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Inflammasomes in the Pathophysiology of Kidney Diseases

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Key Words
Inflammasome · NLRP3 · Chronic kidney disease · Acute kidney injury

Abstract
Background: The inflammasome is a complex of proteins in the cytoplasm that consists of three main components: a sensor protein (receptor), an adapter protein and caspase-1. Inflammasomes are the critical components of innate immunity and have been gradually recognized as a critical mediator in various autoimmune diseases; also, their role in chronic kidney disease and acute kidney injury has been gradually accepted. ***Summary:*** Inflammasomes triggered by infectious or sterile injuries transfer proinflammatory mediators into mature ones through innate danger-signaling platforms. Information on inflammasomes in kidney disease will help to uncover the underlying mechanisms of nephropathy and provide novel therapeutic targets in the future. ***Key Messages:*** The inflammasomes can be activated by a series of exogenous and endogenous stimuli, including pathogen- and danger-associated molecular patterns released from or caused by damaged cells. The NACHT, LRR and PYD domain-containing protein 3 (NLRP3) in the kidney exerts its effect not only by the 'canonical' pathway of IL-1β and IL-18 secretion but also by 'noncanonical' pathways, such as tumor growth factor-β signaling, epithelial-mesenchymal transition and fibrosis. In both clinical and experimental data, the NLRP3 inflammasome was reported to be involved in the pathogenesis of chronic kidney disease and acute kidney injury. However, the underlying mechanisms are not fully understood. Therapies targeting the activation of the NLRP3 inflammasome or blocking its downstream effectors appear attractive for the pursuit of neuropathy treatments.

The notion of inflammasomes was first reported by Tschopp and colleagues [1] in 2002 to describe a caspase-activating complex, which is a critical component of innate immunity. In recent years, the role of the inflammasomes has been gradually recognized in genetic syndromes, idiopathic autoinflammatory diseases, environmental diseases and cancer. In addition, increasing knowledge has implicated that inflammation may contribute to the development of kidney diseases. Although inflammation means to repair an initial insult, once the reaction becomes uncontrollable, it leads to tissue injury and inflammatory disorders. Pattern recognition receptors (PRRs) are essential to pass signals of pathogens, or damage and then induce immune responses. Under both physiological and pathological conditions, PRRs are widely expressed in the kidney [2]. Therefore, it is very likely that inflammasomes are involved in the pathogenesis of nephropathy. Here, we primarily discuss the recent progress in research on the

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NACHT, LRR and PYD domain-containing protein 3 (NLRP3) inflammasome in the pathophysiology of kidney diseases.

Introduction of the Inflammasome

The inflammasome is a complex of proteins in the cytoplasm that consists of three main components: a sensor protein (receptor), an adapter protein and caspase-1 [3]. According to the receptor, inflammasomes are divided into two families: the NOD-like receptor (NLR) family and the pyrin (PYD) and HIN200 domain-containing protein (PYHIN) family. The sensor protein in inflammasomes includes NLRP1, NLRP2, NLRP3, NLRP6, NLRP12, IPAF (also called 'NLRC4'), AIM2 and IFI16 [4], of which the NLR families are the ones most mentioned. The inflammasomes can be activated by a series of exogenous and endogenous stimuli. The stimuli include pathogen-associated molecular patterns, such as bacterial toxins and viral nucleic acids [5], and danger-associated molecular patterns (DAMPs) released from or caused by damaged cells, such as reactive oxygen species (ROS), adenosine triphosphate (ATP), hypotonic stress, uric acid crystals, noxious exogenous factors and so forth [6].

Globally, the NLRP3 inflammasome is the best characterized; it is a multiprotein complex (>700 kDa) in the cytoplasm. It consists of specific members of the NOD-like receptor protein (NLRP) subfamily, an adaptor protein of apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1 [7]. In detail, the receptor protein (NLRP) contains a NACHT structure in the central region (which is also called 'the NOD domain'), a C-terminal leucine-rich repeat (LRR) domain and a caspase recruitment domain (CARD) or PYD in the N terminus. The ASC protein is a compound of PYD and CARD, which could interact with N-terminal PYD in NLRP3 and subsequently activate procaspase-1 [8]. The NLRP3 inflammasome is activated by germline-encoded PPRs by recognizing the antigens of pathogen-associated molecular patterns or DAMPs, and its activation leads to the secretion of IL-1β, IL-18 and a novel form of programmed cell death, pyroptosis [9]. There are two signaling pathways associated with the activation of the NLRP3 inflammasome. The first one is derived from Toll-like receptors (TLRs), tumor necrosis factor receptor or IL-1R on the cell membrane, and activation of these PPRs results in increased transcription and translation of pro-IL-1β and pro-IL-18 through nuclear factor-κB [10]. To date, a variety of families of PRRs have been found in the kidney. The crosstalk between the NLRP3 inflammasome and PRRs in the kidney has drawn a great deal of attention from researchers. For example, TLR2 upregulated the expression of pro-IL-1β and inflammasome components, inducing NLRP3 activation and subsequent renal tubular epithelial cell necrosis [11]. Potassium efflux through the P2X7R channel, ROS and phagocytosis, namely, second signals, are supposedly three models of the activation of the NLRP3 inflammasome [12]. However, the detailed mechanism is still unclear. Through these two kinds of signals, the NLRP3 receptor proteins interact with ASC by PYD-PYD interactions, and ASC subsequently activates procaspase-1 by binding to its CARD. Then, the activated caspase-1 performs enzymatic cleavage on the promature cytokines to produce the mature IL-1β and IL-18, which will later be secreted as inflammatory cytokines [12]. Additionally, accumulating evidence revealed that NLRP3 in the kidney exerts its effect not only by this 'canonical' pathway mentioned above but also by 'noncanonical' pathways, such as through tumor growth factor-β signaling, epithelial-mesenchymal transition and fibrosis [9], which will be mentioned in detail below.

The inflammasome is regulated at both the transcriptional and posttranscriptional levels. Overwhelming NLRP3 activation induces inflammatory renal damage, yet the regulation of this process remains unclear. One of the ASC isoforms colocalized with caspase-1 but not with NLRP3, showing an inhibitory effect against NLRP3 [13]. Yang et al. [14] found that the orphan nuclear receptor small heterodimer partner (SHP) negatively regulated the NLRP3 inflammasome by competitively binding ASC with NLRP3. SHP deficiency in mouse models of kidney tubular necrosis and peritoneal gout has led to mitochondrial dysfunction and proinflammatory cytokine secretion. Moreover, the pyrin-only proteins, pyrin-containing NOD proteins, CARD-only protein, inhibitory CARD and ICEBERG also inhibit the formation of an active inflammasome [15, 16].

The expression of inflammasome components inside the kidney is not fully understood. Lech et al. [17] detected the mRNA expression profiles of NLR genes in human and mouse solid organs, which suggests that the expression of inflammatory-related genes in the kidney is much lower than that in the spleen, except for NLRP2 and NLRP10. However, mice express higher levels of NLR genes compared with levels in the spleen, except for NLRP3. Lichtnekert et al. [18] showed that in antiglomerular basement membrane nephritis mice, a lack of IL-1R partially protected against segmental lesions and crescent

formation as well as against tubular atrophy, while IL-18 deficiency was only able to reduce partial tubular atrophy. They further found that ASC, NLRP3 and caspase-1 deficiency did not affect glomerular pathology in the antiglomerular basement membrane disease model. Isolated glomeruli were unable to secrete mature IL-1β, but bone marrow dendritic cells could. Kidney immune cells, but not intrinsic glomerular cells, are capable of either secreting active IL-1β or activating caspase-1. Similar results were verified in samples of patients with different progressive glomerulopathies. NLRP3, ASC, caspase-1 and IL-18, but not IL-1β, were expressed by tubular epithelial cells [18, 19]. They believed that the infiltrating immune cells rather than glomeruli local cells might induce inflammatory signaling. However, a study by Niemir et al. [20] revealed that podocytes are the major source of glomerular IL-1β production. Zhang et al. [21] further showed that murine podocytes expressed NLRP3, ASC and caspase-1, and in mice with hyperhomocysteinemia, IL-1β increased in the glomeruli. Given that podocytes act like dendritic cells and infiltrating macrophages [22], their ability to participate in inflammation is convincing. Whether these controversial results are the result of different stimuli remains unknown. However, more data and research are needed to verify the expression of inflammation in the kidney. Knockout of targeted inflammatory genes in specific cells might help to resolve this issue.

Inflammasome and Chronic Kidney Disease

In tissue from human renal biopsies, increased expression of NLRP3 mRNA was detected in nondiabetic kidney diseases and associated with renal function, indicating that NLRP3 could be involved in chronic kidney disease (CKD) pathogenesis [23]. IL-18 and caspase-1 are expressed in human renal tubular epithelium, which were elevated with CKD [24, 25]. Bone marrow chimeras revealed that NLRP3 mediated the inflammatory processes in both hematopoietic and nonhematopoietic cellular compartments. However, it is likely that the NLRP3 expressed in kidney resident cells, instead of that expressed in bone marrow-derived cells, plays a more critical role in diabetic nephropathy [26].

The unilateral ureteral obstruction (UUO) model is a conventional CKD animal model. Renin-angiotensin system blockade inhibited NLRP3 inflammasome activation and then increased water channel AQP2 expression in the UUO mouse model [27]. Vilaysane et al. [23] observed less tubular injury, inflammation and fibrosis in association with a reduction in caspase-1 activation, as well as maturation of IL-1β and IL-18 in NLRP3 kidney-specific knockout mice 2 weeks after UUO operation. However, the mechanism of NLRP3-induced injury in the UUO model remains confusing. Pulskens et al. [28] reported that NLRP3 prevented early renal interstitial edema and preserved vascular integrity through the noncanonical effect, with little impact on renal fibrosis and inflammation. Wang et al. [29] identified that NLRP3 was required for tumor growth factor-β signaling and Smad activation, which led to epithelial-mesenchymal transition and fibrosis. Furthermore, the process was independent of the inflammasome. Therefore, the effect of NLRP3 on kidney injury remains controversial and should be evaluated comprehensively.

Proteinuria has been recognized as a critical prognostic factor for CKD. Previous studies have shown the toxicity of ultrafiltered proteins to the renal proximal tubule cells, which activated the expression of abundant chemokines, adhesion molecules and proinflammatory cytokines [30]. Therefore, it is reasonable to speculate that inflammatory activation is involved in the pathogenesis of CKD. Fang et al. [31] reported that inflammasome activation, including caspase-1, IL-1β and IL-18, in the kidneys of patients with proteinuria was associated with the severity of albuminuria on human renal biopsies regardless of the pathology type (IgA nephropathy, focal segmental glomerulosclerosis, minimal change disease, or membranous nephropathy). They further investigated the mechanism and found that the endocytosis of ultrafiltered albumin in tubules might induce endoplasmic reticulum stress, which plays an important role in NLRP3 inflammasome activation. Meanwhile, our study showed that the NLRP3 inflammasome/caspase-1/mitochondria axis mediated the mouse proximal tubular cell defect [32], which might be the mechanism of the mouse proximal tubular cell tight junction injury by albumin [33]. In albumin-overloaded mice, we observed severe tubular structure damage, cell apoptosis and epithelial cell phenotype transition, as well as mitochondrial dysfunction. Meanwhile, the inflammatory cascade was activated. By applying a mitochondrial SOD2 mimic, MnTBAP, the damaged condition was improved. Furthermore, genetic disruption of NLRP3 could attenuate albumin-induced renal tubular cell injury. Although the crosstalk of mitochondria and the endoplasmic reticulum stress signaling pathway has been widely investigated [34–36], it remains unclear whether this crosstalk affects inflammatory activation. Other than tubules, podocytes could also be dam-

aged by inflammasome activation in albuminuria. The endocytosis of albumin into human podocytes from urine samples upregulated IL-1β and tumor necrosis factor RNA expression [37]. Studies have found that thioredoxin-interacting protein (TXNIP) signaling activated NLRP3 and subsequently triggered podocyte injury [38, 39]. Moreover, Chang et al. [3] mentioned the possible involvement of inflammasomes in the transformation from minimal change disease to focal segmental glomerulosclerosis, which needs further investigation.

Additionally, many DAMPs released during kidney injury can trigger NLRP3, such as ROS, uric acid, extracellular ATP and extracellular matrix components such as biglycan [40]. Oxidative stress has been reported to be associated with NLRP3 inflammasome activation. Abais et al. [39] demonstrated that TXNIP, the endogenous inhibitor of the antioxidant thioredoxin and ROS sensor, binding to NLRP3 is the key signaling mechanism for the activation of inflammasomes by NADPH oxidase-derived ROS in hyperhomocysteinemia. Mitochondrial ROS activated the NLRP3 inflammasome, triggering sterile inflammation in the kidneys [26, 41]. Meanwhile, ATP produced by mitochondria released from damaged cells triggered the NLRP3 inflammasome [42]. Uremic toxicity has also been one of the killers of CKD. Soluble uric acid acts like a DAMP and stimulates the NLRP3 inflammasome through mitochondrial ROS generation in macrophages. Meanwhile, uric acid promotes chemokine secretion by tubular cells, which further results in macrophage recruitment [43]. The NLRP3 inflammasome also contributes to the development and maintenance of endothelial dysfunction in response to uremic toxicity [44]. Furthermore, the downstream molecules of NLRP3 inflammasome activation, IL-1 and IL-18, are blamed for CKD-related complications, such as vascular injury [45–47] and sepsis [48, 49].

Inflammasome and Acute Kidney Injury

Noninfectious inflammation is the nightmare that haunts kidney diseases. Acute kidney injury (AKI) is exacerbated by proinflammatory cytokines and leukocytes, whereas regulatory cells and immunomodulatory cytokines attenuate injury [50]. Both human and animal models of AKI have shown an increase in IL-1β and/or IL-18. Cisplatin treatment and ischemic/reperfusion mouse models are the two main animal models of AKI. Data from these two models indicate that inflammasomes contribute to AKI [51]. However, recent studies on these two models have revealed some confusing but intriguing results. Lee and colleagues [52] demonstrated that caspase-1 is a mediator of both cisplatin-induced AKI and ischemic AKI. However, in cisplatin-induced AKI, the activation of caspase-1, IL-1β and IL-1α was independent of the NLRP3 inflammasome, indicating that NLRP3 might only have a small impact on cisplatin-induced AKI. Instead, the NLRP1 protein was increased in cisplatin-induced AKI, probably upstream of caspase-1 activation. A further study has shown that the caspase-1 inhibitor protected proximal tubular cells from cisplatin-induced injury, while another study found that the renal function of AKI was exacerbated because of the prevention of autophagy via caspase inhibition [53], suggesting that there are two sides to the coin. However, research data on the ischemic/reperfusion AKI model remain inconsistent. The protective role of NLRP3 deficiency in AKI was confirmed, but neither the ASC deficiency nor the IL-1/IL-18 blockade had a defined effect [42, 54], which suggests the noncanonical effect of NLRP3. Actually, NLRP3 may additionally exert inflammasome-independent effects following tissue injury, revealing a novel noncanonical effect of NLRP3 in preserving renal integrity and protection against early tubular injury and interstitial edema following progressive renal injury [28]. In a study from Shigeoka et al. [54], decreased apoptosis was observed. It has been shown that the inhibitors of apoptosis proteins can influence NLRP3 activation positively or negatively, and there are some striking similarities between inflammasomes and apoptosomes [55–57]. Meanwhile, a recent study indicated that endoplasmic reticulum stress was involved in angiotensin-II-induced NLRP3 inflammasome activation [58]. Angiotensin II increased the expression of NLRP3, ASC, caspase-1, IL-β and IL-18, which could be inhibited by pretreatment with the endoplasmic reticulum stress inhibitor 4-PBA. Furthermore, the mechanism of uric acid crystal-induced AKI is now believed to be more than just a urinary tract obstruction. Monosodium uric, the culprit of uric nephropathy, is phagocytized and subsequently induces lysosomal rupture, impairing mitochondrial function. The damaged mitochondria generate ROS and affect NLRP3 activation [59]. Akira and colleagues [60] have recently proposed a model of mitochondrial dysfunction-induced NLRP3 activation. The concentration of NAD^+ decreases because of aberrant mitochondria homeostasis, which inactivates SIRT2 and results in the accumulation of acetylated α-tubulin. Acetylated α-tubulin mediated the dynein-dependent transport of mitochondria. ASC on mitochondria interacts with the NLRP3 on the endoplasmic reticu-

lum and activates the inflammasome. Autophagy sequesters and isolates the damaged lysosomes, protecting proximal tubular cells against inflammation [61]. Therefore, the crosstalk between inflammasomes and other signaling pathways is worthy of further research.

Additionally, both in vivo and in vitro studies have shown that the NLRP3 inflammasome could translate the stimuli of crystals or particles into innate immune activation via the secretion of proinflammatory cytokines, such as IL-1β and IL-18. This finding brings up the novel mechanism of crystalline nephropathies and kidney stone disease [62]. Activation of the inflammasome complex is required for the generation of renal IL-17A, an important proinflammatory cytokine in AKI [63]. The underlying mechanism recognized will give support to the therapeutic inhibition of IL-17A in AKI.

Treatment

Sterile inflammation is undoubtedly an important component of kidney diseases. Therapies targeting the activation of the NLRP3 inflammasome or blocking its downstream effectors appear attractive for the pursuit of neuropathy treatments. Although the related drug research is still limited in this area, research on other diseases is inspiring. Mutations in the gene encoding NLRP3 have been recognized to be associated with various autoinflammatory syndromes, including familial cold autoinflammatory syndrome, the Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease, which also belongs to cryopyrin-associated periodic syndrome [64]; nephropathy was also involved [65, 66]. Excessive production of IL-1 by monocytes/macrophages triggered by the NLRP3 inflammasome is the central pathophysiology of cryopyrin-associated periodic syndrome. The IL-1 receptor antagonist anakinra (the fusion protein of the IL-1 receptor), IgG Fc rilonacept and canakinumab (a human anti-IL-1 monoclonal antibody) have been used as agents for treatment. Drugs inhibiting IL-1, $P2X_7R$ and caspase-1 have also been studied. Phase 1 and 2 studies of a $P2X_7R$ antagonist have shown the agent's safety, but the clinical efficacy has not been determined [67, 68]. There is also limited evidence about the efficacy of caspase-1 inhibitors. Although there are few data regarding the inflammasome mutation in renal diseases, interventions targeting the NLRP3 inflammasome/IL-1β/IL-18 axis are still the most promising candidates for alleviating renal inflammation.

Perspective and Conclusions

To date, the research on inflammasomes in kidney diseases is still very limited. Further studies might focus on the pathophysiological changes in cell-specific knockout animal models for inflammasome-related proteins. The signaling pathways of inflammasomes should be further explored. Furthermore, the noncanonical effects of NLRP3 are interesting. In clinical research, examining inflammasomes obtained from serum and tissues might facilitate the finding of promising biomarkers for diseases. Drugs that are inflammasome-related antagonists, such as IL-1, caspase-1 and $P2X_7R$ inhibitors, have been developed, but their application still has a long way to go. Therapeutic agents targeting the NLRP3 inflammasome are still lacking and should be further examined.

In conclusion, inflammasomes triggered by infectious or sterile injuries transferred proinflammatory mediators into mature ones through innate danger-signaling platforms. The NLRP3 inflammasome plays a critical but also unexplored role in the pathophysiology of kidney diseases and is likely to be a therapeutic target in the future.

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Disclosure Statement

All the authors declare no competing interests, including relevant financial interests, activities, relationships and affiliations.

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