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REVIEW

Inflammasome activation in podocytes: a new mechanism of glomerular diseases

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Abstract

Introduction Inflammasome is a multi-protein complex which is an important constituent of innate immunity. It mainly consists of three parts, apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), caspase protease, and a NOD-like receptor (NLR) family protein (such as NLRP1) or an HIN200 family protein (such as AIM2). Inflammasome is widely studied in many autoimmune diseases and chronic inflammatory reactions, such as familial periodic autoinflammatory response, type 2 diabetes, Alzheimer's disease, and atherosclerosis. Activation of inflammasome in the kidney has been widely reported in glomerular and tubular-interstitial diseases. Podocytes play a critical role in maintaining the normal structure and function of glomerular filtration barrier. Recently, it has been demonstrated that podocytes, as a group of renal residential cells, can express all necessary components of NLRP3 inflammasome, which is activated and contribute to inflammatory response in the local kidney.

Methods Literature review was conducted to further summarize current evidence of podocyte NLRP3 inflammasome activation and related molecular mechanisms under different disease conditions.

Results Podocytes are a key component of the glomerular filtration barrier, and the loss of podocyte regeneration is a major limiting factor in the recovery of proteinuria. Through a more comprehensive study of inflammasome in podocytes, it will provide new targets and possibilities for the treatment of kidney diseases.

Keywords Inflammasome · Podocytes · Glomerular diseases · NLRP3

Introduction

Inflammasome is a multi-protein complex involved in the assembly of intracytoplasmic pattern recognition receptors (PRRs). It mainly consists of three parts, apoptosis-associated speck-like protein containing caspase recruitment domain (ASC), caspase protease, and a sensor molecule (nucleotide-binding domain-like receptors (NLRs), absent in melanoma 2-like receptors (ALRs), or the recently identified pyrin). It plays a critical role in natural and acquired immune responses. The basic mechanisms of inflammasome have been thoroughly studied. When the sensors (NLRs, ALRs or pyrin) recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the ASC recruits and activates the pro-inflammatory protein caspase-1 which can cleave the precursors of interleukin-1β (IL-1β) and interleukin-18 (IL-18), resulting in the production of mature cytokines, thereby generating the corresponding biological effects. Meanwhile, inflammasome can also activate pyroptosis, which is a special way of cell death [1].

Inflammasome can be roughly classified into three categories: NLRs, ALRs, and pyrin based on the difference of sensor molecules. Previous studies have elaborated on their specific deconstructions and compositions. NLR family contains a central nucleotide binding domain (NBD), and the majority of the members also contain a variable N-terminal

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domain and a C-terminal leucine-rich repeat (LRR) domain. In addition, according to the differences in the N-terminus, the NLRs can be further divided into NLRP (N-terminus contains a pyrin domain) and NLRC (N-terminal contains a caspase activation and recruitment domain). The function of NLR family members varies with the category. Current research suggests that NLRP1, NLRP3, and NLRC4 can directly participate in the formation of inflammasome. However, studies on NLRP6 and NLRP12 are still unclear. Studies showed that they were indirectly involved in the regulation of inflammasome or participation in the composition of the inflammatory body under special stimulation [2]. The N-terminal PYD and the C-terminal hematopoietic interferon-inducible nuclear protein which contains 200-amino acid repeat (HIN200) domain are characteristic markers of the ALR family classification. Among the ALR families, the most unique is AIM2 (absent in melanoma 2), which is known for its interaction with the PYD of ASC and its direct involvement in the formation of inflammasome [3]. Although other ALR family members have similar functions to AIM2, current mainstream research is still focused on AIM2 [4]. Pyrin is a recently discovered type which is considered as an inflammasome-forming protein. It was first discovered to be associated with the activation of inflammasome in a mouse model expressing familial Mediterranean fever mutation containing pyrin, which exhibits ASC and IL-1-mediated autoinflammation [5]. Moreover, a recent study provided definitive evidence that the pyrin inflammasome responded to Rho-modified toxins produced by various bacterial species, although direct interactions between Rho and pyrin have not been detected [6].

NLRP3 is the most widely studied inflammasome and plays an important role in a variety of kidney diseases [7]. Numerous endogenous and exogenous factors are available to stimulate the generation of NLRP3 through different mechanisms. Current researches believe that the most probable mechanisms are as follows. (1) Lysosomal disruption-mediated activation pathway. Studies have found that urea, cholesterol crystals and sterile particles could enter the cell through endocytosis, thereby destroying the stability of lysosomal membrane and activate lysosomal protease, leading to the activation of NLRP3 and promoting the production of IL-1β [8]. Artificial lysosomal rupture could also activate NLRP3, and the inhibition of lysosomal cathepsin B inhibited the activation of caspase-1. However, IL-1β production was not reduced [8]. This indicates that lysosomal destruction and cathepsin B production only play a partial role in the activating process of NLRP3. (2) Potassium outflow-mediated activation pathway. Various microbial toxins, enzymes and extracellular ATP promoted the rapid efflux of potassium ions by activating the receptor of extracellular adenosine triphosphate (eATP) (P2X7R), thereby inducing the recruitment of the hemichannel protein pannexin-1 and activating its opening on the cell membrane, which in turn activated NLRP3 [9].(3) Reactive oxygen species (ROS)-mediated activation pathway. Previous studies have found that all NLRP3 activators could induce the production of ROS, and both ROS inhibitors and scavengers blocked the activation of the NLRP3 [10]. Zhou et al. suggested that it might be related to a thioredoxin-interacting protein (TXNIP). Inflammasome activators such as uric acid crystals significantly activated ROS and induced the dissociation of TXNIP from thioredoxin, allowing it to bind to NLRP3. TXNIP deficiency inhibited the activation of NLRP3 inflammasome and the subsequent secretion of IL-1β [11].

The glomerular filtration barrier consists of capillary endothelial cells, glomerular basement membrane (GBM), and podocytes. The podocytes, also known as the glomerular visceral epithelial cell, is a highly specific terminally differentiated cell located outside the GBM, surrounding the glomerular capillary loop, which constitutes the last layer of the glomerular filtration membrane barrier. It plays an important role in maintaining the structure and function of the normal glomerular filtration barrier, and the disruption of its structural or functional integrity leads to proteinuria. In 2012, Zhang et al. firstly revealed the existence of NLRP3 in glomerular podocytes, but the specific role of these inflammasome in podocytes have not been studied and elaborated in detail [12]. Over time, more studies have found that inflammasome plays an important role in podocytes injury [13]. Parthenolide and Bay 11–7082 are two recognized inhibitors of NF-κB [14]. Studies have shown that these two substances also inhibited the activation of NLRP3 by affecting ATPase activity, independent of their inhibitory effect on NF-κB [14]. The application of parthenolide and Bay 11–7082 resulted in a decrease in podocyte chemokine expression [15]. Monocyte chemoattractant protein-(MCP-) 1, a small cytokine belonging to the CC chemokine family, is associated with the migration and infiltration of macrophages in diabetic nephropathy (DN) [16]. Studies have found that parthenolide inhibited the expression of MCP-1 in podocytes, indicating that NLRP3-targeted therapy may alleviate DN by inhibiting the inflammatory response of podocytes [17].

Drugs targeting IL-1, such as recombinant IL-1Ra (anakinra), neutralize anti-IL-1β antibodies (canakinumab) and IL-1β trap (rilonacept) are widely used in clinical applications. Randomly assigning 10,061 participations, canakinumab treatment reduced the risk of major cardiovascular adverse events in CKD patients (hazard ratio: 0.82; 95% confidence interval: 0.68–1.00; $p = 0.05$). Observation in patients with baseline proteinuria or diabetes achieved a similar effect. For indicators such as eGFR, creatinine, urine albumin to creatinine ratio (uACR) or reported adverse renal events, the application of canakinumab has neither clinically significant benefits nor substantial damage [18]. In a two-site, double-blind trial of 42 patients with CKD, they

received IL-1β trap (rilonacept) or placebo for 12 weeks. The rilonacept treatment has improved brachial artery flow-mediated dilation without changing aortic pulse-wave velocity and reduced systemic inflammation, which proved its benefit to alter vascular function in CKD patients [19].

Another important clinical application for IL-1-related drugs is familial Mediterranean fever (FMF). FMF is a spontaneous autosomal recessive disease, characterized by recurrent fever and peritonitis. Some patients may develop proteinuria and nephrotic syndrome [20]. At present, colchicine is the most preferred treatment for FMF [21]. However, for patients who are unresponsive to colchicine treatment or develop amyloidosis, anti-IL-1 therapy is an effective alternative to control the onset and reduce proteinuria [22–24].

In this review, we summarize the current evidence of inflammasome activation in podocytes and related molecular mechanisms in different kidney diseases.

Different types of inflammasome in the kidney

Inflammasomes consist of ALRs, NLRs and pyrin. At present, the researches mainly focused on ALRs and NLRs. There are few studies on pyrin. AIM2 is the most widely studied inflammasome in ALRs and is expressed in glomeruli, tubules, and infiltrating leukocytes. It has been currently studied in systemic lupus erythematosus (SLE), renal fibrosis model and HBV-associated glomerulonephritis (HBV-GN) [25–27]. The AIM2 gene was significantly increased in leukocytes, but there was no significant increase in renal biopsy from SLE patients as compared to the control individuals [27]. In a mouse model of unilateral ureteral obstruction (UUO), AIM2 deficiency attenuated the renal injury, fibrosis, and inflammation compared to wild-type (WT) littermates [26]. In terms of HBV-associated glomerulonephritis (HBV-GN), AIM2 expression is positively correlated with HBV-mediated inflammation in patients with HBV-GN and AIM2 knockdown reduced caspase-1, IL-1β, and IL-18 expression in HBV-infected and HBV-uninfected human glomerular mesangial (HGM) cells, which indicated the role of AIM2 in potentiating inflammation and leading to renal damage [25].

Similarly, NLRP3 is currently the most well-recognized and researched in NLR family, and it is also the most extensive and in-depth type of inflammasomes in kidney diseases. NLRP3 is the first inflammasome found in the kidney-derived cells and is the most widely studied inflammasome among NLR family in the field of kidney diseases, such as diabetic nephropathy (DN), IgA nephropathy, hyperhomocysteinemia, and crystal-induced kidney injury [12, 28–30]. However, other members of the NLR family have been studies in only a few works on kidney diseases. Recently, a study demonstrated that variants in NLRP1 protected against the development of DN and diabetes metabolites were able to regulate NLRP1 expression [31]. Moreover, the level of NLRC4 was found to be prominently upregulated in the kidneys of 24-month-old (elderly group) rats, which indicated its contribution to the renal aging process [32]. Meanwhile, the activation of NLRC4 was found as a parallel mechanism in addition to the NLRP3-inflammasome to induce pro-IL-1β processing and activation, leading to the progression of DN [33]. Further exploration is needed to clarify the specific distribution and function of other inflammasome members in the kidney.

Inflammasomes in podocytes

Hyperhomocysteinemia

Hyperhomocysteinemia (hHcys) is involved in the development and progression of a variety of sclerosing diseases. It can induce impaired endothelial function, thrombosis, disorders of cholesterol and triglyceride anabolism, and activation of monocytes [34]. In kidney diseases, hHcys can directly cause podocyte damage and lead to glomerular sclerosis [35].

Zhang et al. first demonstrated that murine podocytes expressed three essential components of NLRP3 inflammasome complex and the stimulation of Hcys promoted the formation and activation of NLRP3 inflammasome. By local ASC gene silencing or caspase-1 inhibition, hHcys-associated albuminuria, foot process effacement of podocytes, loss of podocyte slit diaphragm molecules, and glomerulosclerosis at the late stage were significantly improved [12]. Moreover, NLRP3 gene was found to be critical for the formation and activation of inflammasomes in podocytes of hHcys mice. Podocyte proteins, especially the deletion of podocin and nephrin, and overexpression of desmin, play an important role in the process of glomerular diseases and proteinuria production. In folate-free (FF) diet-induced hHcys mice, uninephrectomized NLRP3 knockout (NLRP3−/−) mice had enhanced expression of podocin and nephrin, but downregulation of desmin compared to wild-type (NLRP3+/+) mice, revealing that the activation of NLRP3 plays a crucial role in podocyte injury of hHcys [36].

HHcys-induced ROS has been identified as a crucial mechanism for NLRP3 activation. Scavenging of superoxide ($O_2^{\bullet-}$) by 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPOL) and removal of hydrogen peroxide (H_2O_2) by catalase substantially inhibited hHcys-induced NLRP3 inflammasome formation and activation as well as caspase-1 activation and IL-1β production in mouse podocytes and in the glomeruli of hHcys mice [37]. NADPH oxidase (NOX) is a pivotal enzyme in the redox signal pathway and a major

source of ROS in the body. Previous studies have showed that NOX inhibition attenuated the aggregation of inflammasome proteins and inhibited the activation of inflammasome in mouse podocytes. In vivo, NOX inhibition also protected glomeruli and podocytes from hHcys-induced damage, as shown by decreased proteinuria, albuminuria, and glomerular sclerosis [38]. However, the mechanisms by which ROS activates inflammasomes remain to be explored. Some studies have suggested that TXNIP binding to NLRP3 is a key signaling mechanism necessary for ROS-induced NLRP3 inflammasome formation and activation of hHcys mice [39]. But whether this is the main mechanism and whether there are other potential mechanisms between them still need further research.

Based on the fact that NLRP3 inflammasome plays an important role in the process of hHcys-induced podocyte injury, whether it can be a potential new target for the treatment of podocyte injury is the focus of attention. Rac1 activator, uridine triphosphate (UTP), mimicked L-Hcy (the active Hcy form)-induced NLRP3 inflammasome activation, while Rac1 inhibitor NSC23766 blocked inflammasome activation as well as podocyte dysfunction. In vivo, hHcy-induced glomerular NLRP3 inflammasome formation and activation were also mimicked by UTP and inhibited by NSC23766 at the same level as NLRP3 knockout mice. Taken together, these results indicated that inflammasome activation in podocytes might be a therapeutic target for glomerular injury [40]. Li et al. considered anandamide (AEA), a compound with anti-inflammatory properties, as a new treatment for hHcys-induced podocyte injury targeting NLRP3 inflammasome and suggested that the mechanism of NLRP3 inflammasome inhibition was through its cyclooxygenase-2 (COX-2) metabolite, prostaglandin E2-ethanolamide (PGE2-EA) [41]. Another study applied DHA metabolites, resolvins, resolvin D1 (RvD1), and 17S-hydroxy DHA (17SHDHA), which also had potential anti-inflammatory effects, and found that these could inhibit NLRP3 inflammasome activation by suppressing Hcys-induced formation of lipid raft redox signaling platforms and subsequent $O_2^{\bullet-}$production in podocytes [42]. However, the above compounds were examined for their anti-inflammatory effects, and there is a lack of reports on the effects of NLRP3-specific agonists or inhibitors, such as MCC950, parthenolide, isoliquiritigenin, or Bay11-7082 in hHcys-induced podocyte injury. (Fig. 1).

Diabetic nephropathy

Diabetic nephropathy (DN), also known as Kimmelstiel–Wilson syndrome, is one of the most common microvascular syndromes of diabetic mellitus and is a significant cause of end-stage renal disease (ESRD). In the high

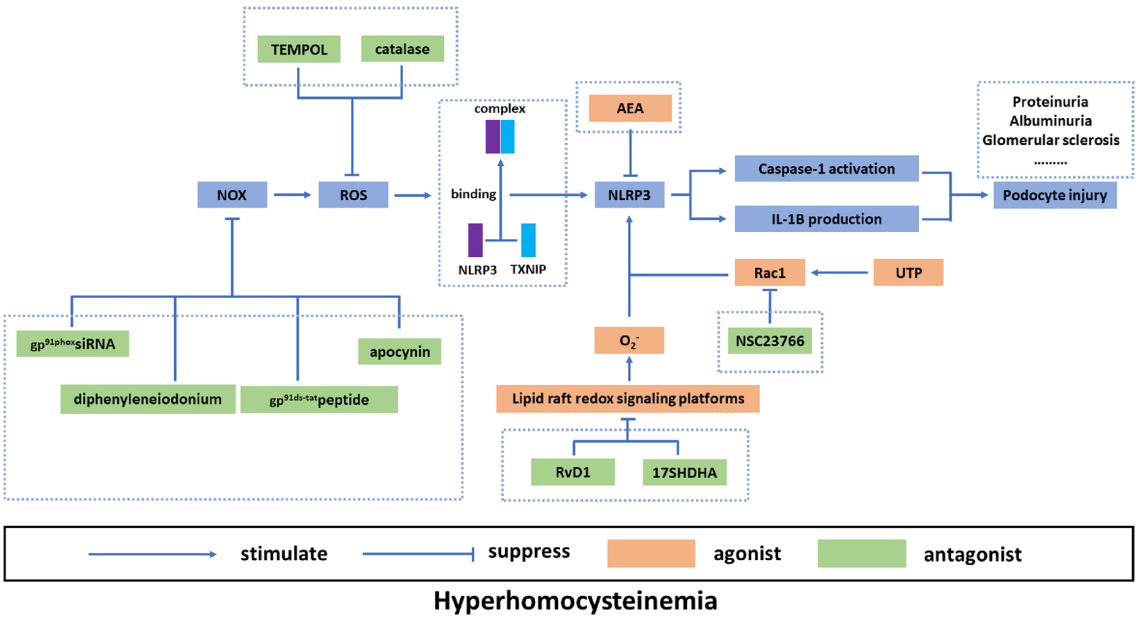

Fig. 1 Mechanism of NLRP3 inflammasome-induced glomerular injury in hyperhomocysteinemia. TEMPOL and catalase substantially inhibited hHcys-induced NLRP3 inflammasome formation and activation by inhibition of ROS. NOX inhibition attenuated ROS-induced NLRP3 inflammasome formation and activation. TXNIP binding to NLRP3 is a key signaling mechanism necessary for ROS-induced NLRP3 inflammasome formation and activation. Rac1 activator (UTP) mimicked inflammasome formation and activation and its inhibitor (NSC23766) had adverse effect. Anti-inflammatory compounds, AEA, RvD1 and 17SHDHA, could inhibit NLRP3 inflammasome activation. TEMPOL, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl; ROS, reactive oxygen species; NOX, NADPH oxidase; UTP, uridine triphosphate; AEA, anandamide; RvD1, resolvin D1; 17SHDHA, 17S-hydroxy DHA

glucose environment in vivo or in vitro, podocyte apoptosis is induced while the normal cell morphology is damaged, leading to glomerular sclerosis, which eventually produces a large amount of proteinuria [43].

Studies have found that in vivo and vitro, high glucose stimulation could induce the activation of NLRP3 inflammasome, and blocking its activation by NALP3/ASC shRNA and caspase-1 inhibition alleviated IL-1β production and eventually attenuated podocyte and glomerular injury [44]. NLRP3–/– or caspase-1 knockout (caspase-1–/–) diabetic mice showed significantly less albuminuria and fractional mesangial area (FMA) in comparison with wild-type diabetic mice [45]. NLRP3 inhibitor, parthenolide, could effectively reduce kidney inflammation and insulin resistance in diabetic mice [46]. Intraperitoneal injection of anti-IL-1β in albuminuric mice significantly attenuated the progressive decline in GFR and retained the number of podocytes without affecting albuminuria or ultrafiltration of single nephron [47]. Canakinumab is a monoclonal antibody targeting IL-1β. It was approved by the FDA in 2009 for the treatment of cryopyrin-associated periodic syndromes (CAPS). Recently, canakinumab was discovered to reduce the risk of cardiovascular disease by 15% [48], while another study is even more "magical". The highest dose of canakinumab reduced the risk of lung cancer by 67% and 77%, respectively [49]. The application of canakinumab in kidney diseases, especially diabetic nephropathy, has been gradually discovered. In a phase IIb clinical trial, among 556 men and women with good glycemic control but high risk of cardiovascular disease, the group who continued to use canakinumab for 4 months had significantly reduced inflammatory indicators in the circulatory system, including CRP, IL-6, and fibrinogen [50]. Another study compared patients with type 2 diabetes or impaired glucose tolerance who used placebo ($n=94$) or canakinumab 150 mg per month ($n=95$) for 12 months, although the structure and function of carotid and aorta had no differences and there were significant differences in systemic inflammation markers (CRP, IL-6) and lipoprotein (a) level [51].

As an important mechanism of inflammasome activation, studies have found that ROS, especially mitochondria-derived ROS, also played a crucial role in NLRP3-dependent inflammasome activation in DN [45]. Advanced glycation end products (AGEs), which could induce mitochondrial ROS generation through a RAGE (receptor for AGEs)-dependent mechanism, was found to promote NLRP3 expression and IL-1β cleavage in podocytes and reversed by RAGE inhibition. Meanwhile, mitochondria-targeted antioxidant (MitoTempo) treatment markedly reduced the levels of NLRP3, cleaved IL-1β, albuminuria, and FMA in comparison with control db/db mice [45]. As in hHcys, studies have verified the role of TNXIP in ROS-induced NLRP3 inflammasome formation and activation in DN. TNXIP binding to NLRP3 was also a pivotal mechanism of NLRP3 inflammasome activation and, at the same time, TNXIP could activate NLRP3 inflammasome by inducing NOX activation in podocytes [44, 52]. Other pathways that mediate NLRP3 inflammasome activation have also been discovered. Knockdown of TLR4 (Toll-like receptor 4), which participated in the course of inflammatory responses, inhibited the activation of NALP3 inflammasome in HG-treated podocytes, as manifested by the downregulation in NLRP3, ASC and cleaved caspase-1 protein levels and the reduction in caspase-1 activity [53]. Luteolin is currently used to treat some diabetic complications. Recently, studies have found that luteolin significantly inhibited NLRP3 inflammasome activation and subsequent IL-1β secretion in HG-induced podocytes. Knockdown of NLRP3 eliminated the effect of luteolin on apoptosis, indicating that the clinical effect of luteolin was closely related to NLRP3 inflammasome [54]. In general, the NLRP3 inflammasome mediates podocytes and glomerular injury in DN and blocking its activation may be a potential direction for DN treatment. (Fig. 2).

Obesity-related nephropathy

Obesity is an important and independent risk factor for the occurrence and progression of type 2 diabetes mellitus, cardiovascular diseases, and non-diabetic chronic kidney disease (CKD) [55]. Experimental and clinical studies have demonstrated that adipose tissue, especially visceral fat, generates bioactive substances that contribute to the glomerular structural and functional changes, leading to obesity-associated glomerular injury [56].

Studies have found that the formation and activation of inflammasomes are an important initiating mechanism contributing to obesity-associated podocyte injury and consequent glomerular sclerosis. Confocal microscopic and co-immunoprecipitation analysis showed that the high fat diet (HFD) enhanced the formation of inflammasome, as shown by colocalization of ASC with NLRP3, and were mostly located in podocytes as demonstrated by co-localization of podocin with NLRP3 [57, 58]. However, this inflammasome aggregation was not observed in ASC knockout (ASC−/−) mice and local ASC shRNA-transfected mice, and at the same time, caspase-1 activity, IL-1β production and glomerular injury index were also significantly attenuated, accompanied by decreased proteinuria, albuminuria, loss of podocyte foot processes and loss of pod cell membrane separator cells [58].

Recent studies suggested that the activation of NLRP3 inflammasome in the podocyte damage of obesity-related glomerulopathy was mediated by the ATP-P2X7 receptor. The binding of ATP and P2X7R induced rapid opening of the cation channel, leading to outflow of potassium ion and depletion of intracellular potassium ion, which were the

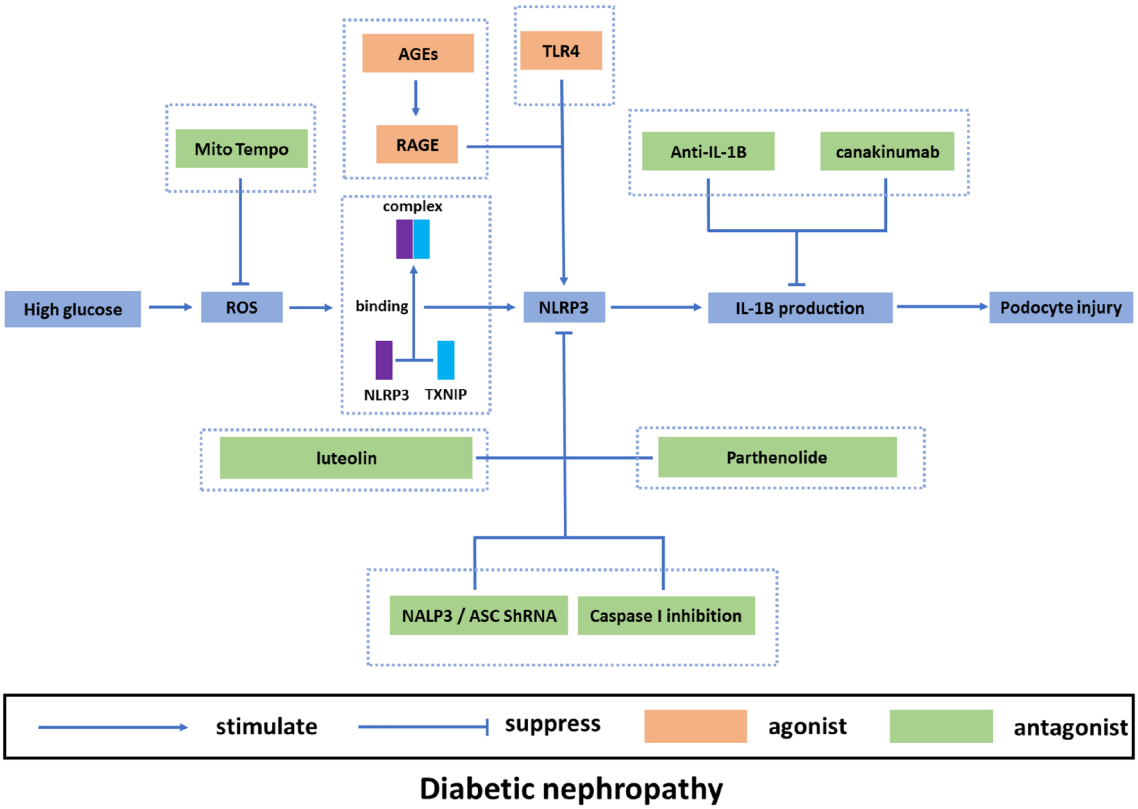

Fig. 2 Mechanism of NLRP3 inflammasome-induced glomerular injury in diabetic nephropathy. NALP3/ASC shRNA and caspase-1 inhibition alleviated IL-1β production and eventually attenuated podocyte and glomerular injury. NLRP3 inhibitor, parthenolide, could effectively reduce kidney inflammation and insulin resistance. Intraperitoneal injection of anti-IL-1β significantly attenuated the progressive decline in GFR and retained the number of podocytes. Canakinumab, a monoclonal antibody targeting IL-1β, reduced systemic inflammation markers in diabetic patients. AGEs binding with its receptor RAGE promoted NLRP3 expression and IL-1β cleavage in podocytes. MitoTempo treatment markedly reduced the levels of NLRP3. TNXIP binding to NLRP3 was a pivotal mechanism of NLRP3 inflammasome activation. Knockdown of TLR4 inhibited the activation of NALP3 inflammasome in HG-treated podocytes. Luteolin significantly inhibited NLRP3 inflammasome activation and subsequent IL-1β secretion in HG-induced podocytes. IL-1β, interleukin-1β; AGEs, advanced glycation endproducts; RAGE, receptor for AGEs; MitoTempo, mitochondria-targeted antioxidant. TLR4, toll-like receptor 4

important mechanisms for NLRP3 inflammasome activation [59]. P2X7R silencing or applying P2X7R antagonist (KN-62 or A438079) in cultured mouse podocytes inhibited the activation of NLRP3 inflammasome as well as the morphological changes of podocyte damage and the expression changes of podocyte-associated molecules [59, 60].

ROS was another major mechanism for activation of inflammasome in obesity-related nephropathy, which promoted the activation of TNXIP/NLRP3 signaling pathway and aggravated podocyte injury. The current study suggested that miR-377 played a pivotal role in glomerular podocyte oxidative stress; inflammation and injury driven by high fructose and inhibition of miR-377 by antioxidants may be promising therapeutic strategies targeting ROS-induced NLRP3 activation [61].

Abnormal lipid metabolism is a key pathogenesis of obesity-related glomerulopathy, but its specific mechanism has not been fully elucidated. CD36 is a fatty acid transporter protein that mediates lipid uptake. A recent study has found that CD36-mediated lipid accumulation was associated with podocyte injury in obesity-related glomerulopathy, while blocking NLRP3 could attenuate podocyte injury, suggesting that abnormal lipid metabolism might be another important mechanism for the activation of inflammasome [62].

In addition, Coptidis Rhizoma, a classical traditional Chinese herb, ameliorated obesity-related glomerulopathy probably through the inhibition of NLRP3 activation [63]. Also, Coptidis Rhizoma is well known for its hypoglycemic and hypolipidemic properties. In addition to the effect of improving obesity-induced podocyte injury through NLRP3, whether there are other metabolic mechanisms remains to be explored. As several studies have suggested traditional Chinese medicine as an effective treatment for podocyte injury [61], the specific efficacy and mechanism have yet to be explored in greater depth (Fig. 3).

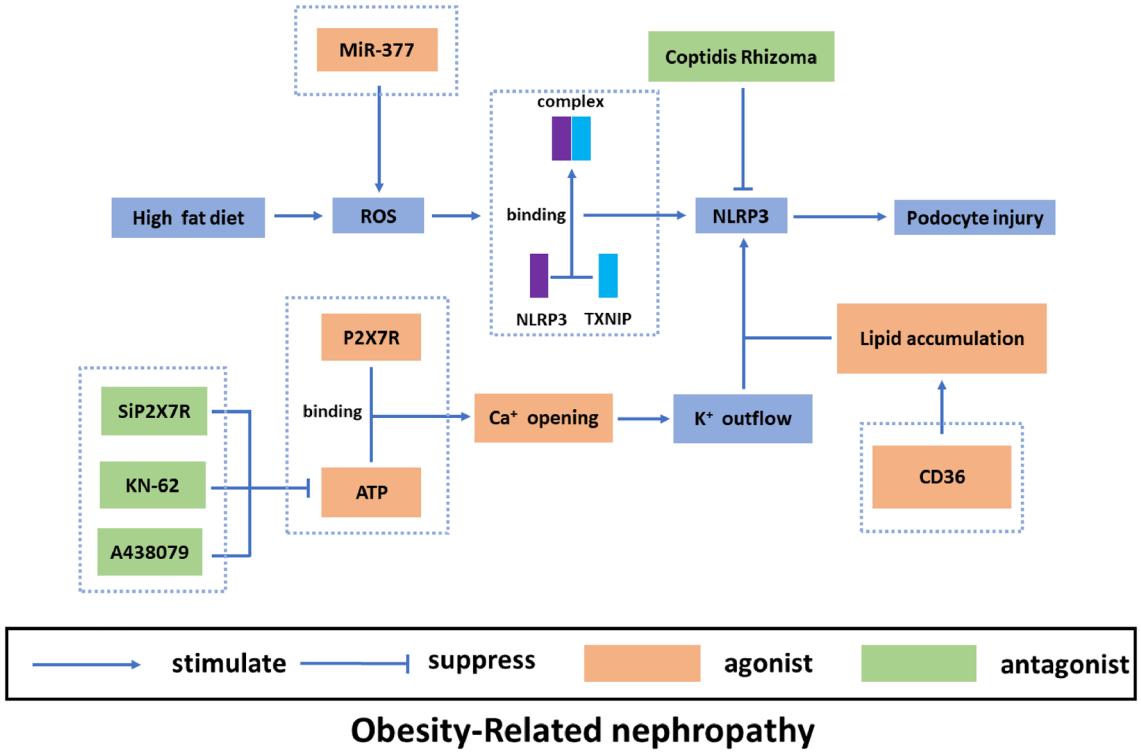

Fig. 3 Mechanism of NLRP3 inflammasome-induced glomerular injury in obesity-related nephropathy. The binding of ATP and P2X7R induced rapid opening of cation channel, leading to outflow of potassium ion, which was the important mechanism for NLRP3 inflammasome activation. P2X7R silencing or applying P2X7R antagonist (KN-62 or A438079) inhibited the activation of NLRP3 inflammasome. ROS promoted the activation of TNXIP/NLRP3 signaling pathway and aggravated podocyte injury. Inhibition of miR-377 by antioxidants alleviated ROS-induced NLRP3 activation. CD36-mediated lipid accumulation promoted NLRP3 activation and podocyte injury. Coptidis Rhizoma, a classical traditional Chinese herb, ameliorated obesity-related glomerulopathy probably through the inhibition of NLRP3 activation. ATP, adenosine triphosphate; P2X7R, receptor of extracellular adenosine triphosphate

Hypertension-related nephropathy

Clinically, many patients develop excessive aldosterone due to lesions in the adrenal cortex, resulting in retention of water and sodium, increased blood volume, and ultimately hypertension. At the same time, studies have shown that excessive aldosterone contributed to the pathogenesis of kidney diseases, inducing inflammation in renal vessels, tubular cells, and fibroblasts [64–67]. However, little is known about the role and mechanism of excess aldosterone in podocyte injury. Recently, Bai et al. demonstrated that aldosterone infusion induced downregulation of nephrin and podocin, podocyte foot processes and albuminuria, which was remarkably improved in mice with NLRP3 gene deletion. In vitro, exposure of podocytes to aldosterone significantly increased apoptosis and down-regulated nephrin, while enhancing NLRP3, caspase-1 and IL-18 expression in a dose- and time-dependent manner. Silencing NLRP3 by the siRNA method strikingly attenuated the above changes [68]. Taken together, these results demonstrate the important role of NLRP3 inflammasome in mediating aldosterone-induced podocyte injury.

Angiotensin II (Ang II) induces hypertension in the contraction of systemic arterioles and, in addition, promotes the secretion of aldosterone from the adrenal cortex. A recent study has identified the role of NLRP3 inflammasome in Ang II-induced podocyte injury [69]. The study showed that Ang II activated the NLRP3 inflammasome in podocytes and that, by NLRP3 silencing, Ang II-induced podocyte apoptosis and loss of the podocyte-specific proteins nephrin and podocin were distinctly attenuated. The same result was obtained in NLRP3−/− mice [69]. Isoliquiritigenin (ISL) is a flavonoid compound found in licorice root and several other plants. It has anti-oxidant, anti-inflammatory and anti-tumor activities, as well as a hepatoprotective effect on steatosis-induced oxidative stress [70–73]. ISL has a stronger inhibitory effect on NLRP3 than parthenolide, and could inhibit NLRP3 activated ASC oligomerization [74]. Low concentrations (1–10 μM) of ISL also decreased NLRP3-dependent IL-1β production [74]. Studies have reported that ISL reduced Ang II-induced hypertensive renal injury by inhibiting inflammatory cytokines, excessive extracellular matrix deposition, and apoptosis induced by oxidative stress [75]. At the same time, studies have found that ISL protected

both LPS and cisplatin-induced acute kidney injury [76, 77]. However, the above studies were all aimed at renal tubular injury, and there is lack of research on the effect of ISL on podocyte-specific injury. (Fig. 4).

Primary glomerulonephritis (PGN)

PGN is the most common type of CKD and is a leading cause of ESRD. The degree of podocyte injury is often applied to determine the pathological changes of PGN and is an important indicator of prognosis [78].

Given that inflammation is the most important mechanism of glomerular diseases including primary and secondary glomerulonephritis, in 2015, Xiong et al. first identified that the formation and activation of NLRP3 inflammasomes in podocytes were a pivotal initiating mechanism resulting in PGN [79]. In patients' tissue with PGN, an increased level of NLRP3 mRNA was found correlative with a decrease in nephrin mRNA level and an increase in desmin mRNA level. Immunofluorescence analysis also showed increased protein expression of NLRP3 and caspase-1 in glomeruli of PGN patients [79]. Recently, studies found that NLRP3 inflammasome was also involved in podocyte injury induced by interleukin-17A or CD36 in primary nephrotic syndrome [80, 81]. Activation of ROS may be a crucial mechanism, but more in-depth mechanisms remain to be explored [80]. (Fig. 5).

Lupus nephritis

Lupus nephritis (LN) is one of major manifestations of SLE, in which proteinuria is a major feature of LN and the

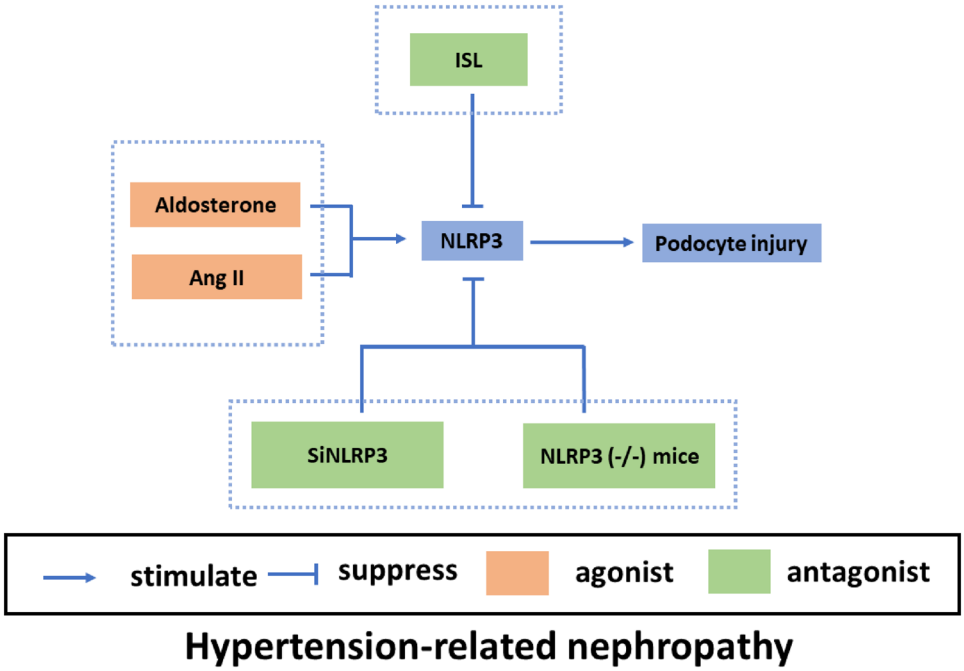

Fig. 4 Mechanism of NLRP3 inflammasome-induced glomerular injury in hypertension-related nephropathy. Silencing NLRP3 by the siRNA in vitro or in the mice with NLRP3 gene deletion attenuated aldosterone and Ang II-induced podocyte injury. ISL reduced Ang II-induced hypertensive renal injury for inhibitory effect on NLRP3. Ang II, angiotensin II; ISL, isoliquiritigenin

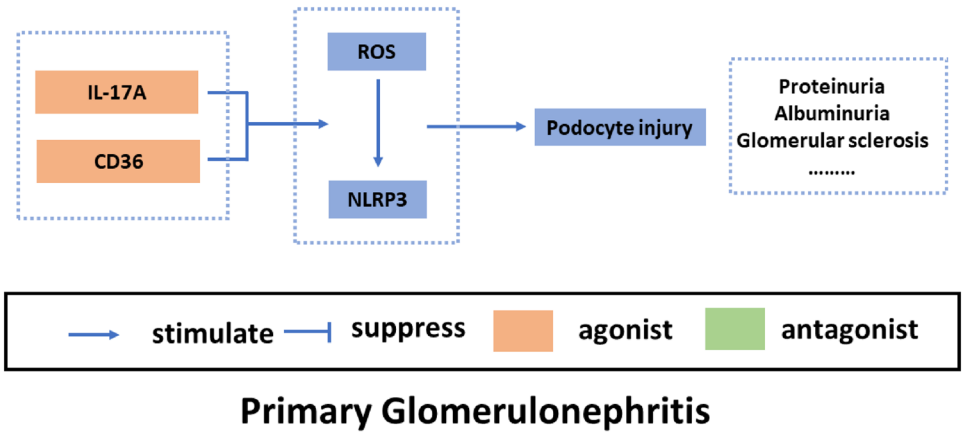

Fig. 5 Mechanism of NLRP3 inflammasome-induced glomerular injury in primary glomerulonephritis. NLRP3 inflammasome was involved in podocyte injury induced by IL-17A or CD36 in primary nephrotic syndrome. Activation of ROS may be a crucial mechanism. IL-17A, interleukin-17A

development of proteinuria is associated with podocyte dysfunction [82]. Activated NLRP3 inflammasome was found in podocytes of lupus-prone mice and LN patients and inhibition of NLRP3 with MCC950, a selective inhibitor of NLRP3, improved proteinuria, renal tissue lesions and podocyte foot process effacement in lupus-prone mice [83].

Recently, studies found that in addition to its basic functions, NLRP3 is involved in complex regulatory networks, by which these new regulatory mechanisms are widely involved in the synergy and antagonism of NLRP3 functions. Fu et al.'s study demonstrated that Pim-1-mediated Pim-1/NFATc1 pathway could significantly affect NLRP3 function in LN, and significantly protected the structure of podocyte while improving its physiological function [84]. Another study suggested that the activation of NLRP3 in podocytes was largely dependent on RIP3, which has been shown to have an important role in regulating podocyte function and there is a great possibility to become a potential critical pathway for the treatment of LN [85]. These findings indicate that NLRP3 is widely activated in podocytes and is involved in the development and progression of LN, which means that the treatment of NLRP3 may be a new target for LN therapy. (Fig. 6).

HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is a special type of kidney disease caused by HIV infection. It is mainly manifested by a large amount of proteinuria and rapid decline of renal function in the short term. The pathological features are characterized by podocyte hyperplasia/hypertrophy, foot process fusion, severe tubular interstitial inflammation, and tubular microcapsule expansion. The disease is the leading cause of end-stage renal failure (ESRD) in HIV-infected patients [86].

Important features of HIV-associated nephropathy include dysregulated growth and loss of podocytes. A recent study demonstrated that NLRP3 inflammasome activation in podocytes contributed to HIV-induced pyroptosis, as NLRP3 inflammasome complex formed in podocytes of HIV-transgenic mice (Tg26) and caspase-1 inhibitor attenuated HIV-induced pyroptosis [87]. At the same time, HIV-induced podocyte pyroptosis could be partially inhibited by TEMPOL and by glyburide (an inhibitor of potassium efflux), suggesting that the generation of ROS and potassium efflux might be the potential mechanisms of NLRP3 activation and pyroptosis in HIV-induced podocyte injury [87]. (Fig. 7).

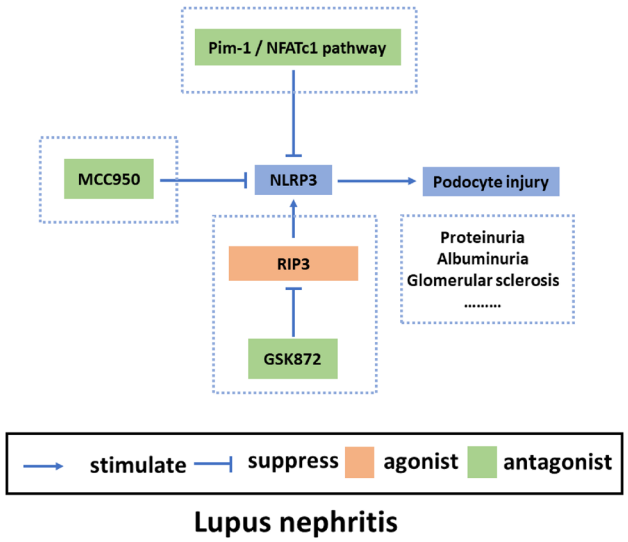

Fig. 6 Mechanism of NLRP3 inflammasome-induced glomerular injury in lupus nephritis. MCC950, a selective inhibitor of NLRP3, improved proteinuria, renal tissue lesions and podocyte foot process effacement in lupus-prone mice. RIP3 activated NLRP3 inflammasome in podocytes during LN, while GSK872, an RIP3-specific inhibitor, inhibited the development of LN. LN, Lupus nephritis

Conclusions and perspectives

Podocytes are a key component of the glomerular filtration barrier, and the loss of podocyte regeneration is a major limiting factor in the recovery of proteinuria. Previous studies have shown that inflammation is an important factor in podocyte injury [88]. Inflammasome, especially NLRP3, mediates a variety of pathophysiological processes in podocyte injury and have a critical impact on proteinuria. IL-1β and IL-18 are two common cellular interleukins produced by the activation of inflammasome, both of which have extensive biological activities that can lead to the occurrence and development of inflammation and disturbances in cell metabolism [89]. IL-1β reduced low-density protein (LDL), triggered SREBP cleavage-activating protein (SCAP), sterol regulatory element-binding protein 2 (SREBP-2), and mediated feedback inhibition of LDL receptor (LDLr) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase expression, thereby reducing cholesterol accumulation in podocytes induced by LDL [90]. Activated caspase-1 may act on more than 120 substrates related to glycolysis and lipid metabolism. In addition, the maturation of caspase-1 can also lead to podocyte pyroptosis [91]. In this article, we focus on inflammasome and provide a detailed overview of its role and mechanisms in podocyte injury induced by various kidney diseases (Fig. 8). Intervention of inflammasome in podocytes provides a novel approach to maintain the integrity of the glomerular filtration barrier and ameliorate podocyte injury-related kidney diseases.

However, there are still many challenges to be explored in the study of inflammasome in podocytes. Firstly, there is still a lack of studies involving podocyte-specific conditional

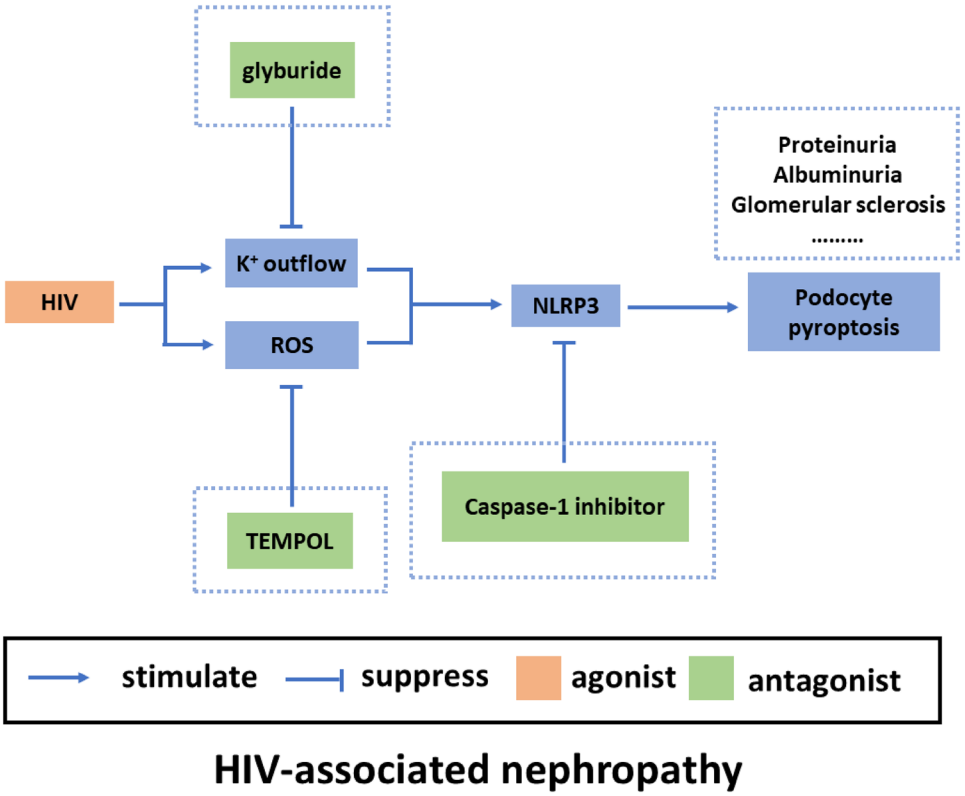

Fig. 7 Mechanism of NLRP3 inflammasome-induced glomerular injury in HIV-associated nephropathy. Caspase-1 inhibitor attenuated HIV-induced podocyte pyroptosis. TEMPOL (an inhibitor of ROS) and glyburide (an inhibitor of potassium efflux) inhibited NLRP3 activation and pyroptosis in HIV-induced podocyte injury. TEMPOL, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl; ROS, reactive oxygen species

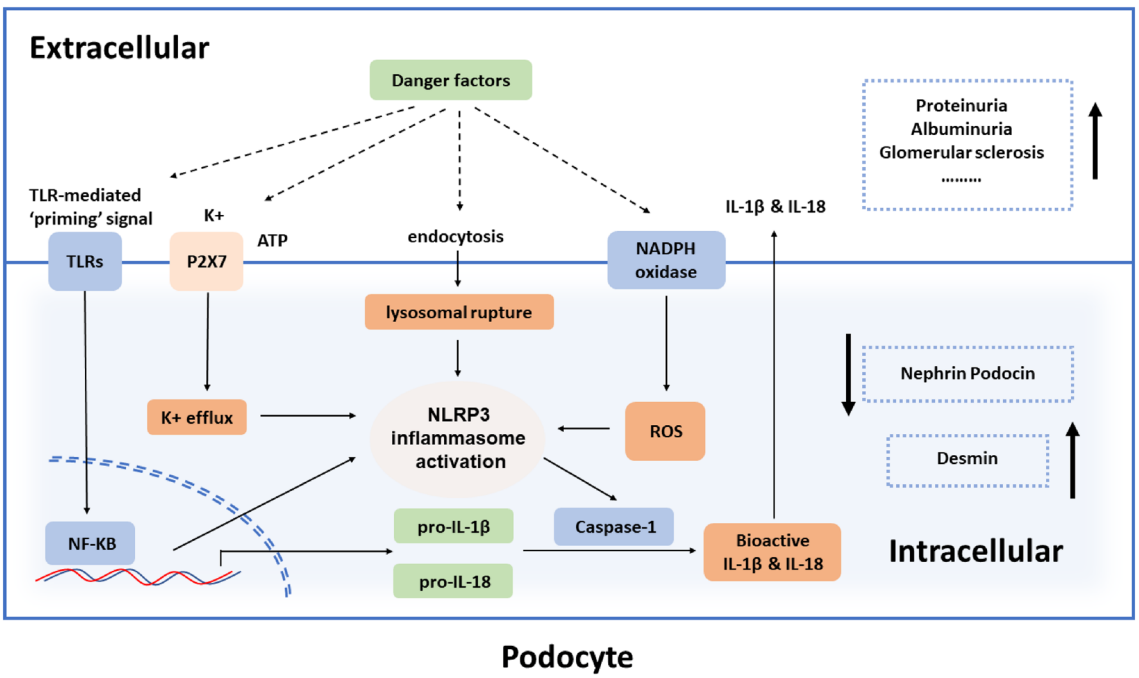

Fig. 8 Formation and activation of NLRP3 inflammasome in podocyte. Many danger factors can activate NLRP3 inflammasome through different intermediate mechanisms including K + efflux through the P2X7R, lysozyme rupture, and ROS production. NLRP3 inflammasome can also be activated through TLRs, leading to increased transcription via NF-κB. Formation and activation of the NLRP3 inflammasome complex induce the activation of caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 producing corresponding mature cytokines, resulting in their extracellular release. IL-1β and IL-18 suppress the expression of nephrin and podocin and promote the expression of desmin in podocyte, resulting in glomerular injury. P2X7, purinergic 2X7; ROS, reactive oxygen species; TLRs, toll-like receptors

knockout mice, therefore, direct evidence is vacancy. Secondly, the progression of glomerular diseases is the result of multiple kidney-inherent cell interactions, as well as the interaction with immune cells. Given that the inflammasome is present in a variety of kidney-derived cells and inflammatory cells, we cannot exclude the pattern of paracrine. Accordingly, the effect of blocking the activation of inflammasome in a certain cell line on disease progression remains unclear. We believe that in the near future, the study of inflammasome in kidney diseases will be more thorough, thus providing new targets and possibilities for the treatment of kidney diseases.

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Conflict of interest There are no conflicts of interests to declare.

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