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Therapy Targeted to the NLRP3 Inflammasome in Chronic Kidney Disease

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Abstract
Background: The NLRP3 inflammasome is a cytoplasmic polymeric protein complex composed of the cytoplasmic sensor NLRP3, the apoptosis-related spot-like protein ASC, and the inflammatory protease caspase-1. NLRP3 activates and releases IL-1β through classical pathways, and IL-18 mediates inflammation and activates gasdermin-D protein to induce cellular pyroptosis. Numerous studies have also emphasized the non-classical pathway activated by the NLRP3 inflammasome in chronic kidney disease (CKD) and the inflammasome-independent function of NLRP3. ***Summary:*** The NLRP3-targeting inflammasome and its associated pathways have thus been widely studied in models of CKD treatment, but no drug that targets NLRP3 has thus far been approved for the treatment of CKD. ***Key Messages:*** We herein reviewed the current interventional methods for targeting the NLRP3 inflammasome in various CKD models, analyzed their underlying mechanisms of action, classified and compared them, and discussed the advantages and follow-up directions of various interventional methods. This review therefore provides novel ideas and a reference for the development of targeted NLRP3-inflammasome therapy in CKD.

Introduction

Nucleotide oligomerization domain-like receptor family pyrin domain-containing-3 (NLRP3) is a type of cytoplasmic sensor composed of the central NACHT domain, C-terminal leucine-rich repeats, and an N-terminal pyrin domain (PYD) that can be used as a pattern recognition receptor. The cytoplasmic polyprotein complex that is composed of the apoptosis-related speck-like protein (ASC) and inflammatory protease caspase-1 is referred to as the NLRP3 inflammasome [1]. This complex participates in the response to an endogenous danger signal (damage-associated molecular pattern or DAMP [2]) or an exogenous signal (pathogen-associated molecular pattern or PAMP [2, 3]) to promote the release of inflammatory factors and to induce cellular apoptosis.

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NLRP3 is mainly expressed in kidney innate cells and immune cells [4]. Numerous studies have shown that the NLRP3 inflammasome and its downstream effectors are activated in the development of chronic kidney disease (CKD) [5], including diabetic nephropathy (DN) [6], lupus nephropathy [7], IgA nephropathy (IgAN) [8], and crystalline nephropathy [9]. The NLRP3 inflammasome participates in the inflammation and injury of CKD via both classical and non-classical signaling pathways. Therefore, targeting the NLRP3 inflammasome and its downstream factors has become a potential option in the treatment of CKD and commensurate with target and disease model, the therapeutic effect varies. This review focuses on the role and therapeutic effects of various interventional methods that target the NLRP3 inflammasome in various CKDs, and we discuss the choice of targeted NLRP3 applications for CKD in the future.

The NLRP3 Inflammasome in CKD

NLRP3 consists of three domains: a carboxyl terminal leucine-rich repeat domain that possesses self-inhibition and signal-recognition functions, a central adenosine triphosphatase (ATPase) domain known as NACHT that expresses ATP enzyme activity and mediates self-oligomerization, and an amino-terminal PYD responsible for recruiting apoptosis-related spotted proteins containing CARD (ASC) [1, 10]. As a signal sensor that receives PAMPs and DAMPs [11], NLRP3 undergoes self-oligomerization through a homotype PYD-PYD domain interaction. Oligomeric NLRP3 then recruits ASC through a homotype NACHT domain interaction, induces ASC to gather into a macromolecular focus called the ASC spot, and then recruits procaspase-1 through a homotype CARD-CARD domain interaction. These actions then form an NLRP3-ASC-caspase-1 protein complex [11–14] that is called the NLRP3 inflammasome. The NLRP3 inflammasome can be divided into three typical components: sensors, adapters, and effectors that comprised NLRP3, ASC, and caspase-1, respectively. Activation of the NLRP3 inflammasome induces procaspase-1 to cleave itself to release caspase-1, mediates the maturation and secretion of IL-1β and IL-18, and cleaves and activates gasdermin-D (GSDMD) protein in the cytoplasm [15–17]. The activated GSDMD protein is subsequently transported to the cell membrane to form holes that can release IL-1β, IL-18, and other cellular contents [18]; and induces inflammatory cell death referred to as pyroptosis [15, 19, 20]. The activation of the NLRP3 inflammasome can then be partitioned into three stages: the start stage (stage I), activation stage (stage II), and effect stage (stage III) (Fig. 1). The start signals may come from PAMPs (such as viral RNA, microbial toxins, and bacterial surface components) and DAMPs (such as uric acid crystals, ATP, aluminum adjuvants, and β-amyloid peptides), Toll-like receptor (TLR) and nucleotide oligomerization domain-like receptor (NLR) ligands, TNF-α, or IL-1 that activate the transcriptional expression of NLRP3, pro-caspase-1, and pro-IL-1β through the Myd88-NF-κB pathway [3, 11, 21–24] – forming the NLRP3 inflammasome. The signal in the activation stage comes from cellular and molecular events induced by PAMPs and DAMPs such as mitochondrial dysfunction, release of mitochondrial reactive oxygen species (mtROS), K+ efflux, lysosomal destruction, and adenine triphosphate (ATP) – inducing the lysis of the NLRP3 inflammasome and the release of caspase-1 [25–29]. The effect stage is separated into classical and non-classical pathways. In the classical pathway, caspase-1 cleaves pro-IL-1β, pro-IL-18, and GSDMD, releasing IL-1β and IL-18 to mediate inflammation; and N-terminal-gasdermin-D creates cracks in the cell membrane and induces cellular pyroptosis [30]. In the non-classical pathway, human caspase 4/5 (homologous to mouse caspase-11) may be activated by lipopolysaccharide (LPS) released by bacterial infection, playing a regulatory role independent of caspase-1 [6]. Some studies have also revealed that NLRP3 is independent of the inflammasome and involved in mitochondrial potassium efflux that activates the NLRP3-ASC-caspase-8 pathway to mediate the release of inflammatory cytokines or ROS release in mitochondria to regulate the TGF-β-Smad-signaling pathway and thereby promote renal fibrosis [5, 30].

There are various modes of initiation and activation of the NLRP3 inflammasome in CKD, there exist classical/non-classical and inflammasome-dependent/-independent forms, and there are numerous interventional approaches that can affect NLRP3. Herein, we classify the modes targeting the NLRP3 inflammasome as follows. (1) In class I, the NLRP3 inflammasome and its downstream factors are found to exert inhibitory effects in clinical and experimental studies; however, the mechanism remains unknown or the therapy requires further verification. (2) In class II, clinical and experimental studies have demonstrated a clear mechanism of action for these therapies targeting the NLRP3-inflammasome pathway, and according to its targeting stage, it is divided into a/b/c categories. Class IIa targets NLRP3 at the start stage, class IIb targets NLRP3 at the activation stage, and class IIc targets NLRP3 at the effect stage (Fig. 2).

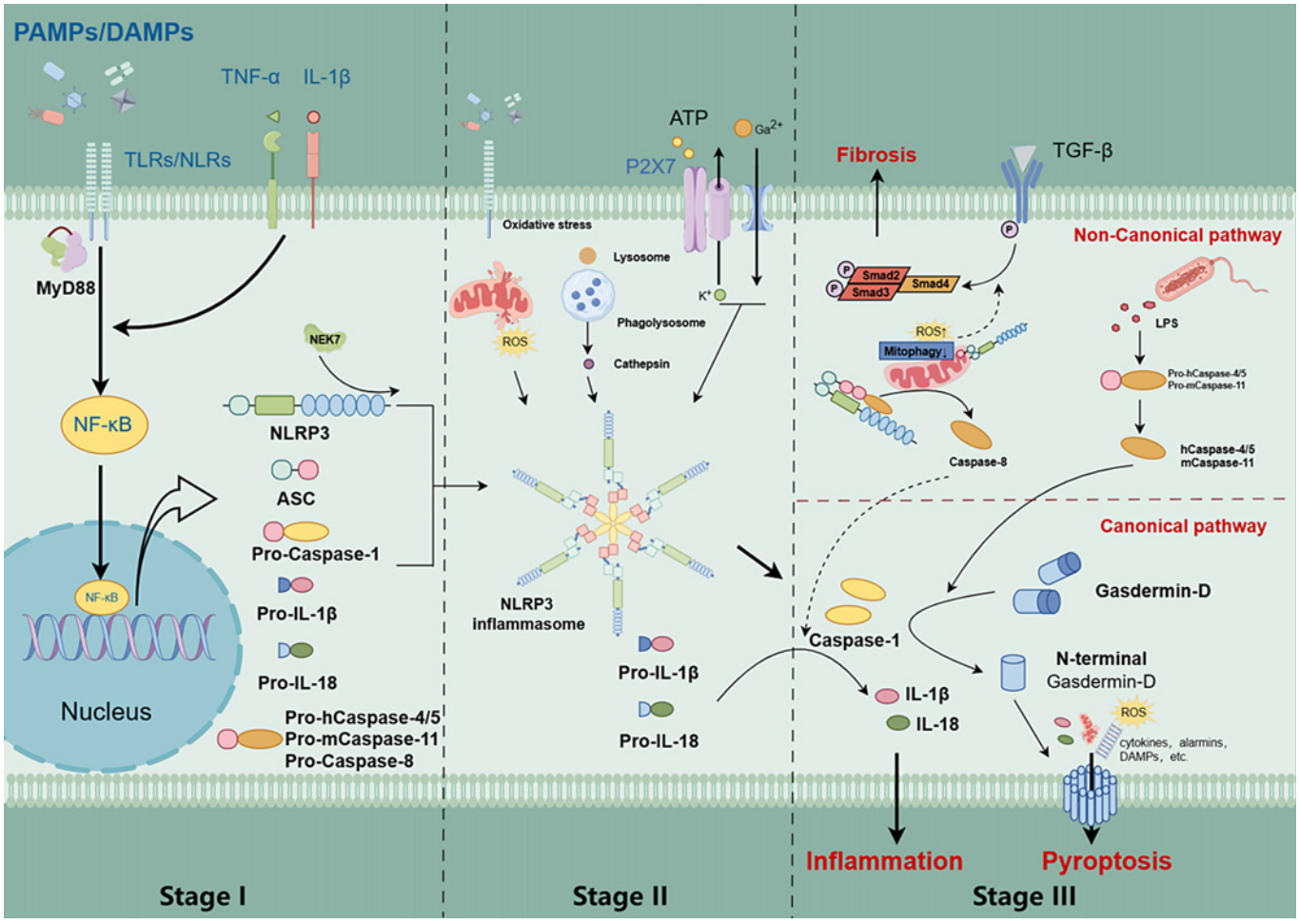

Fig. 1. NLRP3 mediates inflammation and injury in CKD. NLRP3 plays a role in the kidney in inflammasome-dependent and inflammasome-independent pathways, and its inflammasome-dependent role can be divided into classical and non-classical. In the classical pathway of the NLRP3 inflammasome, renal cells receive signals from PAMPs and DAMPs through TLRs or NLRs and activate NF-kB-signaling pathways, resulting in increased expression of NLRP3 inflammasome components and some precursors, constituting the initiation stage of NLRP3 activation. Then, in the activation stage, PAMPs and DAMPs induce cellular and molecular events such as mitochondrial dysfunction, the release of mitochondrial reactive oxygen species (mtROS), K+ efflux, lysosomal destruction, adenine triphosphate (ATP), etc.; induce oligomerization of NLRP3; and recruit ASC and procaspase-1 to form inflammasome complexes that activate caspase-1. In the effect stage, activated caspase-1 cleaves pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18, respectively, mediating the inflammatory response. Caspase-1 also cleaves gasdermin-D to form activated gasdermin-D with an N-terminal – forming crevices in the cell membrane – releases intracellular DAMP signals, and mediates cell scorching. The non-classical pathway of NLRP3 inflammasome action principally depends on human caspase-4/5, which is homologous to mouse caspase-11. The inflammasome can bind LPS directly through the CARD domain, activate caspase-4/5 and caspase-11, cleave pro-IL-1β and gasdermin-D, and induce inflammation and cellular pyroptosis. In addition, caspase-8 also mediates the release of IL-1β through the NLRP3-ASC-caspase-8 pathway. The inflammasome-independent action of NLRP3 in CKD primarily mediates renal fibrosis. NLRP3-ASC activates ROS in the mitochondria, and these ROS enhance the phosphorylation of regulatory Smad proteins induced by TGF-β, thus promoting the expression of profibrotic genes. Myd88, myeloid differentiation factor; NEK7, NIMA-related kinases; TGF-β, transforming growth factor-β.

Targeting the NLRP3 Inflammasome in Treating CKD

As a special organ with a function of excreting metabolic wastes, drugs, and toxins, the kidney may be exposed to DAMPs or PAMPs for a lengthy period. Thus, NLRP3 can be activated in renal monocytes, renal tubular epithelial cells (TEC), glomerular endothelial cells, mesangial cells, and podocytes. Next, we will review targeting NLRP3 to treat CKDs that include DN, lupus nephritis (LN), IgAN, crystalline nephropathy, and obstructive nephropathy.

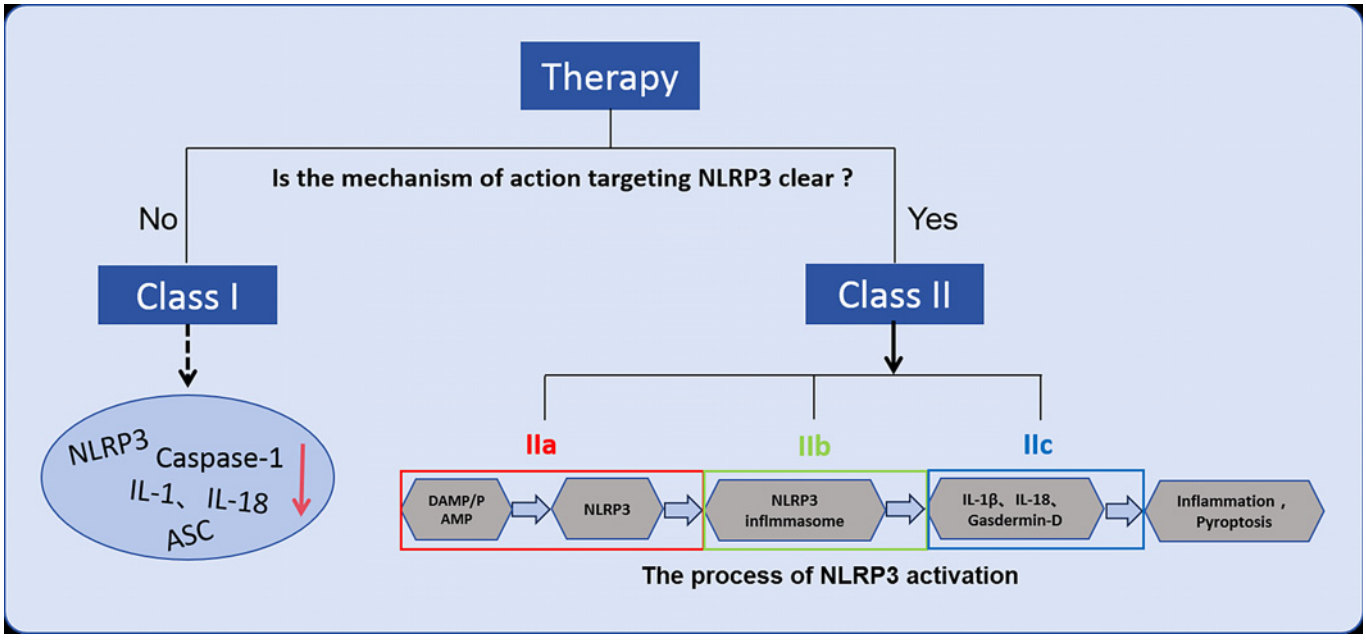

Fig. 2. Classification of pathways to target the NLRP3 inflammasome in CKD models. Class I is an intervention that can reduce NLRP3 and its downstream effectors in the study of CKD, but the specific inhibitory mechanism(s) remains unclear. Class II interventions have been found to act on some key factors in the activation of the NLRP3 inflammasome and portray a targeted role. The class IIa mode principally acts on cells to receive DAMPs/PAMPs. The class IIb mode mainly acts on the process from the signal to the initiation stage of oligomerization of NLRP3, where the NLRP3 inflammasome is induced by an activational signal, releases caspase-1, and performs a cutting role; while the class IIc mode chiefly targets IL-1β, IL-18, and activated gasdermin-D, exerting an action at the effect stage.

Diabetic Nephropathy

DN is one of the most common microvascular complications of diabetes and one of the main causes of end-stage renal disease. The characteristic clinical manifestation of DN is persistent albuminuria and/or progressive decrease in glomerular filtration rate. Its pathological features include thickening of the glomerular basement membrane, extracellular matrix deposition, renal interstitial fibrosis, nodular glomerulosclerosis and decreased number of endothelial cells. These changes lead to structural and functional damage to the kidneys, which can eventually progress to renal failure. DN is characterized by typical aseptic inflammation [31]. Hyperglycemia and its related metabolic rearrangements can be used as DAMPs detected by NLRP3 and activate the NLRP3 inflammasome through mitochondrial ROS [26]. Previous studies have shown that the activation of specific NLRP3 inflammasomes in podocytes promotes the development of DN in mice, which is exhibited as increased albuminuria, glomerular mesangial dilation, and increased thickness of the glomerular basement membrane [6]. There are many drugs that can be used in the DN model, most of which are anti-hyperglycemic medications and natural herbal drugs that manifest inhibitory effects on NLRP3, but their mechanism(s) of action requires further corroboration, and thus, this group of drugs is relegated to class I intervention [32–34]. Class II intervention then occupies a corresponding role in the DN model by inhibiting the initiation and activation of NLRP3.

Class I Intervention in DN

Research has in recent years shown that in addition to common diabetes drugs such as insulin [32, 35] and biguanides [33], natural herbal compounds such as curcumin [36], salidroside [37], and dihydroquercetin [34] also inhibit NLRP3 and its downstream factors in a DN model. Insulin, for example, is able to inhibit the activation of ASC in an LPS-induced cell/animal model [32, 35]. Interventional therapy can improve albuminuria, but barely mitigates renal tissue damage; this therefore requires further study in a DN model. Biguanides increase DRP1 phosphorylation in an AMPK-dependent manner to inhibit oxidative stress and further inhibit NLRP3 activation, but its effects on renal inflammation and injury remain arcane [33]. While curcumin, salidroside, dihydroquercetin, and other natural herbal compounds have not been studied in

DN, they are nevertheless capable of inhibiting the expression of NLRP3 and its downstream factors. These substances act in a protective capacity in the kidney, including reducing urinary microalbumin excretion, hyperglycemia, and lipid metabolism disorder, and reducing renal damage [34, 36, 37].

Class IIa Intervention in DN

Natural betaine and Huangkui capsule have been demonstrated to inhibit NF-κB/NLRP3 and to reduce the initiation of NLRP3 activation; and interventional treatment in a DN mouse model reduced urinary protein, creatinine, urea nitrogen, uric acid, glomerular mesangial hyperplasia, and renal fibrosis [38, 39]. Some authors found that miRNA and miR-10 (including miR-10a and-10b) were enriched in the kidney, being mainly expressed in renal TECs and glomerular podocytes; and were negatively correlated with activation of the NLRP3 inflammasome in the kidneys of mice and patients with diabetic kidney disease (DKD). Prophylactic treatment can reduce macrophage infiltration, mesangial proliferation, renal fibrosis, podocyte injury, and proteinuria in two types of diabetic models, streptozotocin (STZ)-induced mice and *db*/*db* mice, but only improves renal inflammation and proteinuria in established DKD mice, and cannot reverse renal injury. MiR-10a/b primarily targets 3′ untranslated regions (UTRs) of NLRP3 mRNA to negatively regulate the NLRP3 signal and disrupt the cleavage of casp1 and the maturation of IL-1b [40, 41].

Class IIb Intervention in DN

MCC950 is one of the most promising inhibitors available to specifically block the activation of NLRP3, IL-1β, and IL-18 and principally acts on the NACHT domain of NLRP3, blocking conformational change and oligomerization of NLRP3 [42]. MCC950 is rarely used in the DN model, but it is intriguing that preventive administration can improve renal function and injury in a model of diet-induced type 2 diabetic insulin resistance [43]. In a model of insulin deficiency in type 1 diabetes induced by streptozotocin, prevention and treatment exacerbated renal inflammation and injury, including mesangial dilatation and glomerulosclerosis [44]. CY-09 is a novel NLRP3 inflammasome-specific inhibitor that directly binds to the ATP-binding region of the NLRP3 protein, inhibiting its ATP-hydrolytic activity; this then attenuates its oligomerization and subsequent inflammasome-complex assembly in a dose-dependent manner. Interventional treatment in a DKD mouse model reduced renal inflammation, oxidative stress, apoptosis, and fibrosis [45]. AB38b is a newly synthesized biphenyl diester derivative with an Nrf2-activation property. By activating the Nrf2 gene (a known antioxidant transcription factor), AB38b is able to inhibit the ROS/TXNIP/NLRP3-signaling pathway, significantly reducing the levels of the NLRP3 inflammasome in diabetic rats, improving renal function, and delaying renal fibrosis [46] (Table 1).

Lupus Nephritis

LN is a common and serious complication in patients with systemic lupus erythematosus. The clinical manifestations of LN range from mild asymptomatic proteinuria or hematuria to severe nephrotic syndrome or acute progressive nephritis syndrome [7]. A cohort study of patients with LN revealed that the expression rates of NLRP3, ASC, caspase-1, IL-1β, and IL-18 were significantly augmented in the kidneys of patients with LN; and that these molecules were mainly expressed in glomerular mesangial cells, podocytes, TECs, and macrophages [47]. Other studies have shown that the activation of NLRP3 in podocytes promoted the development of LN [48]. Curcumin, piperine, and other natural compounds are also used in LN models, and these may inhibit NLRP3 by regulating immunity [49–51]. Xenon as a specific treatment has been used alone in a LN model as an IIa intervention, generating renal protection; and there is a possibility that it can used in other CKD models [52].

Class I Intervention in LN

Curcumin is also used in the treatment of LN, and can inhibit NLRP3 and its downstream factors, reducing proteinuria and renal inflammation [49]. Vitamin D receptor and the NLRP3 inflammasome have been found to occupy a key role in the pathogenesis of LN). Other studies have shown that vitamin D receptor agonists regulate the NF-κB/NLRP3/caspase-1/IL-1β/IL-18 axis and inhibit NF-κB nuclear translocation, thus improving renal injury and proteinuria [53]. The specific mechanism, however, remains to be further clarified.

Class IIa Intervention in LN

Xenon is an inert anesthetic gas with good cytoprotective and anti-inflammatory properties. In the LN model, xenon not only reduces the level of serum antibody and complement but also inhibits the activation of the NF-κB/NLRP3 inflammasome, reducing the production of ROS, further improving renal function and pathologic damage, and inhibiting apoptosis [52].

Class IIb Intervention in LN

Piperine is a natural compound found in black pepper and other related herbs that contain numerous biologic activities such as immune regulatory, anti-cancerous, anti-

Table 1. Effects and mechanisms of targeting the NLRP3 inflammasome in DN

Method	Classification	Target	Effects on renal tissue/function	References
Insulin	I	ASC	Improvement of albuminuria	Ganugula et al. [32] (2022), Chang et al. [35] (2021)
Biguanides	I	Oxidative stress	Unclear	Li et al. [33] (2016)
Curcumin, salidroside, dihydroquercetin, and others	I	Uncertain	Protection of renal function and reduction of renal damage	Ganugula et al. [32] (2022), Ding et al. [34] (2018), Lu et al. [36] (2017), Zhou et al. [37] (2022)
Natural betaine and Huangkui capsule	IIa	NF-κB/NLRP3	Reduction in urinary protein and creatinine; reduction of glomerular mesangial hyperplasia and renal fibrosis	Duan et al. [38] (2022), Han et al. [39] (2019)
Mi-RNA10	IIa	3 ′UTR of NLRP3 mRNA	Prevention: reduction of renal tissue and functional damage Intervention: reduction in inflammation and improvement of renal injury	Ding et al. [40] (2021), Li et al. [41] (2022)
MCC950	IIb	NACHT domain of NLRP3	Prevention (IR): improvement in renal function and injury Prevention or Intervention (ID): aggravation of renal inflammation and injury	Tapia-Abellán et al. [42] (2019), Zhang et al. [43] (2019), Østergaard et al. [44] (2022)
CY-09	IIb	ATP-binding region of NLRP3	Reduction in renal inflammation, oxidative stress, apoptosis, and fibrosis	Yang and Zhao [45] (2022)
AB-38b	IIb	ROS/TXNIP/NLRP3-signal-transduction pathway	Improvement in renal function and delay of renal fibrosis	Du et al. [46] (2020)

oxidative, anti-inflammatory, and anti-asthmatic effects. In the lupus nephropathy model, targeting ATP-activated protein kinase (AMPK) significantly inhibited the activation of the NLRP3 inflammasome, diminished the release of pro-inflammatory cytokines, and reduced renal injury [50]. MCC950 is also used in LN to improve glomerular function and injury [54] (Table 2).

IgA Nephropathy

IgAN is a common primary glomerulonephritis worldwide. Its underlying pathogenesis involves mesangial deposition of galactose-deficient IgA1 immune complexes that leads to up-regulation of innate immunity and activation of the complement cascade [55]. Immune complexes containing IgA1 activated the NLRP3 inflammasome in the kidney [56], and knockout of NLRP3 or a kidney-targeting delivery of an NLRP3 shRNA improved renal function and renal injury in a mouse IgAN model [8]. There are presently numerous treatments for targeting the NLRP3 inflammasome in the IgAN model. For instance, class I therapies such as *Bifidobacterium* [57] and ginsenoside (compound K) [58] reduce the expression of NLRP3 and its downstream factors, and are used as adjuvant therapies in IgAN. Of the class II therapies, most are derived from natural herbal treatments and have been found to inhibit the initiation of NLRP3 activation, potentially acting on the NF-κB/NLRP3 pathway [59–62]. Whether the effectors of these drugs possess the same characteristics is worthy of further study. As targeted therapies, LCC18 [63] and tris(dibenzylideneacetone)dipalladium (TrisDBA) [64] significantly improve renal function and injury in an IgAN model.

Class I Intervention in IgAN

Probiotics/*Bifidobacteria* has the potential to be used as adjuvant therapies for IgAN. In the IgAN model, investigators determined that probiotics and their metabolite short-chain fatty acids (SCFAs) reduced urinary

Table 2. Effects and mechanisms of targeting the NLRP3 inflammasome in LN

Methods	Classification	Target	Effects on renal tissue/function	References
Curcumin	I	Uncertain	Reduction in albuminuria and renal inflammation	Zhao et al. [49] (2019)
Vitamin D receptor agonist	I	NF-κB/NLRP	Improvement of kidney injury and proteinuria	Huang et al. [53] (2021)
Xenon	IIa	NF-κB/NLRP3 and ROS	Improvement in albuminuria and reduction of immunoprecipitation and kidney injury	Yang et al. [52] (2020)
Piperine	IIb	AMPK	Reduction in renal injury and apoptosis	Peng et al. [50] (2018)
MCC950	IIb	NACHT domain of NLRP3	Improvement of albuminuria and renal damage	Fu et al. [54] (2017)

protein and renal injury by inhibiting the NLRP3/ASC/caspase-1-signaling pathway [57]. Ginsenosides (e.g., compound K) and triptolide were also found to attenuate the expression of NLRP3 and its downstream factors in an IgAN model, and to exact a protective role in the kidney [58, 65]. The mechanism(s) underlying these actions, however, remains unclear.

Class IIa Intervention in IgAN

Artemisinin + hydroxychloroquine, icariin, Zhen-wu-tang, osthole, and other Chinese herbal or traditional medicines were also verified in the IgAN model by inhibiting NF-κB/NLRP3; reducing the initiation of NLRP3 activation; improving the levels of albuminuria, serum creatinine, and urea nitrogen; and alleviating renal injury [59–62]. LCC18 is a benzamide-linked small molecule that in two complementary IgAN models established in C57BL/6 and GDDY mice abrogated the initiation of the NLRP3 inflammasome as mediated by the by MAPKs/COX-2 axis and blocked NLRP3 oligomerization and inflammasome assembly by inhibiting the binding of NLRP3 to NEK7 and ASC. LCC18 also protected renal function by activating autophagy and inhibiting the activation of the NLRP3 inflammasome [63]; it is expected to become a candidate drug for the treatment of IgAN.

Class IIb Intervention in IgAN

TrisDBA is a small-molecule palladium complex used in the treatment of B-cell malignant tumors, and some researchers postulate that it can alleviate immune complex (IC)-mediated diseases, especially IgAN. Additional studies revealed that TrisDBA treatment of IgAN mice significantly improved renal function, proteinuria, and renal damage and inflammation; and reduced the formation of mitochondrial ROS. The mechanisms underlying TrisDBA action include inhibition of the MAPK-signaling pathway and passivation of ROS-mediated inflammation, enhancing SIRT1- and SIRT3-mediated autophagic induction, and autophagy-mediated NLRP3 inflammasome suppression [64] (Table 3).

Crystalline Nephropathy

Crystalline nephropathy is a common type of kidney disease. In the model of crystalline nephropathy, the formation and deposition of crystals are key to renal injury, and these activities have been demonstrated to be involved in NLRP3 in numerous studies, and are related to the production of ROS induced by crystals [66–69]. These researchers also ascertained that the IL-1 antagonist anakinra did not protect the kidneys from lens damage in a model of oxalate-induced crystalline nephropathy, while NLRP3 inhibitors acted in anti-inflammatory and anti-fibrotic fashions. In vitro experiments substantiated that NLRP3 regulated the TGF-β/SMA-signal transduction pathway and macrophage phenotype in fibroblast activation and proliferation in an inflammasome-independent manner [70, 71]. These data provide a novel explanation for the increased differential effects at different stages of targeted NLRP3-inflammasome activation. There are many ways to target the NLRP3 inflammasome in the model of crystalline nephropathy, although the mechanism of action is arcane: Plantaginis semen polysaccharides (PSPs) [72], vitexin [73], MiR-223-3p [74], and atorvastatin [75] are targeted at the initiation stage of the NLRP3 inflammasome; while MCC950 [67] and polydatin [69] are targeted at the activation stage. We posit that greater attention be afforded to the effects of various treatments in improving renal fibrosis.

Table 3. Effects and mechanisms of targeting the NLRP3 inflammasome in IgAN

Method	Classification	Target	Effects on renal tissue/function	References
Bifidobacterium	I	NLRP3/ASC/ caspase-1 pathway	Reduction in albuminuria and kidney injury	Tan et al. [57] (2022)
CK, triptolide	I	uncertainty	Renal protective effect	Wu et al. [58] (2020), He et al. [65] (2015)
Artemisinin + hydroxychloroquine, icariin, Zhen-Wu-Tang, osthole	IIa	NF-κB/NLRP3	Improvement in the levels of albuminuria, serum creatinine, and urea nitrogen; reduction of renal injury	Bai et al. [59] (2019), Hua et al. [60] (2013), Li et al. [61] (2020), Zhang et al. [62] (2017)
LCC-18	IIa	MAPKs/COX-2; NEK7-NLRP3-ASC; Autophagy	Reduction in proteinuria and renal pathologic damage	Yang et al. [63] (2021)
TrisDBA	IIb	Autophagy	Improvement of renal function and renal pathologic changes	Wu et al. [64] (2020)

Class I Intervention in Crystalline Nephropathy

PSPs, chloroquine, and vitexin are able to reduce the expression of NLRP3, ASC, and caspase-1; reduce urinary protein and uric acid; and improve renal interstitial inflammatory infiltration and fibrosis in a hyperuric acid nephropathy model [72, 73, 76]. It has been reported that the ELR-CXC chemokine and its receptor CXCR1/2 are critical in many inflammatory diseases. When the CXCR1/CXCR2 antagonist G31P was used in the hyperuric acid nephropathy model, it functioned in a manner similar to that of plantain polysaccharides, but the mechanism of its inhibition of NLRP3 remains unelucidated [77]. Carvanol and the deletion of receptor-interacting protein 3 (RIP3) may reduce uric acid and renal injury by regulating the NRLP3/NF-κB pathway [78, 79].

Class IIa Intervention in Crystalline Nephropathy

MiR-223-3p directly binds to the 3′-UTR of NLRP3 to inhibit its expression, and lncRNA X inactive-specific transcript (XIST) competitively binds to MiR-223-3p to increase the translation of NLRP3; thus, the application of MiR-223-3p structural analogs combined with XIST can inhibit NLRP3 [74]. In a calcium oxalate nephropathy model, MiR-223-3p reduced the deposition of renal CaOx in oxidative renal injury. Methyl gallate is a gallotannin that is widely distributed in edible plants and reflects antioxidant, anti-inflammatory, and anti-tumor effects [80]. It can regulate NF-κB- and MAPK-signaling pathways; inhibit the assembly of the NLRP3 inflammasome by blocking ROS overproduction and oligomerization of NLRP3 in the hyperuricemic nephropathy model; reduce the levels of uric acid, creatinine, and urea nitrogen; and improve arteriosclerosis, glomerulosclerosis, and renal tubulointerstitial fibrosis [81]. Atorvastatin also attenuated renal inflammation and injury induced by calcium oxalate crystals and improved crystal deposition by inhibiting the TLR/NF-κB/NLRP3 pathway [75].

Class IIb Intervention in Crystalline Nephropathy

MCC950 (also referred to as CP-456,773) targets the NACHT domain of NLRP3 and blocks conformational change and oligomerization of NLRP3 [82]. MCC950 principally targets NLRP3 in CD11c dendritic cells in crystalline nephropathy, and this inhibits tubulointerstitial inflammation and fibrosis, and reduces serum urea nitrogen and creatinine levels in crystalline nephropathy [67]. Polydatin is a type of plant rhizome extract with anti-inflammatory, antioxidant, and anti-tumor effects. In the calcium oxalate, crystal-induced renal injury model, polydatin inhibited the activation of the NLRP3 inflammasome by reducing ROS in the cytoplasm and mitochondria, effectively alleviating inflammatory damage and crystal deposition in the kidney [69] (Table 4).

Obstructive Nephropathy

Obstructive nephropathy is a condition in which the flow of urine in the urinary system is obstructed, resulting in impaired kidney function and structure. Obstructive nephropathy may occur acutely or may develop slowly. Previous studies have revealed that NLRP3 is involved in CKD caused by unilateral ureteral obstruction (UUO). In the UUO model and compared with the control group, the inflammation, injury, and fibrosis of renal tubules in NLRP3-KO mice were significantly mitigated. These detrimental effects were related to the diminution in the levels of NLRP3,

Table 4. Effects and mechanisms of targeting the NLRP3 inflammasome in crystalline nephropathy

Method	Classification	Target	Effects on renal tissue/function	References
PSPs, Chloroquine, G31P, vitexin	I	NLRP3/ASC/ caspase-1 pathway	Reduction in albuminuria and uric acid; improvement in renal interstitial inflammatory infiltration and fibrosis	Zhao et al. [72] (2021), Ding et al. [73] (2021), Cui et al. [76] (2023), Ye et al. [77] (2018)
Carvanol and RIP3	I	NF-κB/NLRP3	Reduction in uric acid, CRP, and kidney damage	Riaz et al. [78] (2022), Wang et al. [79] (2018)
XIST inhibition/ MiR-223-3p	IIa	3′UTR of NLRP3 mRNA	Abatement of CaOx, renal calcium deposition, and oxidative renal injury	Lv et al. [74] (2021), Sun et al. [75] (2020)
Methyl gallate, atorvastatin	IIa	NF-kB and MAPK	Improvement in renal function and renal pathologic damage	Sun et al. [75] (2020), Liang et al. [80] (2023), Liu et al. [81] (2021)
MCC950	IIb	NACHT domain of NLRP3	Reduction in tubulointerstitial inflammation and fibrosis; serum urea nitrogen and creatinine	Ludwig-Portugall et al. [67] (2016), Sakai et al. [82] (2016)
Polydatin	IIb	ROS	Relief of oxidative stress and inflammatory damage	Liu et al. [69] (2023)

caspase-1, and IL-1β; and the drop in ROS production in mitochondria and elevation in the level of autophagy [83, 84]. In studies related to autophagy, authors established that autophagy in distal TECs protected the onset of renal fibrosis by regulating Smad4-dependent TGF-β pathway in the UUO model [85, 86]; and that autophagic damage also raised the expression of NLRP3, caspase-1, IL-1β, and mitochondrial ROS [87]. These studies suggest that NLRP3 plays an inflammasome-dependent/independent role in UUO, and emphasizes the non-inflammasome-dependent role of NLRP3; these two activities regulate each other with autophagy. In addition to the class I interventional methods such as ghrelin [88] and curcumin [89] adopted in the UUO model to reduce the levels of NLRP3 (using an undefined mechanism), there exist class IIa intervention methods such as biochanin A (BCA) [90] and NSC828779 [91] that target TGF-β1/Smad2/3, NF-kB/NLRP3, and IIb class intervention activators of PGC-1α on mitochondria [92]. It should be noted that there are differences in the effects of these interventions.

Class I Intervention in Obstructive Nephropathy

Drugs such as ghrelin [88], psoralen (PS) [93], cyclic helical B peptide (CHBP) [94], giglitine [95], and Tongluo Yishen decoction [96] have been used in a UUO model of CKD, and these substances reduced the expression of NLRP3 and its downstream factors, reduced renal cell apoptosis, inhibited renal fibrosis, and generally manifested protective effects on the kidney. Curcumin has been shown to exert an antifibrotic effect in the past, but this effect may be related to autophagy in the UUO model [89]. Some investigators have determined that compound K plays a protective role in many stages – as shown for NF-kB/NLRP3, TGF-β1/Smad2/3, and ROS in UUO – but its specific underlying mechanism of action requires further study [97].

Class IIa Intervention in Obstructive Nephropathy

In the mouse UUO model, BCA treatment significantly reduced the expression of NLRP3, caspase1, IL-18, and IL-1β proteins; reduced renal tubular injury and accumulation of abnormal extracellular matrix; and inhibited the expression of the TGF-β1/Smad2/3-signaling axis and the activation of NF-kB in the kidney. BCA additionally inhibited the expression of fibrin in renal fibroblasts activated by TGF-β1 in vitro [90]. Authors have suggested that BCA exerts a therapeutic effect on renal fibrosis in the UUO model, and that its improvement is achieved through the TGF-β1/Smad2/3- and the NF-kB/NLRP3-signal-transduction pathways. A research team synthesized the salicylanilide derivative NSC828779 that specifically inhibited the activation of NF-kB. In the UUO mouse model and mechanically induced constant- pressure renal TEC model, NSC828779 treatment improved renal cell damage, significantly reduced the severity of renal inflammation and fibrosis in UUO mice, and significantly decreased the level of urinary cytokines [91]. This small-molecule specific inhibitor is thus worthy of further study.

Class IIb Intervention in Obstructive Nephropathy

PGC-1α is a key regulator of mitochondrial biogenesis. In the UUO model, the expression of PGC-1 α and mitochondrial dynamic-related genes was inhibited, and the NLRP3 inflammasome activated, resulting in inflammation and fibrosis [84, 92]. Since the activation of NLRP3 is related

Table 5. Effects and mechanisms of targeting the NLRP3 inflammasome in obstructive nephropathy

Method	Classification	Targeting	Effects on renal tissue/ function	References
Ghrelin, PS, CHBP, gemigliptin, Tongluo Yishen decoction	I	Uncertain	Reduction in renal cell apoptosis and inhibition of renal fibrosis	Ling et al. [88] (2019), Lee et al. [93] (2023), Qi et al. [94] (2020), Seo et al. [95] (2019), Jia et al. [96] (2022)
Curcumin	I	Autophagy	Improvement of renal fibrosis	Lu et al. [89] (2021)
CK	I	NF-κB/NLRP3; STAT3; TGF-β1/ Smad2/3		Hsu et al. [97] (2020)
BCA, NSC828779	IIa	TGF-β1/Smad2/3; NF-κB/NLRP3	Alleviation of renal interstitial injury and inflammatory factor accumulation	Ram et al. [90] (2022), Yang et al. [91] (2021)
PGC-1α	IIb	Mitochondria	Reduction in renal cell injury and fibrosis	Nam et al. [92] (2022)

to mitochondrial damage, an activator of PGC-1 α (e.g., metformin) has been applied to the analysis of renal damage in UUO [92]. The function of mitochondria is improved via the induction of plasmids and an activator, the levels of NLRP3 and oxidative stress in the kidneys are reduced, and renal inflammation and fibrosis are thereby improved (Table 5).

Discussion

We herein reviewed the role of NLRP3 in CKD, as well as the mechanisms and effects of different interventional methods in diverse disease models. We can infer the actual mechanism of an intervention, although that for class I intervention is unelucidated. For the class I intervention that solely reduces inflammatory factors or urinary protein, we speculate that it may only reduce the NLRP3 initiation signal from its primary pathogenesis, and reduce the initiation of NLRP3 activation so as to attenuate the expression of NLRP3 (this is the case for curcumin and CK). The class I intervention whose mechanism needs to be further verified involves the inhibition of the NLRP3 inflammasome in the initiation or activation stage, but its role in the model may be unsatisfactory due to its low efficiency or inconsistent verification (e.g., the application of *Bifidobacterium* in IgAN). Theoretically speaking, the advantage of the class II intervention mode that acts only in the initiation phase over that in the activation phase lies in the independent action of the inflammasome in NLRP3, and this is currently known to be manifested in the profibrotic phenotype of TEC fibrosis; however, this distinction has not been shown in recent studies. There may be reasons for this: first, less attention has been given to the changes in renal tubular function and injury in these studies; in addition, most of the class IIb interventions were specific inhibitors that were more efficient than some class IIa drug interventions, and therefore the difference was not significant. In addition, class IIc interventions such as caspase-1 inhibitors and IL-1 inhibitors (which do not appear in this analysis) are often used to verify the non-classical pathway of the NLRP3 inflammasome, and there are few treatments that target the NLRP3 pathway in CKD models. According to its pathway of action and the components involved in some studies, class IIc intervention is often not as effective as that for class IIa or IIb inhibitors, and its scope of application therefore needs further exploration.

We also find that the same intervention wields distinct functions in different disease models; such is the case for MCC950. As a specific inhibitor of NLRP3, MCC950 mainly targets the NACHT domain of NLRP3 and prevents the polymerization of NLRP3 to the NLRP3 inflammasome. MCC950 can, for example, act in a protective role through preventive administration in the diet-induced type 2 diabetic model of insulin resistance. However, in the model of insulin deficiency in type 1 diabetes induced by streptozotocin, preventive and therapeutic administration exhibits an antithetical effect, and this variation thus needs to be further examined. In addition, in the mouse model of LN, MCC950 may be more likely to target NLRP3 in podocytes, and its improvement of glomerular injury and its abrogation of podocytes are therefore more obvious. In crystalline nephropathy, MCC950 principally targets NLRP3 in CD11c dendritic cells, and the improvement

of renal function and injury is also more marked in renal tubules. This shows the diversity of active signaling pathways for the NLRP3 inflammasome in different diseases and also indicates the specificity of inhibiting NLRP3 in the same diseases. This reminds us that we need to be more rigorous in the translation of treatment of the NLRP3 inflammasome to clinical application.

This paper did not entail the adverse effects of targeting NLRP3, and thus, we only explored the future research direction of targeting the NLRP3 inflammasome in the treatment of CKD. More-specific NLRP3-targeting drugs such as MCC950 and CY-09 directly prevent the formation of the NLRP3 inflammasome, and a large number of targeting studies have therefore been conducted. Theoretically, these specific NLRP3 inhibitors can be used to treat all NLRP3-driven diseases, but as mentioned earlier, their effects vary in different CKDs, and there is a lack of experimental models that involve long-term use; thus, potential side-effects cannot be ignored. Another potential avenue for development is the adoption of natural herbal compounds that are used in all disease models, including betaine, carvanol, and Zhenwu decoction. Studies have shown that these drugs may inhibit the activation of NLRP3 by targeting the NF-κB/NLRP3 pathway. Their advantages are that these treatments have been used for many years, and that their side-effects are relatively clear. However, the development of specific and efficient NLRP3-targeting drugs necessitates additional investigation so as to clarify their components and mechanisms of action. In addition, xenon, as an ideal anesthetic inert gas, has played an unexpected role in targeting NLRP3 in LN models. Previous studies have found that xenon plays a protective role in renal ischemia-reperfusion [98, 99], renal transplantation [100], and gentamicin-induced renal injury models [101], which gives it an advantage in the development of renal protective therapies. Although there is still a lack of sufficient data on its application in CKD, it is still worth developing some clinical trials due to its stability.

In addition to the CKD model described above, NLRP3 is also being studied in acute kidney injury (AKI), such as acute renal injury induced by ischemia-reperfusion [102], LPS [103, 104], iodinated contrast agent [105], cisplatin [106] and glycerol induced rhabdomyolysis acute nephropathy in mice [107]. During the pathogenesis of these AKI models, NLRP3 gene knockout, specific inhibitors, drugs and other interventions can reduce NLRP3 levels while alleviating disease progression, indicating that NLRP3 is involved in the pathogenesis of these AKI models. However, due to the diversity and complexity of these AKI models, the lack of studies on the mechanism of action, and the lack of cases in clinical studies, this paper has not reviewed the studies targeting NLRP3 inflammasome in AKI.

Insights into the classical/non-classical and inflammasome-dependent/independent effects of the NLRP3 inflammasome in CKD have garnered substantial progress in recent years, and various targeted inhibitors such as NLRP3, ASC, and caspase-1 have been discovered. However, due to the universality and complexity of NLRP3, there is no suitable targeted drug for clinical application as yet. In this paper, we reviewed the current interventional methods of targeting the NLRP3 inflammasome in CKD models, and classified these interventions according to their possible targets in the expectation of generating novel concepts and reference points for the development of NLRP3-targeting drugs.

Conflict of Interest Statement

The authors report no declarations of interest.

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Author Contributions

Guixia Ding, Aihua Zhang: developing the idea for the review, oversight, and leadership responsibility for the review; Yong Ji and Hu Hua: writing the paper and literature research; Aihua Zhang and Hu Hua: funding acquisition; and Zhanjun Jia and Hu Hua: review and editing. All authors were involved in the critical review and final acceptance of the submission.

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