogens, etc.

shown to reduce the secretion of IL-1 β , which is related to biglycan [58]. NLRP3 ubiquitination is also involved in inflammation activation [59]. BRCA1-BRCA2-containing complex subunit 3 (BRCC3), a deubiquitinating enzyme, can deubiquitinate the NLRP3 LRR domain and promote NLRP3 inflammasome activation [60]. Activated NLRP3 recruits ASC, which consists of two major domains (PYD and CARD), and caspase-1 to form a complex called the inflammasome. Inflammasomes induce the activation of caspase-1, resulting in the cleavage of pro-IL-1 β and pro-IL-18 and inducing the release of proinflammatory cytokines, such as IL-1 β and IL-18. In addition, the mature form of caspase-1 can cleave gasdermin D to further induce the form of programmed cell necrosis known as pyroptosis [61, 62].

NLRP3 can work in a canonical (inflammasome-dependent) or noncanonical manner (inflammasome-independent). Canonical inflammasomes convert procaspase-1 into its mature form, caspase-1, whereas noncanonical inflammasomes activate procaspase-11. Moreover, NLRP3 can promote epithelial-mesenchymal transition (EMT) in epithelial cells by enhancing TGF- β 1 signalling and R-Smad activation via inflammasome-independent mechanisms [4, 63, 64]. These findings greatly increase our understanding of the activation and function of NLRP3.

In addition to NLRP3, NLRP1, NLRP2, NLRP6, and NLRP7 are also able to form inflammasomes [65–67]. Moreover, NLRP12 may also assemble inflammasomes [4, 6]. During *Yersinia pestis* infection, NLRP12 has been reported to recognise acylated lipid A, and *NLRP12*^{-/-} mice are more susceptible to infection and have reduced IL-18 levels than wild-type (WT) mice. The recognition of *Y. pestis* expressing a stimulatory LPS by TLR4 leads to the upregulation of acute haemolytic transfusion reactions (AHTR) involving NLRP12 and proinflammatory cytokines, such as IL-18 and IL-1 β . NLRP12 then recognises a ligand produced during *Y. pestis* infection and assembles into an inflammasome that processes IL-18 and IL-1 β [68]. A recent study demonstrated that NLRP12 interacts with NLRP3 and NLRC4 to induce IL-1 β maturation through caspase-1 activation [69]. Redundancy between NLRs may occur, and other NLRs may also participate in optimal responses to infection. These findings support the concept that NLRs work together to optimally protect the host.

NLRP10 has no LRR domain, which is important for the detection of PAMPs or DAMPs [70]. NLRP10 ablation markedly suppresses activation of the NF- κ B signalling pathway and impairs the function of NLRP12 [71]. In this context, NLRP10 may play a regulatory role in the inflammatory response via its association with NLRP12 [72].

ROLE OF NLRs IN RENAL DISEASES

Recent studies have demonstrated that multiple NLRs play essential roles in renal diseases, including acute kidney injury (AKI), obstructive nephropathy (ON), diabetic nephropathy (DN), lupus nephritis (LN), uric acid nephropathy (UAN), and renal cell carcinoma (RCC).

NLRs in acute kidney injury

AKI is a group of life-threatening syndromes characterised by a sudden decrease in the glomerular filtration and the accumulation of waste products [73, 74]. As a risk factor for CKD and end-stage renal disease (ESRD), AKI is associated with high morbidity and mortality [40, 75, 76]. AKI is always caused by ischaemia–reperfusion injury (IRI). The IRI model is widely accepted in AKI-related research [40, 77–79]. Other models include sepsis, oxalate, and nephrotoxic drugs, such as cisplatin, which is a chemotherapeutic drug that is used clinically [80–82]. Although the mechanisms underlying AKI remain unclear, an extensive inflammatory response is regarded as a major contributor to the initiation and progression of AKI. Emerging

studies indicate the importance of NLRs in the pathophysiology of AKI [73, 83–85] (Table 1).

NOD1 and NOD2 in acute kidney injury. NOD1 and NOD2 are the first reported NLRs found in the renal TECs of both mice and humans. Studies indicate the protective effect of NOD2 deficiency in IRI, and a more robust protective effect can be seen after the simultaneous deficiency of NOD1 and NOD2. Consistently, mice with Rip2 deficiency are also protected against IRI [12]. Although NOD1 deficiency shows less functional protection than NOD2 knockout, it has a great impact on neutrophil recruitment in vivo [86]. Additionally, progranulin, an autocrine growth factor, ameliorates renal injury and inhibits apoptosis in part by negatively regulating the NOD2-dependent pathway in mouse kidneys with AKI induced by IR [87]. In addition, ligustrazine, a type of bioactive alkaloid, can protect against AKI by inhibiting NOD2 expression and apoptosis in mice following ischaemia/reperfusion (IR) injury [88]. These findings support the therapeutic potential of NOD1 and NOD2 inhibition in AKI.

NLRC4 in acute kidney injury. NLRC4 is a member of the NOD-like receptor family that can form inflammasome complexes and lead to the subsequent activation of caspase-1 and the secretion of IL-1 β and IL-18. NLRC4 expression is enhanced after IR injury, which is related to T cell immunoglobulin domain and mucin domain-containing molecule-3 (Tim-3) signalling. The administration of RMT3-23, a Tim-3 neutralising antibody, can reduce NLRC4 expression and macrophage infiltration, suggesting that Tim-3-mediated NLRC4 inflammasome activation participates in IR-induced AKI [78]. Although studies concerning the role of NLRC4 in AKI are scarce, this finding presents a novel perspective on the potential action of NLRC4 in IR-induced AKI.

NLRX1 in acute kidney injury. According to its localisation in the mitochondrial matrix and its distinct structure, NLRX1 has a unique effect on AKI. The expression of NLRX1 is decreased in the human kidney in IRI and is positively correlated with increased TEC apoptosis and oxidative stress. Furthermore, NLRX1 deletion contributes to mitochondrial dysfunction and TEC apoptosis during IRI. Mechanistically, NLRX1 can suppress oxidative phosphorylation and excessive ROS formation in IRI to regulate mitochondrial function [48]. Consistently, NLRX1 inhibits type I IFN signalling and NF- κ B activation to exert its anti-inflammatory effects [89, 90]. Based on the above data, NLRX1 is regarded as a pivotal target in mediating a protective effect against renal tissue injury during IRI.

NLRC5 in acute kidney injury. Notably, the expression of NLRC5 has been shown to be markedly increased in mice suffering from IR-induced and cisplatin-induced AKI [40]. NLRC5 expression was also shown to be significantly elevated in HK-2 cells induced by IR. NLRC5 is also involved in NF- κ B-mediated renal inflammation [91]. Ablation of NLRC5 inhibits oxidative stress and apoptosis in HK-2 cells by enhancing the PIK3/Akt signalling pathway [92]. NLRC5 deficiency can reduce inflammatory responses and attenuate cisplatin-induced renal injury. Mechanistically, NLRC5 knockout prevents the activation of CD4⁺ T cells by restoring the expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) [40]. A recent study showed that NLRC5 activates the inflammatory response and exacerbates TEC apoptosis by negatively regulating CEACAM1, which can act through well-known antiapoptotic signalling pathways, including extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt in NRK-52E cells [40]. Moreover, NLRC5 has been recognised as a key regulator of MHC class I gene expression and may work with NLRP3 to induce inflammasomes [93, 94]. Thus, targets of NLRC5 may have novel therapeutic implications in patients suffering from AKI.

Table 1. NLRs involved in different AKI.

Induction models	NLRs involved	Regulation	Function	Mechanism	Reference
cisplatin	NLRP3	Induction	Histological damage, inflammatory response and apoptosis	Activate P2X7 receptors in renal tubular epithelial cells	[253]
	NLRCS	Induction	Activate inflammation response; Exacerbate TEC apoptosis	Negative regulation of CEACAM1 pathway	[40, 93, 94]
IR	NLRP6	Inhibition	Inhibit inflammation; nephroprotective effect	Downregulate ERK1/2 and p38 MAPK phosphorylation	[140, 254]
	NOD1 and NOD2	Induction	Promote tubular epithelial apoptosis and inflammation	Activate downstream proteins Rip2	[12, 87]
	NLRCS	Induction	Activate macrophage; release proinflammatory cytokines and chemokines	Activate Tim-3-mediated NLRCS inflammasome	[78]
	NLRX1	Inhibition	Inhibit tubular epithelial apoptosis and tubular oxidative stress; antiinflammation	Suppress the oxidative phosphorylation and excessive formation of ROS; inhibit type I IFN signalling and NF- κ B activation	[48, 89, 90]
	NLRCS	Induction	Promote tubular epithelial cell apoptosis; Develop posts ischemic inflammation	Negative regulation of CEACAM1 signalling Transcriptional regulator of MHC class I genes	[40, 93, 94]
Sepsis	NLRP3	Induction	Promote inflammatory response; promote tubular apoptosis (leucocyte-associated); impair wound healing (renal-associated)	Biglycan; TLR2/4 dependent manner, interact with purinergic receptor (P2X7R); ATP released from damage cell (mitochondria); Activate mROS-TXNIP pathway; Activate MAPK signalling pathway	[55, 58, 73, 96, 217, 253]
	NLRP3	Induction	Promote renal inflammation	Promote oxidative stress; Inhibit TLR4-NF- κ B/NLRP3 inflammasome pathway; Regulate Nrf2 pathway	[116, 118, 119, 255]
Oxalate	NLRP3	Induction	Trigger local inflammation; Induce necroptosis and MPT-related cell necrosis	TEC releasing ATP for activation of NLRP3/ASC/caspase-1 axis	[121, 122, 256]
Rhabdomyolysis	NLRP3	Induction	Promote inflammation, cell apoptosis, and tubular injury	Through TXNIP-NLRP3-ASC inflammasome chain	[125, 126]
Paraquat	NLRP3	Induction	Release inflammatory cytokines (TNF- α /IL-1 β /IL-18)	Regulate NF- κ B and death-associated protein kinase (DAPIK)	[128]
Contrast	NLRP3	Induction	Promote kidney inflammation and apoptosis	TLR4/NLRP3 inflammasome pathway	[130]

Table 2. Function of NLRP3 in different renal diseases.

Renal disease	Regulation	Role in renal disease	Signalling pathway	Reference
Acute kidney injury	Induction	Promote inflammation, cell apoptosis, and tubular injury	TLR2/TLR4/P2X7R-NLRP3; mROS-TXNIP-NLRP3 pathway; MAPK signalling pathway; TLR4-NF-κB/NLRP3; NF-κB and DAPK-regulated NLRP3 inflammasome	[73, 95, 96, 116, 119, 125, 128]
Obstructive nephropathy	Induction	Promote renal inflammation and fibrosis (canonical) prevent from interstitial oedema, preserve renal integrity, attenuate renal injury	NLRP3-ASC-caspase-1-IL-1β; ROS-TXNIP-NLRP3 pathway; TGF-β/Smad signalling; IKKβ/IκB/NF-κB axis; Reduce claudin-1,-2,-5 and VE-Cadherin expression	[51, 54, 63, 141, 144, 146]
Diabetic kidney disease	Induction	Promote progression of diabetic nephropathy; Promote inflammation and fibrosis; Induce pyroptosis; Induce podocyte apoptosis	ROS/TXNIP/NLRP3 pathway; NLRP3-ASC-caspase-1-IL-1β; Syk/JNK/NLRP3 signalling; ATP-P2X4 signalling pathway; P2X7R/NLRP3 pathway; TLR4/NF-κB/NLRP3 pathway;	[153, 160, 161, 163, 164, 167, 170, 182, 257–261]
IgA nephropathy	Induction ^a (transient)	Promote chronic inflammation, tubular injury and fibrosis	TGFR/NLRP3 axis	[215]
Renal cell carcinoma	Inhibition	Suppress tumour growth, regulate tumour metastasis	Liver X receptors/NLRP3	[234]
Lupus nephritis	Induction	Promote production of inflammatory cytokines	NF-κB/NLRP3 inflammasome	[200]
Diet-induced nephropathy	Induction	Promote macrophage infiltration and SREBP2 and LDLR-mediated cholesterol accumulation	NLRP3/ACS/caspase-1 pathway	[217]
Crystal nephropathy	Induction	Promote renal inflammation response; Involved in regulated renal tubular cell necrosis (necroptosis)	NLRP3/ASC/caspase-1 axis RIPK3/MLKL/NLRP3 TNFR pathway	[218–220]
HIV-Associated Nephropathy	Induction	Promote podocyte pyroptosis and damage	NLRP3/ACS/caspase-1 pathway	[222]
Uric acid nephropathy	Induction	Promote inflammation response and inflammatory progression	miR-122-5p/BRCC3 pathway NLRP3/ACS/caspase-1 pathway	[225, 227]

^aNLRP3 is predominantly expressed in renal tubular cells (HPTC), a loss of NLRP3 expression is correlated to advancing IgAN where loss of tubular epithelial phenotype and cellular demise exist.

NLRP3 in acute kidney injury. NLRP3, an important member of the NOD-like receptor family, is composed of an LRR, an NOD domain, and an N-terminal effector domain [7]. In addition to its interleukin-associated and pyroptosis-inducing effects, NLRP3 contributes to immunity and tissue injury [54]. NLRP3 contributes to renal injury in a cell-specific manner. NLRP3 is expressed in leucocytes and is related to tubular apoptosis, and NLRP3 in the kidney has been reported to interfere with the tissue repair process [95]. Several studies have indicated the critical role of NLRP3 in different types of AKI (Table 2).

IR-induced acute kidney injury. Recent studies have provided evidence that the NLRP3 inflammasome plays a crucial role in IR-induced AKI. One study showed that the NLRP3 inflammasome was activated in IR-induced AKI and peaked after 3 days of reperfusion, and mitochondrial damage and cytochrome c redistribution were tested in WT IR mice [96]. The accumulation of damaged mitochondria had a positive effect on ROS overproduction, mainly in the proximal tubules, which could further activate the NLRP3 inflammasome and induce subsequent inflammation through the mROS-TXNIP-NLRP3 pathway [97, 98].

TEC pyroptosis is one of the main pathological features of renal IRI. ROS can induce NLRP3 through TEC pyroptosis in renal IR, which in turn initiates ROS production [99]. Additionally, ATP released from necrotic cells also participates in activating the NLRP3 inflammasome. Furthermore, according to this hypothesis, NALP3 may function via downstream activation of the MAPK signalling pathway during I/R injury [73]. Inhibiting the inflammatory response protects the kidneys from further damage. In *NLRP3*^{-/-} mice, kidney injury and inflammation activation were attenuated, and the deletion of NLRP3 further protected the kidney from acute tubular necrosis and apoptosis [96, 100]. Moreover, another study showed that *NLRP3*^{-/-} mice but not *Asc*^{-/-} or *caspase-1*^{-/-} mice were protected from IRI, suggesting a direct effect of NLRP3 on TECs leading to IRI, which is independent of inflammasome formation [101]. A recent study showed that in *caspase-11*^{-/-} mice, IR-induced NLRP3 inflammasome activation, renal functional deterioration, and tubular morphological changes were significantly attenuated [102]. P2X7R is associated with the release of IL-1β via activation of the NLRP3 inflammasome. P2X7R deficiency protects against renal IRI and attenuates NLRP3 inflammasome formation [103].

Notably, NLRP3 has been identified as a target for ameliorating IR-induced AKI. MitoTEMPO, a mitochondrial antioxidant, could reduce the overproduction of mROS, thereby inhibiting the activation of the NLRP3 inflammasome. By using siRNA targeting TXNIP (siTXNIP), the interaction between TXNIP and the inflammasome can be inhibited, and the levels of IL-1 β and IL-18 are lowered [96]. Cathelicidin-related antimicrobial peptide (CRAMP) has been shown to have a renal protective effect against I/R-induced AKI. In addition, CRAMP deficiency in mice can exacerbate inflammatory responses and apoptosis through NLRP3 inflammasome overexpression. Thus, CRAMP exerts a renoprotective effect by suppressing the activation of the NLRP3 inflammasome and further inflammation and apoptosis [104]. This evidence suggests that NLRP3 participates in IR-induced AKI through both inflammasome-dependent and inflammasome-independent mechanisms.

Cisplatin-induced acute kidney injury. In recent years, an increasing number of studies have shown that the NLRP3 inflammasome may promote the progression of cisplatin-induced AKI. The levels of NLRP3, as well as its related factors caspase-1 and IL-1 β , are significantly upregulated by cisplatin [105]. The upstream mechanisms regulating NLRP3 have also been studied. Autophagy activated by cisplatin can inhibit NLRP3 expression and inflammasome assembly [105]. The upregulation of P2X7R contributes to the development of cisplatin-induced nephrotoxicity, most likely via the NLRP3 pathway. Moreover, cancer patients are commonly prescribed proton pump inhibitors (PPIs), such as lansoprazole, for gastrointestinal complications. Evidence shows that lansoprazole promotes cisplatin-induced AKI by activating NLRP3 [106].

NLRP3 may be considered a novel therapeutic target for cisplatin-induced AKI. P2X7R blockade with the antagonist A-438079 can reduce kidney injury and oxidative stress by inhibiting the activation of NLRP3 and its downstream compounds ASC and caspase-1 in C57BL/6 mice [46]. Omeprazole, a major PPI, exerts a protective effect against cisplatin-induced damage in both HK-2 cells and rat kidneys by inhibiting the TLR4/NF- κ B/NLRP3 signalling pathway [107]. Treatment with the SS-31 peptide could reduce apoptosis in cisplatin-induced AKI mice and protect the kidneys from injury by inhibiting the activation of the ROS-NLRP3-IL-1 β /caspase-1 pathway in mitochondria [108]. Astragaloside IV protects against cisplatin-induced kidney injury via autophagy-mediated inhibition of NLRP3 in rats [109]. Overall, although the precise mechanisms of cisplatin-induced nephrotoxicity have yet to be elucidated, these findings provide novel insight into the role of NLRP3 in the development and progression of cisplatin-induced AKI, as well as targeting NLRP3 as a therapeutic strategy for cisplatin-induced AKI.

Sepsis-induced acute kidney injury. AKI is a major complication of sepsis. The NLRP3 inflammasome plays a significant role in the occurrence and development of sepsis-induced AKI [110, 111]. The expression of NLRP3, as well as the downstream proinflammatory cytokines IL-1 β and IL-18, is elevated in LPS-induced AKI. Moreover, a recent study showed that the functional difference between M1 and M2 macrophages in sepsis-induced AKI is a result of exosome-mediated pyroptosis regulated by NLRP3 [112]. By inhibiting the NLRP3 inflammasome, kidney tissues can be protected from damage [113]. An increasing number of studies have indicated that long noncoding RNAs (lncRNAs) exert crucial effects on sepsis-induced AKI. Recently, the lncRNA RMRP was shown to facilitate inflammation by activating the NLRP3 inflammasome [114]. In addition, pyroptosis, which is induced by LPS, has been reported to be involved in sepsis-induced AKI. The lncRNA plasmacytoma variant translocation 1 is involved in regulating NLRP3-mediated pyroptosis in septic AKI by targeting miR-20a-5p [115].

It is worth noting that the NLRP3 inflammasome has been identified as a target for treating sepsis-induced kidney injury.

Sirtuin1 (SIRT1), a key member of the sirtuin family, suppresses activation of the NLRP3 inflammasome, and SIRT1 overexpression increases the viability of TECs, thereby protecting against sepsis-induced AKI [110]. Hyperin alleviates the inflammatory response by inhibiting the NLRP3 signalling pathway in sepsis-induced AKI [116]. Exogenous CO released after treatment with CO-releasing molecule 2 has been shown to restore the decline in renal function in sepsis-induced AKI rats in an NLRP3 inflammasome-dependent manner; however, a detailed mechanism for this has yet to be determined [117]. Mangiferin can ameliorate oxidative stress and inflammatory responses in mice with AKI induced by caecal ligation and puncture by inhibiting NLRP3 inflammasome activation and upregulating the expression of the nuclear transcription factor Nrf2 [118]. Cluster of differentiation 39, an inflammatory inhibitor, has been reported to play a protective role in renal TEC damage by reducing NLRP3 activation and partly inhibiting the overexpression of ROS [80].

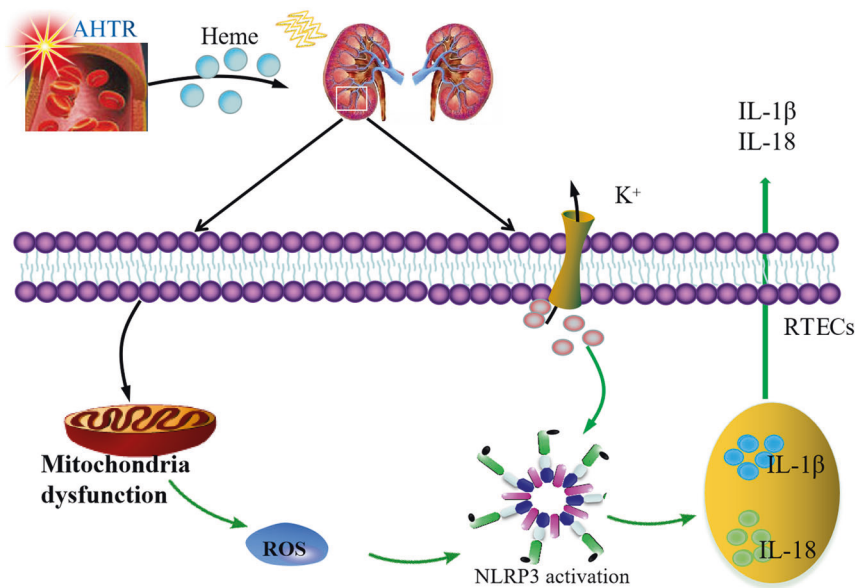
At present, studies are increasingly showing that traditional Chinese medicines or monomers have therapeutic effects on AKI. Harmine, a factor in *Peganum harmala* L, has been shown to protect mice against LPS-induced AKI by reducing oxidative stress and inflammation, and the underlying mechanisms may correlate with the suppression of TLR4-NF- κ B and deactivation of the NLRP3 inflammasome [119]. 5-O-Methylidihydroquercetin (GS1) and cilicicone B (GS2), two traditional Chinese medicines, have protective effects on mice induced by LPS. These agents can reduce the inflammatory response and oxidative stress via the MyD88/TRIF/NLRP3 pathway [120]. These findings indicate that the NLRP3 inflammasome could be a key mediator and therapeutic target in sepsis-induced AKI.

Other types of acute kidney injury. NLRP3 also participates in the development of other types of AKI. Acute calcium oxalosis can induce AKI as a result of CaOx deposition in the distal tubule, which can not only trigger local inflammation via the NLRP3/ASC/caspase-1 axis in dendritic cells but also induce necroptosis, as well as mitochondrial permeability transition-related cell necrosis. In addition, crystals can be absorbed by TECs, causing the cells to release ATP, which can induce subsequent NLRP3 inflammasome activation [121, 122].

Rhabdomyolysis-induced AKI (RIAKI), which has the characteristics and features of muscle damage and toxic contents released into the circulation, is one of the main manifestations of community-acquired AKI [123]. NLRP3 plays a vital role in the development of RIAKI during the early phase. NLRP3 inflammasomes contribute to inflammation, apoptosis, and tubular injury in the kidneys. Initial activation of the NLRP3 inflammasome is predominantly triggered in renal tubular cells. In addition, these manifestations can be ameliorated in mice that are deficient in NLRP3 or its downstream molecules, such as ASC, caspase-1, and IL-1 β [124, 125]. Anisodamine, an acetylcholine receptor antagonist, exerts protective effects against RIAKI through the ER stress-mediated TXNIP-NLRP3-ASC inflammasome axis [126].

Blood transfusion may result in an AHTR, which represents a danger to patients by damaging kidney function. High concentrations of haem in AHTR could promote NLRP3 inflammasome activation in RTECs, leading to renal dysfunction (Fig. 3) [127]. These findings highlight the importance of haem-induced NLRP3 activation in RTECs in kidney function.

The NLRP3 inflammasome also contributes to paraquat-induced AKI regulated by NF- κ B and death-associated protein kinase in rats [128]. With the widespread use of contrast media in diagnosis and treatment, contrast-induced AKI (CI-AKI) has become the third most common cause of hospital-acquired renal failure [129]. The expression of NLRP3 and its adaptor ASC was increased in vitro and in vivo. A cell-based study demonstrated that the NLRP3 inflammasome was related to



AHTR: acute hemolytic transfusion reactions
RTECs: Renal tubular epithelial cells

Fig. 3 Heme in an AHTR activates NLRP3 inflammasome in RTECs leading to renal dysfunction. Blood transfusion, a common therapy in clinic, may result in AHTR occurrence after administration of a blood product. Once AHTR occurs, a mass of heme is produced. High concentrations of heme in an AHTR could promote NLRP3 inflammasome activation in RTECs leading to renal dysfunction.

apoptosis in CI-AKI. Consistently, the absence of NLRP3 can lead to the inactivation of apoptosis-associated proteins and the inhibition of IL-1 β and IL-18 secretion [130]. The NLRP3 inflammasome is activated to promote kidney inflammation and apoptosis, thus participating in the development of CI-AKI via the S100A8/A9-TLR4 pathway [131]. In addition, PINK1-Parkin-related mitophagy reduces TEC apoptosis and renal injury in CI-AKI by inhibiting activation of the NLRP3 inflammasome [132]. The upregulation of microRNA-30c was shown to suppress apoptosis in CI-induced AKI by targeting NLRP3 [133]. α Klotho has been shown to exert therapeutic effects on CI-AKI and reduce contrast-induced renal tubular cell pyroptosis by inhibiting NLRP3 inflammasome activation [134]. Taken together, these findings provide strong evidence for the use of NLRP3 as a therapeutic target in these types of AKI.

NLRP3 in acute kidney injury in patients with COVID-19. Recent studies have shown that AKI occurs in 37%–56% of COVID-19 patients, of which 67% develop stage 3 AKI [135, 136]. SARS-CoV-2 causes specific dysfunction of the kidney proximal tubule by binding to the angiotensin converting enzyme 2 receptor, which is highly expressed in proximal tubule cells [137]. Another mechanism through which SARS-CoV-2 can affect the kidney is the occurrence of a cytokine storm induced by viral infection that may influence the kidney both directly and indirectly by triggering sepsis, hypoxia, shock and rhabdomyolysis [138]. In SARS-CoV-2 infection, overactivation of the NLRP3 inflammasome leads to a cytokine storm [139]. Targeting NLRP3 may be a potential therapeutic strategy for AKI in patients with COVID-19.

NLRP6 in acute kidney injury. NLRP6, a poorly characterised NLR that forms atypical inflammasomes, has recently been shown to have a nephroprotective role in AKI. During nephrotoxic kidney injury, NLRP6 expression is downregulated. NLRP6 deficiency promotes the inflammatory response and exacerbates the severity of nephrotoxic AKI by suppressing ERK1/2 and p38 mitogen-

activated protein kinase (MAPK) phosphorylation, as well as the expression of the nephroprotective gene Klotho [140].

NLRs in obstructive nephropathy

Progressive renal disease is associated with tubulointerstitial inflammation and fibrosis [141]. Ureteral obstruction is characterised by reduced expression of aquaporin water channels and an inflammatory response. In unilateral ureteral obstruction (UUO) nephropathy, evidence shows that the NLRP3 inflammasome is activated and plays a vital role in disease progression.

NLRP3 has a canonical effect on mice through the NLRP3-ASC-caspase-1-IL-1 β axis, which is important in renal inflammation and fibrosis [51, 54]. Consistently, NLRP3-knockout mice show reduced tubular injury, alleviated mitochondrial dysfunction, and reduced tubulointerstitial inflammation and fibrosis, and these effects correlated with the inhibition of caspase-1 activity and IL-1 β /IL-18 production [51, 142]. The upregulation of IL-36 in mouse TECs induced by UUO plays a significant role in the progression of renal tubulointerstitial lesions, which further induce renal inflammation and fibrosis by activating the NLRP3 inflammasome [143]. Furthermore, ROS are a hallmark of ON and have been shown to be essential binding molecules for subsequent NLRP3 inflammasome activation [144]. Apart from the canonical effects, NLRP3 also participates in the pathophysiology of UUO in an inflammasome-independent manner. NLRP3 induces the activation of TGF- β /Smad signalling and the EMT process in renal epithelial cells via an inflammasome-independent mechanism as a further explanation for the inhibition of fibrosis in *NLRP3*^{-/-} mice with UUO [63]. Intriguingly, another study reported the protective effect of NLRP3 against early tubular injury. NLRP3 mRNA expression is elevated in renal TECs and myofibroblasts, prevents interstitial oedema in the kidney, and preserves renal integrity to attenuate renal injury [141]. This controversial result may be associated with the characteristics of the different stages of ON.

Notably, NLRP3 has been viewed as a target of ON treatment. A growing number of agents protect against ON by inhibiting the

NLRP3 inflammasome. For example, aliskiren (an inhibitor of renin), mefunidone (a novel synthetic compound), and fluorofenidone (a low-molecular-weight pyridine agent) downregulate NLRP3 inflammasome components in ON and further inhibit the subsequent release of IL-1 β [145–147]. Additionally, ghrelin, cyclic helix B peptide, and H₂S can alleviate renal fibrosis by suppressing the NLRP3 pathway [148–150]. These findings support the therapeutic potential of NLRP3 inhibition in UOU.

NLRs in diabetic nephropathy

DN is characterised by both glomerular sclerosis and tubulointerstitial fibrosis and is a major cause of ESRD [151, 152]. The mechanisms underlying the development and progression of DN are complicated, and metabolic disorders, such as hyperglycaemia and inflammation, play specific roles. Studies are increasingly demonstrating that several NLRs, including NLRP3, NOD1, and NOD2, play key roles in the pathophysiological process of DN. Notably, a large amount of evidence has been reported in relation to NLRP3.

NLRP3 in diabetic nephropathy. The expression of inflammasome-related factors, such as NLRP3, IL-18, and IL-1 β , is increased in patients and mouse models of DN [153]. Emerging evidence has shown that NLRP3 inflammasome activation is a central mediator of renal inflammation in DN [154]. Knockout or inhibition of NLRP3 suppresses inflammation and fibrosis to protect the kidneys from DN. Inhibition of the NLRP3 inflammasome reduces podocyte damage by suppressing lipid accumulation in DN [155]. Relative NLRP3 mRNA expression is not only an independent predictor of DN but also a potent biomarker for identifying DN in patients with T2DM [156]. However, the mechanisms underlying NLRP3 activation in DN remain unclear. Despite this, evidence indicates that multiple molecules are involved in the regulation of NLRP3 in DN.

NLRP3 and ROS in diabetic nephropathy. Recently, various theories regarding the role of NLRP3 in DN have been suggested, including potassium efflux, lysosome rupture, and ROS overproduction. The latter is widely accepted [7, 157]. High levels of mitochondrial ROS correlate with the upregulated expression of NLRP3/IL-1 β in the human tubular HK-2 cells of patients with DN and *db/db* mice, and this effect can be reversed by treatment with the antioxidant MitoQ, indicating that the mtROS-TXNIP/NLRP3/IL-1 β axis may contribute to tubular injury, while the inhibition of this axis exerts renal protective effects [158, 159]. High glucose levels induce ROS-NLRP3 inflammasome signalling activation, partly via sweet taste receptors (STRs). This response can be reversed by the STR inhibitor lactisole [160].

NLRP3 and TXNIP in diabetic nephropathy. In addition to ROS, TXNIP activates the NALP3 inflammasome in DN. TXNIP binds with the antioxidant thioredoxin (TRX) in the physiological state. In DN, TXNIP is upregulated, and high glucose levels activate the ROS/TXNIP/NLRP3 pathway, which leads to ROS-mediated dissociation of TRX and TXNIP in mesangial cells [161]. Silencing TXNIP inhibits NLRP3 inflammasome activation via the TXNIP-NLRP3 pathway [162, 163]. Thus, TXNIP may play a pivotal role in the pathogenesis of DN through the oxidative stress pathway, and TXNIP inhibition could provide a novel therapeutic strategy for DN [164]. In addition, gp91^{phox}, a subunit of NADPH oxidase, was upregulated in DN mice, enhancing NLRP3 and TXNIP simultaneously. Furthermore, NADPH oxidase activation is driven by TXNIP, which can trigger activation of the downstream NALP3 inflammasome in podocytes [165]. Moreover, one study reported that high glucose levels induced NLRP3 inflammasome activation through the Syk/JNK pathway. JNK activation can be inhibited by the Syk inhibitor BAY61-3606 and Syk-siRNA in HG-induced HK-2 cells and rat

glomerular mesangial cells, subsequently downregulating the expression of NLRP3 and mature IL-1 β [153].

NLRP3 and P2X7R in diabetic nephropathy. Additionally, evidence demonstrates that a lack of P2X7R attenuates renal inflammation, fibrosis, and NLRP3 inflammasome component expression and activation induced by a high-fat diet. These findings indicate that P2X7 may participate in renal inflammation and injury by activating the NLRP3 inflammasome [166]. P2X7R is also related to DN pathogenesis, such as podocyte injury. Ophiocordyceps sinensis, an artificially developed agent, effectively downregulates the expression of P2X7R and NLRP3 to alleviate podocyte injury [167]. In DN, high glucose activates the NLRP3 inflammasome through the ATP-P2X4 signalling pathway to promote the progression of tubulointerstitial inflammation in DN. Consistently, apyrase (extracellular ATP scavenger), suramin (P2 receptor inhibitor), TNP-ATP (P2X receptor antagonist), and 5-BDBD (P2X4 inhibitor) downregulate NLRP3 expression in DN [168–170].

NLRP3, pyroptosis, and lncRNAs in diabetic nephropathy. In addition, pyroptosis induced by high glucose has been reported to function in DN. Pyroptosis is involved in activating ELAVL1, a protein downstream of NLRP3, and caspase-1, which promotes the release of IL-1 β and IL-18. The upregulation of the lncRNA MALAT1 and the downregulation of miR23c expression in streptozotocin-induced diabetic mice and high glucose-treated HK-2 cells abrogates the inhibition of ELAVL1 and promotes downstream NLRP3 expression and ultimately pyroptosis, leading to DN development [171]. In addition, lincRNA Gm4419 knockdown ameliorated inflammation and fibrosis in mesangial cells under high glucose conditions via the NF- κ B/NLRP3 pathway, suggesting that the upregulation of GM4419 contributes to inflammation and fibrosis in mesangial cells [172]. These data suggest that lncRNAs participate in the occurrence and progression of DN by targeting the NLRP3 signalling pathway.

NLRP3 and IL-22 in diabetic nephropathy. IL-22 has anti-inflammatory effects on DN, markedly downregulates the expression of NLRP3, and further suppresses IL-1 β maturation. Wang et al. showed that IL-22 gene therapy not only alleviates systemic syndromes, such as hyperglycaemia, but also inhibits renal fibrosis, the accumulation of ECM, and the proliferation of mesangial cells by suppressing the NLRP3/caspase-1/IL-1 β pathway [173]. The impact of glycation end products (AGEs) on cytokines remains controversial. Advanced AGEs can promote mitochondrial ROS production and activate inflammasomes to release IL-1 β in podocytes via RAGE-mediated signalling [174]. Other studies have suggested that AGEs fail to induce IL-1 β release in bone marrow-derived macrophages and THP-1 cells, inhibiting NLRP3 inflammasome activation [175].

NLRP3 as a target for diabetic nephropathy treatment. An increasing number of studies have inhibited the activation of NLRP3 in the treatment of DN. Generally, targeting NLRP3 leads to the suppression of multiple signalling pathways, such as oxidative phosphorylation, and the excessive formation of ROS and NF- κ B activation. For example, liquiritigenin, thrombomodulin domain 1, and tetrahydrostilbene glucoside can reduce the inflammatory response in DN mice by inhibiting the NF- κ B signalling pathway, suppressing NLRP3 inflammasome activation, and enhancing Nrf2 antioxidant activity [176–178]. Ginsenoside compound K, minocycline, and apocynin exert protective effects against DN by inhibiting oxidative stress and the ROS/NLRP3 and NF- κ B/p38 signalling pathways and stabilising Nrf2 [179–181].

In addition, several Chinese herbs or monomers have been shown to exert protective effects against DN by suppressing the NLRP3 signalling pathway. For example, Huangkui capsule can

reduce renal tubular EMT, which is the major cause of interstitial fibrosis in DN, most likely by inhibiting NLRP3 inflammasome activation and the TLR4/NF- κ B signalling pathway [182]. Piperine, luteolin, and naringin inhibit the inflammatory response in rats by suppressing NF- κ B and NLRP3 activation, thus reducing podocyte apoptosis [168, 183–185]. Salidroside, a component of *Rhodiola rosea*, downregulates the level of ROS and ECM overproduction in mesangial cells treated with high glucose in rats through the TXNIP-NLRP3 inflammasome pathway [163].

These findings underscore the complex mechanisms of NLRP3 in the development of DN and suggest NLRP3 as a potential therapeutic target in DN (Table 2).

NOD1 and NOD2 in diabetic nephropathy. NOD2 is expressed in glomerular mesangial cells, endothelial cells, podocytes, TECs, and inflammatory cells [12]. It was recently discovered that NOD2 receptors also function in DN. In vitro, NOD2 receptors have been reported to induce inflammation and insulin resistance [186]. NOD2 overexpression is positively related to the severity of renal injury in biopsy specimens from patients with DN. Recent studies indicate that glomerular endothelial cells (GEnCs) play a pivotal role in restricting the development of proteinuria and further renal dysfunction [187]. NOD2 activation can promote the endothelial-to-mesenchymal transition (EndMT) in GEnCs via the MEK/ERK signalling pathway. NOD2 knockdown drastically diminished high glucose-induced EndMT [188]. NOD2 deficiency can attenuate the high glucose-induced downregulation of nephrin, which is vital for maintaining podocyte integrity [186]. Furthermore, NOD1 receptors contribute to the pathogenesis and development of DN via the NOD1-RICK-NF- κ B inflammatory signalling pathway, which plays a critical role in the progression of insulin resistance [189]. Consistently, NOD1 is involved in metabolic inflammation and insulin resistance induced by obesity, and NOD1 deficiency protects against high-fat diet-induced insulin resistance [190, 191]. Based on these findings, therapies based on NOD1 may provide a therapeutic benefits.

NLRs in lupus nephritis

The occurrence and development of LN, a serious complication of systemic lupus erythematosus, is thought to be facilitated by inflammation. Evidence shows that the NLRP3 inflammasome in podocytes participates in LN development, contributing to cell injury and proteinuria [192–194]. Furthermore, a positive relationship between NLRP3 activation and disease activity index has recently been demonstrated [195]. The NLRP3 inflammasome promotes the production of inflammatory cytokines, such as IL-1 β and IL-18, which are increased in the renal tissues of MRL/lpr mice. Indeed, the upstream signalling pathways that regulate NLRP3 expression in LN have been extensively studied. The NLRP3 inflammasome is activated in podocytes via the RIP3-dependent pathway, and the inhibition of RIP3 slows disease progression. Studies have reported that glycogen synthase kinase 3 β and P2X7R activation aggravate the development and progression of LN by activating the NLRP3/IL-1 β pathway [196–198]. These data indicate that the NLRP3 inflammasome is involved in the pathophysiology of LN.

The overexpression of A20 (also known as tumour necrosis factor alpha-induced protein 3) has been reported to inhibit immune complex deposition and the inflammatory response in LN induced by pristane by blunting the NF- κ B/NLRP3 pathway in mice [199]. A recent study showed that Fc γ RI silencing attenuated LN injury by suppressing NF- κ B-regulated NLRP3 inflammasome activation and reducing NLRP3 inflammasome-associated inflammatory cytokines in the kidneys of MRL/lpr mice [200]. Blockade of the AMPK pathway further inhibited the activation of NLRP3, exacerbating pyroptosis in TECs and LN progression [201].

To date, NLRP3 has been viewed as a target for alleviating LN severity. For example, the anaesthetic isoflurane reduces renal IC

deposition, as well as the level of BUN, proteinuria, and macrophage infiltration, via NLRP3 activation and inflammasome formation [202]. Xenon, an inert anaesthetic gas, decreases neutrophil infiltration in the glomerulus and thus protects the kidneys from injury by inhibiting activation of the NF- κ B/NLRP3 inflammasome [203]. In addition, tris dipalladium has been shown to alleviate tubulointerstitial inflammation and restore renal function by suppressing MAPK (ERK, JNK)-mediated NLRP3 activation, as well as the autophagy/NLRP3 pathway [204]. Procyanidin B2, icariin, and Bay11-7082 significantly inhibited LN development in MRL/lpr mice by suppressing NLRP3 inflammasome activation [205, 206]. Thus, NLRP3 inhibitors are important therapeutic tools that should be further developed to prevent the progression of LN.

NLRs in other kidney diseases

NLRs in IgA nephropathy. IgA nephropathy (IgAN), which is characterised by IgA1 immune complex deposition in the glomerular mesangium, is one of the most common types of primary glomerulonephritis with chronic, progressive characteristics, and 20%–40% of patients progress to ESRD within 20 years [207, 208]. NLRP3 expression was significantly increased in a mouse model and in patients with IgAN. Mechanistically, IgA immune complexes contribute to mitochondrial dysfunction and the overproduction of mROS by activating the NLRP3 inflammasome in macrophages. NLRP3 deficiency protects against renal injury in IgAN [209]. In addition, IgA1 could induce NLRP3 expression in podocytes and macrophage transdifferentiation in podocytes, resulting in a subsequent inflammatory response and renal fibrosis in IgAN [210].

NLRP3 is regarded as a potential therapeutic target for alleviating the progression of IgAN. For example, osthole and antroquinonol, which are isolated from traditional Chinese medicines, play protective roles in IgAN development by inhibiting ROS production and NLRP3 inflammasome activation [211, 212]. Resveratrol alleviates sclerosis and inflammation in glomeruli by inhibiting mitochondrial damage and NLRP3 inflammasome activation [213]. Compound K, a metabolite of intestinal bacteria, serves as a therapeutic agent for IgAN by enhancing autophagy-mediated NLRP3 inflammasome inhibition [214].

According to recent studies, NLRP3 is predominantly expressed in primary renal tubular cells (PRTC). NLRP3 expression is transiently induced in PRTCs by TGF- β 1 but decreases over time as cells lose their epithelial phenotype in vitro. Surprisingly, lower levels of NLRP3 mRNA expression have been associated with a worse prognosis in IgAN patients. This outcome may be due to the loss of the tubular epithelial phenotype and cell death associated with decreased NLRP3 mRNA and protein levels in the tubules. The loss of NLRP3 in advancing IgAN seems plausible in progressive tubular atrophy and renal fibrosis, although the functional role of NLRP3 in IgAN pathogenesis has yet to be fully elucidated [215].

NLRs in diet-induced nephropathy. Chronic kidney disease can be initiated by related metabolic syndromes. NLRX1, a member of the NLR family that is localised specifically in mitochondria and lacks the necessary domain to form inflammasomes, can induce ROS generation and affect NF- κ B- and JNK-dependent signalling [49]. Diet-induced renal dysfunction can be prevented by NLRX1 deletion in mice. The absence of NLRX1 prevents high plasma creatinine compared with that in Western diet (WD)-fed WT mice and prevents hyperuricaemia after WD feeding compared to control feeding. Tubular PLIN2 surrounding neutral lipid droplets in NLRX1 KO kidneys was reduced compared to WT kidneys. It has been suggested that the prevention of WD-associated nephropathy in NLRX1 deletion plays a protective role in WD-associated nephropathy by inhibiting renal lipid accumulation and toxicity [216]. In addition, the presence of NLRP3 is pivotal for the

development of WD-induced nephropathy, most likely via macrophage infiltration and cholesterol accumulation, which could be reversed by NLRP3-knockout [217].

NLRs in crystal nephropathy. Apart from cytotoxicity, cystine crystals, which accumulate in the lysosome, can induce IL-1 β secretion via the NLRP3 inflammasome, indicating a novel pathway for the pathogenesis of nephropathic cystinosis [218]. Crystals can also induce inflammation by activating NLRP3 and inducing the subsequent secretion of IL-1 β in dendritic cells. The TNF receptor pathway, as well as RIPK3/MLKL, have been reported to activate the NLRP3 inflammasome, eliciting a subsequent renal inflammatory response. Furthermore, certain cytokines can induce necrosis in renal tubules [219]. CaOx crystals can trigger innate immunity via the release of IL-1 β through the NLRP3/ASC/caspase-1 axis in mononuclear phagocytes [122]. In addition, uromodulin can be deposited in the tubule to form nanoparticles, which could function as an endogenous danger signal to activate the NLRP3 inflammasome and its downstream molecule ASC. These reactions should take place when crystals are taken up into lysosomes of monocytes and dendritic cells, leading to cathepsin leakage, oxidative stress, and potassium efflux [220].

NLRs in HIV-associated nephropathy. Podocyte dysfunction plays a vital role in the development of HIV-associated nephropathy (HIVAN) [221]. HIV can mediate podocyte pyroptosis and damage T lymphocytes by promoting NLRP3 inflammasome formation and the activation of the downstream molecule caspase-1. The underlying mechanism may be related to the generation of ROS and K⁺ efflux, since this effect can be partly attenuated by Tempol (an antioxidant) and glyburide (potassium efflux inhibitor) [222]. Further study of this mechanism will help to improve our understanding of HIV and provide a potential new strategy for HIVAN in the future.

NLRs in uric acid nephropathy. UAN is characterised by the overproduction of uric acid, which results in hyperuricaemia. Urate crystal deposition-mediated activation of the NLRP3 inflammasome and IL-1 β release play critical roles in the development and progression of UAN [223, 224]. The lncRNA ANRIL can participate in the pathogenesis of UAN via the miR-122-5p/BRCC3 pathway to further activate the NLRP3 inflammasome [225]. Weicao capsule, a Chinese herbal, can protect against kidney injury by promoting autophagy and inhibiting NLRP3-induced inflammation [226]. G31P, an antagonist of CXCR1/CXCR2, has been shown to alleviate the inflammatory response and inhibit inflammatory progression in UAN by inhibiting NLRP3 activation [227]. These findings suggest that NLRP3 inhibition may be a treatment for UAN.

NLRs in obstructive sleep apnoea-associated CKD. Chronic intermittent hypoxia, which is a major feature of the pathogenesis of obstructive sleep apnoea (OSA), can lead to oxygen deficiency in the kidney, accelerating local ROS generation, and this accumulation can further trigger NLRP3 activation and the subsequent release of the inflammatory cytokine IL-1 β . Furthermore, it has been demonstrated that there may be positive feedback between miR-155 and NLRP3. Consistently, the overexpression of miR-155 can enhance the activation of NLRP3 by inhibiting the FOXO3a gene [228]. This finding provides novel insights into NLRP3 blockade as an OSA-related CKD treatment.

NLRs in renal cell carcinoma

RCC has a high rate of incidence and mortality, ranking second in the uropoietic system [229]. In 75% of cases, clear-cell renal cell carcinoma (ccRCC) is the most commonly diagnosed histological type among RCCs and is related to dysfunction of the von Hippel Lindau gene [230, 231]. Evidence is increasingly demonstrating that NLRs play important roles in RCC.

NLRP3 in renal cell carcinoma. The role of NLRP3 in the progression and development of RCC remains controversial. NLRP3 expression is elevated in human RCC tissues [232]. Consistently, NLRP3, caspase-1, and IL-1 β expression was increased in ccRCC in a pilot study [233]. Notably, NLRP3 is considered to be a potential target for RCC treatment. Resveratrol suppresses tumour cell proliferation, migration, and invasion by inhibiting NLRP3 expression [232].

Interestingly, contradictory results have been reported by other groups. The expression of NLRP3 in ccRCC cancer tissues is dramatically inhibited, and NLRP3 may be a factor for suppressing tumour growth in RCC [234]. Pyroptosis mediated by caspase-1 is involved in inhibiting the formation and development of tumours. The inhibition of BRD4 has an antitumour effect on RCC via NF- κ B-NLRP3-caspase-1-mediated pyroptosis [235]. Liver X receptors (LXR α), which can regulate ccRCC metastasis by suppressing the NLRP3 inflammasome, could be a biomarker for diagnosing and evaluating the prognosis of ccRCC [234]. These findings clearly demonstrate that NLRP3 plays an antitumour role in RCC.

NOD1 and NOD2 in renal cell carcinoma. NOD1 and NOD2 have been found to play roles in cancer. Sequencing data revealed that the NOD2 gene has a close relationship with the prognosis of kidney cancer patients, indicating the potential of NOD2 as a biomarker for the survival of kidney cancer. However, the existing association between NOD2 and kidney cancer requires further investigation [236]. The different levels of NOD1 and NOD2 expression in specific cell types point towards diverse pathways associated with carcinogenesis [237].

NLR5 in renal cell carcinoma. An analysis of human clinical data revealed that NLR5 can promote the proliferation, migration, and invasion of tumour cells via the Wnt/ β -catenin signalling pathway. Moreover, evidence has demonstrated that NLR5 depletion suppresses the proliferation, migration, and invasion of ccRCC cells. In contrast, NLR5 overexpression may promote these behaviours [238]. These findings indicate that NLR5 is a potential therapeutic target for ccRCC.

NLR pathway-targeted pharmacological agents

NLR inflammasomes, which are potent contributors to the activation of inflammatory cytokines, have been confirmed to play general roles in the pathogenesis and progression of kidney diseases. Considering the contribution of inflammasomes in the progression of renal diseases, inflammasome inhibitors seem to have a promising future in the treatment and prevention of renal diseases. An increasing number of recent studies have verified the efficacy of NLRP3 inhibitors on multiple renal diseases. For example, the diarylsulfonylurea-based compound CP-456,773, also known as CRID3 and MCC950, is a selective NLRP3 inhibitor [239]. This compound markedly reduces IL-1 β and IL-18 and strongly attenuates renal fibrosis, attenuating crystal-induced kidney fibrosis and acute allograft damage in rat kidney transplants [240, 241]. MCC950, which blocks the ATPase domain of NLRP3, attenuates apoptosis in CI-AKI by upregulating HIF1A and BNIP3-mediated mitophagy [242, 243]. Increased levels of APOL1 risk variants are an important trigger for APOL1-associated kidney disease development [244].

Glyburide is a sulfonylurea drug that is widely used for the treatment of type 2 diabetes. This drug has a specific inhibitory effect on the NLRP3 inflammasome [245, 246]. However, the doses of glyburide used in vivo to inhibit NLRP3 are very high, which results in hypoglycaemia, so it is limited to treating T2D only [247]. JC124, a novel small molecule, has been confirmed to ameliorate the hypoglycaemic effect of glyburide and exerts protective effects against various inflammatory diseases [248].

Colchicine has been verified to inhibit multiple inflammasome pathways and is used to treat gout, coronary artery disease and

other inflammatory and fibrotic diseases. However, a high dose of colchicine is required to inhibit the NLRP3 inflammasome, and the use of this treatment in patients with renal insufficiency may be limited by the risk of colchicine toxicity because of the increased half-life of the drug [249, 250].

To date, immunomodulatory strategies targeting inflammasomes have focused mainly on the downstream effectors IL-1 and caspase-1. For example, anakinra (recombinant IL-1Ra) targets IL-1 and is effective in treating gout flares in patients with advanced CKD and diabetes [251, 252].

In summary, small molecule inhibitors targeting NLRP3 and other inflammasome components have been considered potential therapeutic agents through findings in experimental models of kidney diseases and in the clinic [5]. Nevertheless,

future studies are needed to determine the exact potential of these NLR inhibitors and may focus on the development of specific and novel NLR inflammasome inhibitors with improved pharmacokinetic properties that are more cost-effective than currently available treatments.

CONCLUSION

Due to the diverse functions of NLRs, understanding their activation and regulation presents new opportunities to modulate histological damage, the inflammatory response, and apoptosis in renal diseases. The exploration of abundant NLRs has expanded our understanding of their roles in kidney diseases. NLRs are differentially expressed in a variety of renal tissues, and upstream

Table 3. Upstream signalling pathways of NLRs involved in renal diseases.

Signalling pathway	Regulation	NLRs	Function	Diseases type	References
Tim-3	Induction	NLRC4	Promote macrophages infiltration and apoptosis	AKI	[78]
Stat1	Induction	NLRC5	Activate inflammation response and exacerbate TEC apoptosis	AKI	[40, 94]
P2X7R/TLR/MAPK/mROS-TXNIP/NF-κB/DAPK	Induction	NLRP3	Pro-inflammation and pro-fibrosis	AKI	[58, 73, 96, 128, 253]
ROS/TXNIP	Induction	NLRP3	Pro-inflammation, tubulointerstitial fibrosis, and oxidative stress	ON	[144]
IKKβ/IκB/NF-κB	Inhibition	NLRP3	Attenuate inflammation and fibrosis	ON	[146]
ATP-P2X4-NLRP3	Induction	NLRP3	Promote progression of tubulointerstitial inflammation	DN	[168–170]
P2X7R-NLRP3	Induction	NLRP3	Promote renal inflammation and fibrosis; Induce podocyte injury	DN	[166, 167]
TLR4/NF-κB	Induction	NLRP3	Promote epithelial-to-mesenchymal transition, promote inflammation and interstitial fibrosis	DN	[172, 182, 262]
STR/ROS/TXNIP	Induction	NLRP3	Promote progression; Promote inflammation	DN	[158, 160–163]
Syk/JNK	Induction	NLRP3	Promote progression of diabetic cardiomyopathy; pro-inflammatory cytokine release	DN	[153]
miR23c	Inhibition	NLRP3	Inhibit pyroptosis	DN	[171]
lncRNA MALAT1	Induction	NLRP3	Promote pyroptosis	DN	[171]
LXRα	Inhibition	NLRP3	Suppress tumour growth	RCC	[234]
TNFR/RIPK3/MLKL	Induction	NLRP3	Necroptosis; Induce inflammation	CN	[219]
miR-122-5p/BRCC3	Induction	NLRP3	Promote inflammatory progression	UAN	[225]

ON obstructive nephropathy, DN diabetic nephropathy, RCC renal cell carcinoma, CN crystal nephropathy, UAN uric acid nephropathy.

Table 4. Downstream signalling pathways of NLRs involved in renal diseases.

Signalling pathway	Regulation	NLRs	Function of NLRs	Diseases type	References
Type I IFN/NF-κB	Inhibition	NLRX1	Inhibit tubular epithelial apoptosis and tubular oxidative stress; suppress oxidative phosphorylation and excessive formation of ROS	AKI	[48, 89, 90]
(ERK1/2)/Akt/NF-κB/IKK	Inhibition	NLRC5	Promote inflammation response and exacerbate TEC apoptosis	AKI	[40]
ERK1/2 and p38 MAPK	Inhibition	NLRP6	Nephroprotective role	AKI	[140, 254]
NLRP3-ASC-caspase-1-IL-1β	Induction	NLRP3	Promote inflammation and fibrosis	AKI; ON; DN; CN	[51, 100, 122, 173]
MEK/ERK	Induction	NOD2	Promote endothelial-to-mesenchymal transition	DN	[188]
RICK-NF-κB	Induction	NOD1	Promote insulin resistance	DN	[189]
Wnt/β-catenin	Induction	NLRC5	Promote proliferation, migration, and invasion of tumour cells	RCC	[238]

ON obstructive nephropathy, DN diabetic nephropathy, RCC renal cell carcinoma, CN crystal nephropathy.

(Table 3) and downstream (Table 4) signalling pathways of NLRs are involved in renal disease. These findings suggest that NLRs may exert important physiological and pathological effects. Increasingly, evidence suggests that targeting NLRs is a new strategy for the treatment of numerous kidney diseases, including AKI, ON, DN, RCC, IgAN, UAN, LN, and crystal nephropathy. In recent years, research on the functions of NLRs in renal diseases has increased exponentially. However, several challenges remain to be addressed. For example, while NLRP3 is a well-studied NLR in many renal diseases, the interplay between NLRP3 and other NLRs remains a topic of uncertainty. Further investigation is also needed to elucidate the inhibitory effects of certain NLRs, such as NLRX1 and NLRP6. In addition, the function of NLRC5 in renal diseases remains controversial. Studying the different roles of NLRs in renal diseases will not only increase our understanding of the pathological processes of the kidney but also provide further evidence that targeting NLRs is a viable strategy for the treatment of renal diseases.

DATA AVAILABILITY

The data used to support the findings of this study are included within the article.

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AUTHOR CONTRIBUTIONS

XMM provided direction and guidance throughout the preparation of this manuscript. JJ, TJZ, and GLR wrote and edited the manuscript. LC collected and prepared the related papers. All authors read and approved the final manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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