Metabolic Dysfunction in the Regulation of the NLRP3 Inflammasome Activation: A Potential Target for Diabetic Nephropathy

Wenli Zhao, Le Zhou, Petr Novák, Xian Shi, Chuang Biao Lin, Xiao Zhu, and Kai Yin

1Department of Cardiology, The Second Affiliated Hospital of Guilin Medical University, Guilin, Guangxi, China
2Guangxi Key Laboratory of Diabetic Systems Medicine, Guilin Medical University, Guilin, Guangxi, China
3Guangxi Health Commission Key Laboratory of Glucose and Lipid Metabolism Disorders, The Second Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541199, China

Correspondence should be addressed to Chuang Biao Lin; 234364610@qq.com, Xiao Zhu; 1365681080@qq.com, and Kai Yin; kaiyinby@qq.com

Received 22 November 2021; Revised 31 March 2022; Accepted 27 May 2022; Published 9 June 2022

Academic Editor: Eusebio Chiefari

Copyright © 2022 Wenli Zhao et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Metabolic dysfunction plays a key role in the development of diabetic nephropathy (DN). However, the exact effects and mechanisms are still unclear. The pyrin domain-containing protein 3 (NLRP3) inflammasome, a member of the nod-like receptor family, is considered a crucial inflammatory regulator and plays important roles in the progress of DN. A growing body of evidence suggests that high glucose, high fat, or other metabolite disorders can abnormally activate the NLRP3 inflammasome. Thus, in this review, we discuss the potential function of abnormal metabolites such as saturated fatty acids (SFAs), cholesterol crystals, uric acid (UA), and homocysteine in the NLRP3 inflammasome activation and explain the potential function of metabolic dysfunction regulation of NLRP3 activation in the progress of DN via regulation of inflammatory response and renal interstitial fibrosis (RIF). In addition, the potential mechanisms of metabolism-related drugs, such as metformin and sodium glucose cotransporter (SGLT2) inhibitors, which have served as the suppressors of the NLRP3 inflammasomes, in DN, are also discussed. A better understanding of NLRP3 inflammasome activation in abnormal metabolic microenvironment may provide new insights for the prevention and treatment of DN.

1. Introduction

According to the statistics of the International Diabetes Federation (IDF) in 2019, the number of diabetes patients between the ages of 20 and 79 was expected to reach 578 million in 2030 [1]. One of the most serious consequences of diabetes is the development of diabetic vascular disease, which manifests clinically as microvascular and macrovascular complications [2]. Diabetic nephropathy (DN) is now one of the most serious microvascular complications of diabetes and is always accompanied by hyperglycemia, lipid metabolism disorder, oxidative stress, elevated advanced glycosylation end products (AGEs), etc. [3]. Although several available therapeutic interventions can delay the onset and progression of DN, the associated morbidity of this disease remains high due to its complex pathogenesis, suggesting that the novel therapeutic approaches are still needed to be explored.

Inflammasomes are a group of cytosolic protein complexes, which are formed to mediate host immune responses to cellular damage and microbial infection [4]. The pyrin domain-containing protein 3 (NLRP3) inflammasome is a classical inflammasome composed of NLRP3, adapter protein apoptosis-related speck-like protein (ASC), and the zymogen procaspase-1 [5]. Recent research has shown that the NLRP3 inflammasome plays an important role in various metabolic inflammatory diseases, such as atherosclerosis (As) and diabetes [6, 7]. NLRP3 monomers are assembled...
into cages and sense abnormal signals in the resting state [8]. The activation of the NLRP3 inflammasome, especially when stimulated by abnormal metabolites of glucose and lipids, can aggravate the maturation and secretion of proinflammatory cytokines (i.e., IL-1β and IL-18) and further trigger inflammatory cascades [9]. Furthermore, the activation of the NLRP3 inflammasome has been implicated in various pathological conditions, ranging from metabolic syndrome to kidney diseases [10]. Interestingly, preventing various pathological conditions, ranging from metabolic disorders, such as hyperglycemia and elevated triglycerides [3]. Diabetes is characterized by clustered metabolic abnormalities, such as hyperglycemia and elevated triglycerides [3]. In a diabetic kidney, specific metabolically induced glucose-dependent pathways are triggered, which induces oxidative stress, hexosamine flux, polyol pathway flux, and accumulation of AGEs [3]. Importantly, binding of AGEs to their receptor (RAGE) promotes the production of cytosolic ROS and stimulates intracellular signal molecules such as nuclear factor-κB (NF-κB) and protein kinase C (PKC), inducing the activation of transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF). Importantly, the metabolite abnormalities in DN can trigger the activation of the NLRP3 inflammasome. There is a dynamic mutual regulatory relationship between metabolism and inflammation, called the metabolic-inflammatory circuit [9]. Chronic inflammatory response increases the risk of insulin resistance in type 2 diabetes mellitus (T2DM). The association between the NLRP3 inflammasome and T2DM is increasingly accepted [12]. As such, we further explore how metabolite abnormalities regulate the NLRP3 inflammasome in kidney-related cells (Table 1 and Figure 1).

2.2. Fatty Acids. Fatty acids (FAs) are one of the most abundant lipids in plasma, including saturated fatty acids (SFAs) (e.g., palmitic acid), monounsaturated fatty acids (MUFA) (e.g., oleic acid), and polyunsaturated fatty acids (PUFAs) (e.g., omega-3 FAs and omega-6 FAs). SFAs levels in plasma of patients with T2D on a high-fat diet were elevated [24]. SFAs, especially their crystals (e.g., palmitate), is known to directly influence inflammatory processes [25]. Specifically, palmitate can activate the NLRP3 inflammasome through lysosomal destabilization in macrophages [26]. Additionally, palmitate inhibits adenosine 5′-monophosphate-activated protein kinase (AMPK) phosphorylation and blocks autophagy, leading to increased levels of ROS in macrophages, which in turn activates the NLRP3 inflammasome and IL-1β secretion during T2D [27]. MUFA can inhibit the NF-κB and NLRP3 activation through direct binding to GPR120 (G protein-coupled receptor 120) or PPARs (peroxisome proliferator-activated receptors) and through AMPK phosphorylation [28]. SFA-induced NLRP3 activation can obviously be inhibited in the presence of MUFA [29], indicating that the balance of SFAs and MUFA is a critical point for NLRP3 inflammasome activation. Interestingly, it is controversial whether regular PUFAs intake can be used as a pharmacological replacement therapy for diabetes. A double-blind randomized clinical trial showed that n-3 PUFAs improve glycemic control in Asians [30]. However, increasing PUFAs had little to no effect on the prevention and treatment of T2D, based on studies of randomized participants from around the world [31]. It is recommended that the protective effect of n-3 PUFAs on T2D may be influenced by ethnicity.

2.3. Cholesterol. Cholesterol is a multifunctional lipid that can be ingested from the diet or synthesized by the endoplasmic reticulum (ER). In patients with poorly controlled and/or insulin-resistant diabetes, both cholesterol production and cholesterol genesis are increased [32]. The
accumulation of cholesterol can form crystals in lysosomes and further disrupt the lysosomal membrane and lysosomal stabilization after entering the cell [33]. Importantly, this destabilization can aggravate the release of histone B into the cytoplasm, which activates the NLRP3 inflammasome and causes the secretion of mature IL-1β [34]. Moreover, the redundant cholesterol in lysosomes can be transported to the ER and further stimulate the NLRP3 inflammasome [35]. In addition, Guo et al. showed that sterol regulatory element-binding protein 2 (SREBP2) cleavage-activating protein- (SCAP-) SREBP2 promotes NLRP3 inflammasome activation, which is largely dependent on cholesterol ER to Golgi translocation [36], indicating that interorganelle cholesterol mobility is essential for the activation of the NLRP3 inflammasome. However, it still needs to be explored why and how cholesterol, as an important regulator of the membrane integrity and fluidity, stimulates the NLRP3 inflammasome in different organelles.

ROC: reactive oxygen species; TXNIP: thioredoxin-interacting protein; FOXO1: forkhead box protein O1; NF-κB: nuclear factor kappa B; PKM2: pyruvate kinase M2; AMPK: adenosine 5′-monophosphate-activated protein kinase; ER: endoplasmic reticulum; SREBP2: sterol regulatory element-binding protein 2; HMGB1: high mobility group box-1 protein; HIF1α: hypoxia inducible factor-1α; PDK1: 3-phosphoinositide-dependent kinase-1.

**Table 1:** Aberrant metabolites activate the NLRP3 inflammasome in kidney-associated cells.

| Stimulus           | Kidney-related cells                      | Mechanism                                                                 | Ref.  |
|--------------------|-------------------------------------------|---------------------------------------------------------------------------|-------|
| Glucose ↑         | Monocytes                                 | K⁺ outflow, Ca²⁺ inward flow/ROS/NLRP3 inflammasome                       | [14, 15] |
|                    | Glomerular mesangial cells                | ROS/p38/FOXO1/TXNIP/NLRP3                                                 | [17–19]| |
|                    | Macrophages                               | P50(NF-κB)/NLRP3 inflammasome                                             | [20]  |
| Saturated fatty acids ↑ | Macrophages                           | Lysosomal destabilization/NLRP3 inflammasome                              | [26]  |
| Cholesterol ↑     | Macrophages                               | Lysosomal destabilization/histone B/NLRP3 inflammasome/IL-1β               | [34]  |
|                    | Macrophages                               | ER to Golgi translocation/SREBP2/NLRP3 inflammasome                       | [35, 36] |
| Uric acid ↑       | Macrophages                               | ROS/NLRP3/IL-1β/NF-κB                                                     | [40]  |
| Homocysteine ↑    | Vascular endothelial cells               | HMGB1/cathepsin V/NLRP3/caspase-1                                         | [47]  |

**Figure 1:** Specific mechanisms of NLRP3 inflammasome activation by abnormal accumulation of metabolites.
2.4. Uric Acid. Uric acid (UA) is a purine metabolite that is produced in high quantities upon cellular injury [37]. Its level is affected by the amount of its production and reabsorption by the kidneys and intestines. Both clinical and epidemiological studies have confirmed that UA plays a vital role in the occurrence and development of insulin resistance, lipid metabolism disorders, and metabolic syndrome [38]. Cohort studies have shown that increased levels of UA are associated with the increased risk of diabetes and DN [39]. Mitochondrial ROS activated by high levels of UA mediates NLRP3 activation and IL-1β secretion and activates NF-κB in cocultured macrophages and proximal renal tubular cells [40]. Notably, when UA exceeds the threshold, it precipitates out of diuretics and forms crystals [41]. The elevated UA crystals can activate the NLRP3 inflammasome to trigger IL-1β-mediated inflammation by directly binding to the lipids on the surface of macrophages [42]. Interestingly, an earlier study also demonstrated that UA crystals induced the dissociation of TXNIP from thioredoxin (TRX) in the presence of ROS, allowing it to bind to NLRP3 and enhance caspase activation [43]. Furthermore, the synergistic effect between FFAs and urate crystals leads to activating the NLRP3 inflammasome [44], suggesting that different metabolites associated with diabetes interact with each other to promote the development of inflammation. With further development of metabolomic technologies, a deeper understanding of the currently known metabolite interaction pathways and possible mechanisms can be gained.

2.5. Homocysteine. Homocysteine (HCY), a sulfur-containing amino acid, is derived from protein catabolism. Elevated levels of plasma HCY (to more than 15 μM, defined as hyperhomocysteinemia (HHCY)) are an independent risk factor in diabetes [45]. Recent findings demonstrated that the increased HCY in the blood can promote NLRP3 inflammasome formation by different mechanisms [46]. For example, HCY is involved in NLRP3 inflammasome and caspase-1 activation and increased vascular endothelial inflammation by raising high mobility group box-1 protein (HMGB1), lysosomal permeability, and lysosomal cysteine protease tissue-necrosis factor V [47]. Additionally, in vascular smooth muscle cells (VSMCs), HCY stimulates NLRP3 inflammasomes through regulating extracellular regulated protein kinases1/2 (ERK1/2) and p38 MAPK pathways [48]. Furthermore, elevated levels of HCY have been found to activate the guanine nucleotide exchange factor Vav2 [49]. Other studies show that Vav2-mediated Rac1 GTPase activity can trigger NLRP3 inflammasome activation by leading to oxidative stress via increasing nicotinamide adenine dinucleotide (NADPH) oxidase activity [50, 51]. It is suggested that the role of HCY in NLRP3 activation partly relies on the Vav2-mediated pathway. Meanwhile, HHCY can increase oxidative stress and its downstream signaling pathway, so whether HHCY activates NLRP3 through oxidative stress activation pathway is worth exploring. HCY has also been shown to increase the hypoxia inducible factor-1α (HIF1α) protein levels [52]. Moreover, HIF-1α upregulates pla2g16 (a novel HIF-1α target gene) gene expression to activate the NLRP3 inflammasome pathway [53]. It is suggested that HCY may activate the NLRP3 inflammasome through hypoxia-related pathways. Besides, HCY induces inflammation in adipocytes in a manner that affects lipid status and causes NLRP3 activation [54], so it is worth exploring whether NLRP3 can be activated in other tissues and cells in a similar manner.

3. The Role of the Abnormal Metabolite-Induced NLRP3 Inflammasome Activation in DN

NLRP3 inflammasome-mediated inflammation is recently recognized in the development of kidney injury [56]. DN undergoes a transition from renal inflammation to fibrosis [57]. Renal NLRP3 overexpression is associated with macrophage infiltration and fibrosis [58]. When the microenvironment is altered, the kidney is in an acute kidney injury (AKI) state, and as the first defender, immune cells maintain cellular homeostasis. In a mild AKI, a renal tubular injury is fully recovered. Notably, a severe AKI becomes chronic with high levels of NLRP3 in serum or urine. This induces a glomerular injury affecting glomerular endothelial cells, thylakoid cells, and podocytes [20, 59, 60]. When the disease progresses further, dominant NLRP3 is predominantly distributed in abnormal renal tubules surrounded by inflammatory infiltration and fibrosis, and tubular epithelial cells are atrophied and dispersed, indicating maladaptive repair [58].

3.1. NLRP3-Mediated Inflammation in DN

3.1.1. Immune Cells. Renal inflammation includes the release of cytokines and chemokines and infiltration of immune cells, and upregulation of inflammatory signaling pathways is involved in the development and progression of DN [61]. Evidence from clinical laboratory studies suggests that infiltration of immune cells (mainly macrophages) is commonly observed in the glomeruli and interstition of renal biopsy specimens at all stages of DN [62]. Overexpression of NLRP3 leading to elevated proinflammatory cytokines IL-1β and IL-18, followed by inflammatory cell infiltration in the glomerulus, was discovered in a study of diabetic nephropathy rats regarding hyperuricemia and dyslipidemia [56]. However, the results of a bone marrow transplantation study suggest that NLRP3 among renal nonhematopoietic cells plays a more important role than natural immune cells in mediating the inflammatory process of DN [63].

3.1.2. Renal Resident Cells. The inflammasome activation is detected in podocytes and endothelial cells during the early stages of nephropathy in db/db mice [11]. In the kidneys of STZ-induced diabetic mice, hyperglycemia induces TXNIP expression, activates Nox to produce ROS, and subsequently triggers the inflammasome activation in podocytes leading to podocyte loss and albuminuria [64]. The inhibition of NLRP3 and ASC by shRNA inhibits the high glucose-induced activation of IL-1β expression and attenuates the podocyte injury [65]. As the disease progresses, the
renal tubular injury becomes one of the key determinants of DN. The role of the NLRP3 inflammasome in the tubular injury has been confirmed in different studies. For example, in proximal renal tubular cells, the activation of the NLRP3 inflammasome by high glucose was also inhibited by the inhibition of the tyrosine protein kinase SYK, suggesting a role for SYK-JNK-NLRP3 signaling in the pathogenesis of DN [66]. Expression of optineurin (an autophagic receptor for damaged mitochondria during mitochondrial phagocytosis) during the process of mitophagy was reduced in tubular epithelial cells from patients with DN compared with those from nondiabetic healthy individuals and was negatively correlated with renal interstitial inflammation [67]. In mouse renal tubular epithelial cells, optineurin overexpression enhanced mitophagy and inhibited high glucose-induced NLRP3 expression, CASP1 cleavage, and IL-1β and IL-18 release [67]. Furthermore, ischemia, toxins, and albuminuria can cause tubulointerstitial inflammation, which can cause an extracellular matrix injury and further exacerbate tubulointerstitial inflammation [68]. A cycle between the extracellular matrix injury and inflammation can be formed, and regulating its balance may be essential for inhibiting the progression of renal fibrosis. Resident fibroblasts also display a more proinflammatory phenotype and actively drive the inflammatory response during renal injury [69].

3.2. NLRP3-Mediated Renal Fibrosis in DN. In essence, renal fibrosis is an integral pathological development in DN [70]. The main mechanisms involved in fibrosis are massive inflammatory cell infiltration [71], epithelial-mesenchymal transition (EMT) [72], endothelial-mesenchymal transition (EndoMT) [71], the activation of interstitial myofibroblasts [73], and the resulting accumulation of extracellular matrix components, which eventually replace the normal renal structure and form scarring, resulting in the loss of renal function (Figure 2).

3.3. Immune Cells. Immune cells have received much attention for their pathogenic role in renal fibrosis. The activation of IL-36 signaling in macrophages and dendritic cells positively regulates IL-1β secretion in a MyD88-dependent manner through NLRP3 inflammasome initiation signaling and promotes the development of kidney inflammation and fibrosis in mice [74]. Other evidence suggests that the inhibition of the NF-κB-ROS-NLRP3 signaling pathway in the macrophage activation attenuates IgA progressive nephropathy and blocks glomerulosclerosis [75]. Moreover, the NLRP3 inflammasome activation in macrophages can promote chemokine signal transduction in the proximal tubule through intercellular crosstalk and eventually contribute to macrophage infiltration and tubulointerstitial fibrosis in the diabetic kidney [40].

3.4. Renal Resident Cells. A study showed the activation of the TLR4-NF-κB-NLRP3 signaling pathway causing EMT and further transition to a fibrotic state [76]. Similarly, the role of the NLRP3 inflammasome in the tubular injury was demonstrated by the attenuation of high-glucose-induced EMT and inhibition of the phosphorylation of SMAD3, MAPK p38, ERK1, and ERK2 (key signaling molecules with roles in proinflammatory and profibrotic responses in tubular cells) in NLRP3-silenced HK-2 cells [77]. NLRP3 inflammasomes, an essential element of the innate immune response, are present in the progression of endothelial dysfunction associated with chronic kidney disease (CKD). Specifically, it was shown that the TLR4-NF-κB-ROS-NLRP3 pathway contributes to inflammation-mediated endothelial dysfunction in CKD [78]. Since NLRP3 is involved in renal lesions, its involvement in the renal EndoMT process can be postulated. A study established the SIRT3-Foxo3a-Parkin pathway as a key factor in maintaining endothelial homeostasis and pointed to an important role of EndoMT in the vascular pathology of renal fibrosis [79]. Moreover, it was shown that the activation of the NLRP3 inflammasome in atherosclerosis via the SIRT3-SOD2-mtROS signaling pathway promotes inflammation in HUVECs [80]. Therefore, it deserves further investigation whether the NLRP3 activation induces renal EndoMT through SIRT3-related pathways. The aberrant activation and proliferation of fibroblasts are thought to be a key cause of renal fibrosis. Evidence exists that the inhibition of PERK-Akt-mTOR-NLRP3 signaling inhibits the renal fibroblast activation and fibroblast proliferation [81]. In addition to this, NF-κB translocation and ROS production in renal thylakoid cells exposed to angiotensin II activate NLRP3 inflammasomes, which can lead to glomerular fibrosis [82]. Several studies have emphasized the importance of immunocyte activation, but it should be kept in mind that no single type of cells can initiate and sustain the overall renal fibrosis in isolation. Renal fibrogenesis explicitly necessitates the participation and interaction of many types of infiltrating cells, as well as resident kidney cells.

Moreover, NLRP3 has inflammasome-independent (noncanonical) effects leading to renal fibrosis in DN [83]. Inflammasome-independent NLRP3 in renal tubular cells plays an important role in the mitochondrial ROS injury by binding to mitochondrial antiviral signaling proteins after the hypoxic injury. In the absence of NLRP3, this mitochondrial regulation increases autophagy and attenuates renal tubular interstitial fibrosis [84]. Furthermore, NLRP3 promotes renal tubular EMT by enhancing TGF-β1 signaling and the R-Smad activation. The effect of NLRP3 on TGF-β1 signaling is independent of inflammasome components [83]. These data identify a novel inflammasome-independent and direct profibrotic role for NLRP3 in the renal tubular epithelium. Moreover, renal fibroblast inflammasome-independent NLRP3 also promotes fibrosis by enhancing TGF-β and Smad signaling without IL-1β production [74]. Thus, in the context of direct injury to renal tubular epithelial cells and fibroblasts, inflammasome-independent NLRP3 plays a key role in renal disease by regulating apoptosis, fibrosis, and the mitochondrial injury. This unique role of NLRP3 in the kidney can be clarified by conditional, cell type-specific regulation of the NLRP3 gene [85]. Activation of these signaling pathways leads to infiltration of circulating inflammatory cells, which amplifies and maintains the inflammatory process in the kidney and
ultimately mediates or contributes to the diabetic renal fibrosis cascade response [86]. In addition to the proinflammatory cascade with NLRP3, the kinin-releasing enzyme-kinin system and protease-activated receptor signaling and the complement system (C5a and C3a) also play a role in fibrosis in diabetic kidney injury [61]. There are still a lot of underlying mechanisms waited to be further explored.

4. Metabolic Drugs Reverse the NLRP3 Inflammasome Activation in the Treatment of DN

Downregulation of inflammatory responses by therapeutic strategies can effectively prevent kidney disease development and improve renal function in patients with diabetes [87]. A growing body of evidence demonstrates that drugs reversing NLRP3 inflammasome activity have therapeutic potential for the treatment of DN, as discussed below (Table 2).

4.1. Metformin. Metformin is currently a first-line antidiabetic agent that reduces glucose through several different pathways: (i) inhibition of hepatic gluconeogenesis, (ii) improved insulin signaling through AMPK activation, (iii) enhanced peripheral insulin sensitivity due to increased glucose consumption, and (iv) induction of glucose transporter protein type 4 (GLUT-4) localization [88]. It has recently been suggested that some glucose lowering may be mediated through the enteroendocrine axis [89, 90]. Recently, there are some data showing that metformin exerts anti-inflammatory effects [91]. For example, upregulated NLRP3 inflammasome activation was found in macrophages collected from T2D patients and was downregulated after treatment with metformin [92]. A clinical randomized placebo-controlled study by Bhansali et al. underscores that in patients with T2D, metformin upregulated mitochondrial autophagy and subsequently improved alterations in mitochondrial morphology and function, independent of a hypoglycemic effect [93]. Then, further research is needed into whether metformin inhibits NLRP3 activation through mitochondrial autophagy. Furthermore, in APOE-/- male mice, metformin can reverse the decreased expression of thioredoxin-1, a stimulator of the NLRP3 inflammasome, which is induced by high glucose [94]. These studies hypothesized that metformin can partly treat diabetic kidney injury by combining with NLRP3 inflammasome-related multiple mechanisms, and whether new mechanism of this pathway exists deserves further investigation.

4.2. SGLT 2 Inhibitors. Sodium glucose cotransporter 2 inhibitors (SGLT-2is) reduce plasma glucose and hemoglobin A1c (HbA1c) levels in patients with T2D by increasing glucose excretion through inhibition of the proximal renal tubular reabsorption segment [95]. SGLT-2is, including dapagliflozin, ertugliflozin, and empagliflozin, are commonly used as clinical drugs. Kawanami et al. have demonstrated that SGLT-2is attenuate DN in diabetes animal models, suggesting a potential renal protective effect in addition to glucose reduction [96]. Recently, in a systematic evaluation and meta-analysis of clinical cardiovascular trials, exploratory results have shown that drugs such as SGLT-2is improve renal regression in patients with T2D [95, 97]. With in-depth studies, the inhibition of the NLRP3 inflammasome comes to the fore role in the process of SGLT 2 treatment [98]. For example, T2D patients treated with dapagliflozin showed reduced IL-1β secretion with increased serum β-hydroxybutyrate (BHB) and reduced serum insulin, and
4.3. **DPP4 Inhibitors.** Dipeptidyl peptidase-4 (DPP4) is a family member of serine proteases. DPP4 inhibitors (DPP-4is) exert hypoglycemic effects by inhibiting the release of DPP4 and glucagon, which in turn leads to increased release of insulin secretion and elevated circulating insulin levels [101]. Sitagliptin, linagliptin, saxagliptin, alogliptin, and vilaglipatin are DPP-4is that can be used alone or in combination with other types of antidiabetic drugs. For example, many meta-analyses have found that in patients with T2D without adequate insulin control, DPP-4is show better glycemic control compared to placebo [102, 103]. Meanwhile, in another meta-analysis, the addition of DPP-4is in patients with T2D with inadequate alpha-glycosidase inhibitor (AGI) control resulted in better glycemic control [104]. More recently, studies have shown that DPP-4is can be used to fight inflammatory kidney damage caused by diabetes [105]. Birnbaum et al. found that saxagliptin reduces kidney injury and prevents DN progression by inhibiting NLRP3 in diabetic mice [106]. Similarly, combination of DPP-4i and SGLT-2i reduces NLRP3/ASC inflammasome activation and attenuates the development of diabetic nephropathy in type 2 diabetic mice [105]. More clinical research is needed to determine the role of DPP-4i in diabetic kidney injury. Currently oral DPP-4is do not reduce adipose inflammation or improve insulin resistance. Meanwhile, an article reported that intrahepatocellular but not intestinal DPP4 reduces adipose inflammation and improves insulin resistance while lowering blood glucose [107, 108]. Therefore, it could be considered that DPP-4i drugs could be redirected by packaging them into nanoparticles delivered to the liver, or attaching siRNAs to certain sugar molecules with specific affinity for hepatocytes could be a potential new target for the treatment of T2D and metabolic diseases.

4.4. **Resveratrol.** Resveratrol (3,5,4′-trihydroxy-trans-stilbene; RES) is a highly concentrated natural plant polyphenol found in red grapes and is also abundant in knotweed, soybeans, peanuts, and mulberries [109]. RES is known to have antioxidant, anticancer, antiobesity, anti-inflammatory, and antiaging effects [110]. Furthermore, current clinical trials have shown that RES also has antihyperglycemic effects [111, 112]. For example, resveratrol has been shown not only to lower blood glucose levels and protect β-cells in patients with type 1 diabetes [113] but also to improve insulin sensitivity in patients with T2D [114]. Notably, a study has shown that anti-inflammatory effects of RES may play a kidney-protective role in different diseases, including in diabetes [115]. Saldanha et al. show that RES inhibits or counters NF-κB activity and coordinates the inflammatory response, thereby improving CKD [116]. More importantly, RES administration attenuated glomerulosclerosis and inflammation, and these were associated with reduced renal mononuclear leukocyte infiltration and inhibition of renal NLRP3 inflammasome activation in progressive IgA nephropathy in mice [117]. Similarly, RES treatment significantly inhibited oxidative stress in diabetic rats with renal 1/R injury undergoing TXNIP-mediated NLRP3 activation [118]. However, the biological effects of RES are greatly limited by its low water solubility, poor stability, and rapid

| Medication | Related mechanisms | Experimental subjects | Ref. |
|------------|--------------------|-----------------------|------|
| Metformin  | Inhibiting the NLRP3 inflammasome | Macrophages in T2D patients, APOE-/- male mice | [92–94] |
| SGLT-2is   | Inhibiting the NLRP3 inflammasome/IL-1β axis | T2D patients | [99, 100] |
| DPP-4is    | Inhibiting the NLRP3 inflammasome | T2D patients, diabetic mice | [106] |
| DPP-4is and SGLT-2is | Inhibiting the NLRP3/ASC inflammasome | T2D mice | [105] |
| RES        | Inhibiting the TXNIP/NLRP3 axis | Mice with IgA nephropathy, diabetic rats with renal 1/R injury | [116–118] |
| IL-22      | Inhibiting the NLRP3/caspase-1/IL-1β axis | T2D in Chinese urban adults, diabetic patients, DN mice | [122, 123] |
| TXNIP DNAzyme | Inhibiting the TXNIP/NLRP3 axis | DN rats | [124] |
| Sar        | Inhibiting NLRP3 | DN rats | [125, 126] |
| Dabrafenib | Inhibiting the RIPK3/NLRP3 axis | DN rat model | [127] |
| Quercetin and allopurinol | Inhibiting the caspase-1/IL-1β/IL-18 axis | STZ-induced DN | [56] |
| DHQ        | Inhibiting the ROS/NLRP3 inflammasome | DN rats | [128] |
| Catalpol   | Inhibiting ASC/NLRP3/caspase-1/IL-1β | DN mice | [129] |
| PIO        | Inhibiting NLRP3/caspase-1/IL-1β/IL-18 | DN mice | [130] |
| Curcumin   | Inhibiting caspase-1/NLRP3 | DN mice | [131] |

SGLT2: sodium glucose cotransporter 2; DPP4: dipeptidyl peptidase-4; RES: resveratrol; Sar: sarsapogenin; DHQ: dihydroquercetin; PIO: pioglitazone; TXNIP: thioredoxin-interacting protein.

Table 2: The partly regulation role of drugs that target the NLRP3 inflammasome in DN treatment.
metabolism in vivo. Therefore, it is important to consider whether advanced technologies such as nanoparticles can be used to improve pharmacokinetics, achieve targeted drug delivery, improve drug utilization, achieve sustained inhibitory effects on the NLRP3 inflammasome, and ameliorate diabetic kidney injury. It also remains to be confirmed whether the effect of different RES doses on inflammation affects these results in terms of efficacy and safety (Figure 3).

4.5. IL-22. IL-22, an important member of the IL-10 family, is a key cytokine that regulates tissue responses during inflammation [119]. The downregulation of IL-22 in vivo has recently been recognized as a risk factor for diabetes [120]. Clinical research shows that plasma IL-22 levels were negatively and dose-dependently associated with the prevalence of T2D in Chinese urban adults [121]. IL-22 gene therapy significantly reduced hyperglycemia and metabolic disorders in diabetic rats. In this context, it has also been investigated whether IL-22 has a therapeutic effect on diabetic kidney injury [122]. Notably, Wang et al. show that IL-22 gene therapy significantly reversed the renal activation of NLRP3 to exert anti-inflammatory functions in DN rats [122]. Clinically, IL-22 gene therapy significantly reduced renal fibrosis and proteinuria excretion in DN 138. Furthermore, Shen et al. developed a novel antivascular endothelial growth factor B (VEGFB)/IL22 fusion protein that was found to improve the inflammatory response associated with NLRP3 and reduce renal lipid accumulation in diabetic patients [123]. Although more clinical studies are needed, IL-22 can be predicted to have great potential in DN therapy in targeting NLRP3 inflammasome activation. Moreover, investigators can focus on the therapeutic opportunities of IL-22 and its involved metabolic regulation in various diabetic kidney diseases.

4.6. Other Drugs. In addition to the above-mentioned drugs, other drugs with potential effects on the upstream activation and downstream transduction mechanisms of the NLRP3 inflammasome are currently being explored. TXNIP is an upstream partner to NLRP3, and the association between them is necessary for downstream inflammasome activation [43]. Tan et al. used TXNIP deoxyribozyme (DNAzyme) to restrain the expression of TXNIP, subsequently downregulating the level of NLRP3 in the renal tubule interstitium of diabetic rats [124]. Two other studies show that sarsasapogenin (Sar), a steroidal sapogenin, markedly constrains the activation of NLRP3 in the renal cortex to play a protective role in diabetic rats [125, 126]. Similarly, Shi et al. used dabrafenib to inhibit receptor-interacting protein kinase-3 (RIPK3), which has been implicated as a regulator of NLRP3 inflammasome signaling. The dabrafenib-induced RIPK3 deficiency alleviates diabetes-induced renal fibrosis, in association with reduced activation of the NLRP3 inflammasome [127]. Additionally, since there is crosstalk between metabolism and inflammation, researchers have attempted to inhibit NLRP3 inflammasome activation by improving metabolic pathways. Quercetin and allopurinol also repress renal NLRP3 inflammasome activation, at least partly, via their antihyperuricemia and antidyslipidemia effects, leading to the amelioration of STZ-induced superimposed nephrotoxicity in rats [56]. In addition, dihydroquercetin (DHQ) [128], catalpol [129], pioglitazone (PIO) [130], and curcumin [131] were also found to possess kidney protection.

![Figure 3: Clinical agents targeting NLRP3 inflammasomes for the treatment of diabetic nephropathy.](image-url)
effects associated with inhibiting NLRP3 activation in diabetic mice. These evidences suggest that targeting the NLRP3 inflammasome in DN may serve as a beneficial strategy for treatment.

5. Conclusions and Future Perspectives

It has become apparent that inflammation is an important element to initiate diabetic microvascular complications, including DN. Activation of the NLRP3 inflammasome is critical for the development of many kidney disorders including CKD, IgA nephropathy, lupus nephritis, and more. However, the onset and offset of these diseases are different due to their etiology and pathological features, but all have sustained NLRP3 inflammasome activation during the disease process, and inhibition of NLRP3 inflammasomes and related pathways may be a convergent strategy for the treatment of many renal diseases. Future research should focus on whether NLRP3 regulates the release of other mediators and thus exacerbates inflammation.

With the advent of epigenetics, it was found that not only can NLRP3 inflammasomes trigger epigenetic alterations [132] but also ShMETTL3 as used by Chien et al. blocks NLRP3 upregulation [133]. These data suggest a possible bidirectional feedback regulatory mechanism between epigenetic modifications and NLRP3-related inflammation. Additionally, red raspberry polyphenols were found to attenuate high-fat diet-induced NLRP3 inflammasome activation and inhibit adipogenic paracrine secretion through histone modifications [134], suggesting that NLRP3 may be a key hub bridging genetics and epigenetics. Now it needs to be further addressed which cell types of NLRP3 inflammasome activation can induce epigenetic reprogramming and further affect the physiological and pathological processes of the organism. The rise of single-cell sequencing able to reveal cellular heterogeneity in cell populations provides a desirable solution for this purpose.

Meanwhile, almost all epigenetic modification processes require the participation of metabolites, and the spatial reorganization of metabolites reveals the importance of metabolic enzyme translocation in epigenetic regulation. Therefore, discovering the role of metabolites in other organelles, such as lysosomes, the endoplasmic reticulum, and the Golgi apparatus, will be the key to understanding how metabolism and epigenetics interact and how organelles interoperate. Research has shown that the small molecule natural product xanthone can inhibit NLRP3 inflammasomes by configuring the cellular metabolic profile, leading to changes in glucose metabolism [135]. Therefore, systematic screening can identify novel NLRP3 inflammasome inhibitors to obtain new bioactive substances as potential drugs.

Abbreviations

DN: Diabetic nephropathy  
NLRP3: Nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing protein 3  
SFAs: Saturated fatty acids  
UA: Uric acid  
RIF: Renal interstitial fibrosis  
SGLT 2: Sodium glucose co-transporter 2  
IDF: International Diabetes Federation  
AGEs: Advanced glycosylation end products  
ASC: Apoptosis-associated speck-like protein  
As: Atherosclerosis  
ROS: Reactive oxygen species  
NF-κB: Nuclear factor κB  
T2D: Type 2 diabetes  
PKC: Protein kinase C  
TGF-β: Transforming growth factor β  
VEGF: Vascular endothelial growth factor  
TXNIP: Thioredoxin-interacting protein  
FOXO1: Forkhead box protein O1  
PKM2: Pyruvate kinase M2  
MUFAs: Monounsaturated fatty acids  
PUFAs: Polyunsaturated fatty acids  
AMPK: Adenosine 5'-monophosphate-activated protein kinase  
PGR120: G protein-coupled receptor 120  
PPARs: Peroxisome proliferator-activated receptors  
ER: Endoplasmic reticulum  
SREBP2: Sterol regulatory element-binding protein 2  
SCAP: Cleavage-activating protein  
TRX: Thioredoxin  
HCY: Homocysteine  
HMGB1: High mobility group box 1 protein 1  
VSMCs: Vascular smooth muscle cells  
ERK1/2: Extracellular regulated protein kinase 1/2  
NADPH: Nicotinamide adenine dinucleotide  
HIF1α: Hypoxia inducible factor-1α  
PDK1: 3-Phosphoinositide-dependent kinase-1  
GFB: Glomerular filtration barrier  
AKI: Acute kidney injury  
GEnCs: Glomerular endothelial cells  
EMT: Epithelial-mesenchymal transition  
EndoMT: Endothelial-mesenchymal transition  
CKD: Chronic kidney disease  
DAMPs: Damage-associated molecular patterns  
PAMPs: Pathogen-associated molecular patterns  
GLUT-4: Glucose transporter protein type 4  
HbA1c: Hemoglobin A1c  
BHB: β-hydroxybutyrate  
DPP4: Dipeptidyl peptidase 4  
DPP-4i: Dipeptidyl peptidase-4 inhibitors  
AGI: Alpha-glycosidase inhibitor  
RES: Resveratrol  
VEGFB: Vascular endothelial growth factor B  
DNAzyme: Deoxyribozyme  
Sar: Sarsasapogenin  
RIPK3: Receptor-interacting protein kinase-3  
DHQ: Dihydroquercetin  
PIO: Pioglitazone.

Conflicts of Interest

The authors declare no conflict of interest.
Authors’ Contributions

W.Z. and L.Z. drafted and compiled the sections of the manuscript. B.L., X.Z., and K.Y. revised and edited the manuscript. P.N. and X.S. prepared the figure and tables. All authors approved the submitted manuscript. Wenli Zhao and Le Zhou contributed equally as the first authors. Chuang Biao Lin, Xiao Zhu, and Kai Yin contributed equally as the corresponding authors.

Acknowledgments

This study was supported by the National Natural Sciences Foundation of China (grant numbers 81970390 and 82060065); Key Project of the Natural Science Foundation of Guangxi Zhuang Autonomous Region, China (grant number 2020JJD140029); and Grant for the Guangxi Medical High-level Key Talents Training (139 plan) and Guangxi Province Postgraduate Cotraining Base for Cooperative Innovation in Basic Medicine, Guinlin Medical University (Gui Xue Wei [2020]7). The figure of the article was drawn by Figdraw (https://www.figdraw.com/).

References

[1] P. Saeedi, I. Petersohn, P. Salpea et al., “Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition,” Diabetes Research and Clinical Practice, vol. 157, p. 107843, 2019.

[2] A. Flyvbjerg, “The role of the complement system in diabetic nephropathy,” Nature Reviews. Nephrology, vol. 13, no. 5, pp. 311–318, 2017.

[3] R. Z. Alicic, M. T. Rooney, and K. R. Tuttle, “Diabetic kidney disease: challenges, progress, and possibilities,” Clinical Journal of the American Society of Nephrology, vol. 12, no. 12, pp. 2032–2045, 2017.

[4] Y. Zhuang, G. Ding, M. Zhao et al., “NLRP3 inflammasome mediates albumin-induced renal tubular injury through impaired mitochondrial function,” The Journal of Biological Chemistry, vol. 289, no. 36, pp. 25101–25111, 2014.

[5] Y. He, H. Hara, and G. Nunez, “Mechanism and regulation of NLRP3 inflammasome activation,” Trends in Biochemical Sciences, vol. 41, no. 12, pp. 1012–1021, 2016.

[6] B. K. Davis, H. Wen, and J. P. Ting, “The inflammasome NLKs in immunity, inflammation, and associated diseases,” Annual Review of Immunology, vol. 29, no. 1, pp. 707–735, 2011.

[7] V. Neudecker, M. Haneklaus, O. Jensen et al., “Myeloid-derived miR-223 regulates intestinal inflammation via repression of the NLRP3 inflammasome,” The Journal of Experimental Medicine, vol. 214, no. 6, pp. 1737–1752, 2017.

[8] L. Andreeva, L. David, S. Rawson et al., “NLRP3 cages revealed by full-length mouse NLRP3 structure control pathway activation,” Cell, vol. 184, no. 26, pp. 6299–6312.e22, 2021.

[9] J. C. Ralston, C. L. Lyons, E. B. Kennedy, A. M. Kirwan, and H. M. Roche, “Fatty acids and NLRP3 inflammasome-mediated inflammation in metabolic tissues,” Annual Review of Nutrition, vol. 37, no. 1, pp. 77–102, 2017.

[10] D. De Nardo and E. Latz, “NLRP3 inflammasomes link inflammation and metabolic disease,” Trends in Immunology, vol. 32, no. 8, pp. 373–379, 2011.

[11] K. Shahzad, F. Bock, W. Dong et al., “Nlrp3-inflammasome activation in non-myeloid-derived cells aggravates diabetic nephropathy,” Kidney International, vol. 87, no. 1, pp. 74–84, 2015.

[12] P. Hong, R. N. Gu, F. X. Li et al., “NLRP3 inflammasome as a potential treatment in ischemic stroke concomitant with diabetes,” Journal of Neuroinflammation, vol. 16, no. 1, p. 121, 2019.

[13] Y. Han, X. Xu, C. Tang et al., “Reactive oxygen species promote tubular injury in diabetic nephropathy: the role of the mitochondrial ros-txnip-nlrp3 biological axis,” Redox Biology, vol. 16, pp. 32–46, 2018.

[14] H. H. L. Tseng, C. T. Vong, Y. W. Kwan, S. M. Y. Lee, and M. P. M. Hoi, “Lysosomal Ca2+ signaling regulates high glucose-mediated Interleukin-1β secretion via transcription factor EB in human monocytes cells,” Frontiers in Immunology, vol. 8, p. 1161, 2017.

[15] X. Xia, B. Lu, W. Dong et al., “Atypical gudermin D and mixed lineage kinase domain-like protein leakage aggravates tetrachlorobenzoxiquone-induced nod-like receptor protein 3 inflammasome activation,” Chemical Research in Toxicology, vol. 31, no. 12, pp. 1418–1425, 2018.

[16] H. Tsubaki, I. Tooyama, and D. G. Walker, “Thioredoxin-interacting protein (TXNIP) with focus on brain and neurodegenerative diseases,” International Journal of Molecular Sciences, vol. 21, no. 24, p. 9357, 2020.

[17] H. Feng, J. Gu, F. Gou et al., “High glucose and lipopolysaccharide prime NLRP3 inflammasome via ROS/TXNIP pathway in mesangial cells,” Journal Diabetes Research, vol. 2016, article 6973175, 11 pages, 2016.

[18] J. B. Nyandwi, Y. S. Ko, H. Jin, S. P. Yun, S. W. Park, and H. J. Kim, “Rosmarinic acid inhibits oxLDL-induced inflammasome activation under high-glucose conditions through downregulating the p38-FOXO1-TXNIP pathway,” Biochemical Pharmacology, vol. 182, article 114246, 2020.

[19] C. Gao, J. Chen, F. Fan et al., “RIPK2-mediated autophagy and negatively regulated ROS-NLRP3 inflammasome signaling in GMCs stimulated with high glucose,” Mediators of Inflammation, vol. 2019, Article ID 6207563, 13 pages, 2019.

[20] H. Yi, R. Peng, L. Y. Zhang et al., “LincRNA-Gm4419 knockdown ameliorates NF-κB/NLRP3 inflammasome-mediated inflammation in diabetic nephropathy,” Cell Death & Disease, vol. 8, no. 2, article e2583, 2017.

[21] Q. Li, K. Leng, Y. Liu et al., “The impact of hyperglycaemia on PDK2-mediated NLRP3 inflammasome/stress granule signalling in macrophages and its correlation with plaque vulnerability: an in vivo and in vitro study,” Metabolism, vol. 107, article 154231, 2020.

[22] J. T. Yu, X. W. Hu, H. Y. Chen et al., “DNA methylation of FTO promotes renal inflammation by enhancing m6A of PPAR-α in alcohol-induced kidney injury,” Pharmacological Research, vol. 163, article 105286, 2021.

[23] Y. Yang, F. Shen, W. Huang et al., “Glucose is involved in the dynamic regulation of m6A in patients with type 2 diabetes,” The Journal of Clinical Endocrinology and Metabolism, vol. 104, no. 3, pp. 665–673, 2019.

[24] S. Spiller, M. Bluhuer, and R. Hoffmann, “Plasma levels of free fatty acids correlate with type 2 diabetes mellitus,” Diabetes, Obesity & Metabolism, vol. 20, no. 11, pp. 2661–2669, 2018.
[25] A. R. Tall and L. Yvan-Charvet, “Cholesterol, inflammation and innate immunity,” Nature Reviews. Immunology, vol. 15, no. 2, pp. 104–116, 2015.

[26] T. Karasawa, A. Kawashima, F. Usui-Kawanishi et al., “Saturated fatty acids undergo intracellular crystallization and activate the NLRP3 inflammasome in macrophages,” Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 38, no. 4, pp. 744–756, 2018.

[27] P. K. Anand, “Lipids, inflammasomes, metabolism, and disease,” Immunological Reviews, vol. 297, no. 1, pp. 108–122, 2020.

[28] G. Ravaut, A. Légiot, K. F. Bergeron, and C. Mounier, “Monounsaturated fatty acids in obesity-related inflammation,” International Journal of Molecular Sciences, vol. 22, no. 1, 2020.

[29] O. M. Finucane, C. L. Lyons, A. M. Murphy et al., “Monounsaturated fatty acids enriched high-fat diets impede adipose NLRP3 inflammasome-mediated IL-1β secretion and insulin resistance despite obesity,” Diabetes, vol. 64, no. 6, pp. 2116–2128, 2015.

[30] S. Sarbolouki, M. H. Javanbakht, H. Derakhshanian et al., “Eicosapentaenoic acid improves insulin sensitivity and blood sugar in overweight type 2 diabetes mellitus patients: a double-blind randomised clinical trial,” Singapore Medical Journal, vol. 54, no. 7, pp. 387–390, 2013.

[31] T. J. Brown, J. Brainard, F. Song, X. Wang, A. Abdelhamid, and L. Hooper, “Omega-3, omega-6, and total dietary polyunsaturated fat for prevention and treatment of type 2 diabetes mellitus: systematic review and meta-analysis of randomised controlled trials,” BMJ, vol. 366, p. i4697, 2019.

[32] L. Monnier, C. Colette, C. Percheron, and B. Descomps, “Insulin, diabetes and cholesterol metabolism,” Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales, vol. 189, no. 5, pp. 919–931, 1995.

[33] P. Duewell, H. Kono, K. J. Rayner et al., “NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals,” Nature, vol. 464, no. 7293, pp. 1357–1361, 2010.

[34] S. R. Mulay, C. Shi, X. Ma, and H. J. Anders, “Novel insights into crystal-induced kidney injury,” Kidney Diseases, vol. 4, no. 2, pp. 49–57, 2018.

[35] M. de la Roche, C. Hamilton, R. Mortensen, A. A. Jayaprakash, S. Ghosh, and P. K. Anand, “Trafficking of cholesterol to the ER is required for NLRP3 inflammasome activation,” The Journal of Cell Biology, vol. 217, no. 10, pp. 3560–3576, 2018.

[36] C. Guo, Z. Chi, D. Jiang et al., “Cholesterol homeostatic regulator SCAP-SREBP2 integrates NLRP3 inflammasome activation and cholesterol biosynthetic signaling in macrophages,” Immunity, vol. 49, no. 5, pp. 842–856.e7, 2018.

[37] T. Keenan, M. J. Blaha, K. Nasir et al., “Relation of uric acid to serum levels of high-sensitivity C-reactive protein, triglycerides, and high-density lipoprotein cholesterol and to hepatic steatosis,” The American Journal of Cardiology, vol. 110, no. 12, pp. 1787–1792, 2012.

[38] Q. Lv, X. F. Meng, F. F. He et al., “High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies,” PLoS One, vol. 8, no. 2, article e56864, 2013.

[39] W. J. Kim, S. S. Kim, M. J. Bae et al., “High-normal serum uric acid predicts the development of chronic kidney disease in patients with type 2 diabetes mellitus and preserved kidney function,” Journal of Diabetes and its Complications, vol. 28, no. 2, pp. 130–134, 2014.

[40] S. M. Kim, S. H. Lee, Y. G. Kim et al., “Hyperuricemia-induced NLRP3 activation of macrophages contributes to the progression of diabetic nephropathy,” American Journal of Physiology. Renal Physiology, vol. 308, no. 9, pp. F993–F1003, 2015.

[41] T. T. Braga, O. Foresto-Neto, and N. O. S. Camara, “The role of uric acid in inflammasome-mediated kidney injury,” Current Opinion in Nephrology and Hypertension, vol. 29, no. 4, pp. 423–431, 2020.

[42] P. Gasse, N. Riteau, S. Charron et al., “Uric acid is a danger signal activating NALP3 inflammasome in lung injury inflammation and fibrosis,” American Journal of Respiratory and Critical Care Medicine, vol. 179, no. 10, pp. 903–913, 2009.

[43] R. Zhou, A. Tardivel, B. Thorens, I. Choi, and J. Tschopp, “Thioredoxin-interacting protein links oxidative stress to inflammasome activation,” Nature Immunology, vol. 11, no. 2, pp. 136–140, 2010.

[44] L. A. Joosten, M. G. Netea, E. Mylona et al., “Engagement of fatty acids with Toll-like receptor 2 drives interleukin-1β production via the ASC/caspase 1 pathway in monosodium urate monohydrate crystal-induced gouty arthritis,” Arthritis and Rheumatism, vol. 62, no. 11, pp. 3237–3248, 2010.

[45] A. H. Hainsworth, N. E. Yeo, E. M. Weekman, and D. M. Wilcock, “Homocysteine, hyperhomocysteinemia and vascular contributions to cognitive impairment and dementia (VCID),” Biochimica et Biophysica Acta, vol. 1862, no. 5, pp. 1008–1017, 2016.

[46] F. Yi, A. Y. Zhang, N. Li et al., “Inhibition of ceramide-redox signaling pathway blocks glomerular injury in hyperhomocysteinemic rats,” Kidney International, vol. 70, no. 1, pp. 88–96, 2006.

[47] Y. Leng, R. Chen, R. Chen et al., “HMGB1 mediates homocysteine-induced endothelial cells pyroptosis via cathepsin V-dependent pathway,” Biochemical and Biophysical Research Communications, vol. 532, no. 4, pp. 640–646, 2020.

[48] L. B. Liu, H. F. Shen, W. Cha et al., “SXBX pill suppresses homocysteine-induced vascular smooth muscle cells dedifferentiation by inhibiting NLRP3 inflammasomes activation via ERK/p38 MAPK pathways,” American Journal of Translational Research, vol. 11, no. 2, pp. 806–818, 2019.

[49] S. M. Conley, J. M. Abais-Battad, X. Yuan, Q. Zhang, K. M. Boini, and P. L. Li, “Contribution of guanine nucleotide exchange factor Vav2 to NLRP3 inflammasome activation in mouse podocytes during hyperhomocysteinemia,” Free Radical Biology & Medicine, vol. 106, pp. 236–244, 2017.

[50] C. Wan, H. Su, and C. Zhang, “Role of NADPH oxidase in metabolic disease-related renal injury: an update,” Oxidative Medicine and Cellular Longevity, vol. 2016, Article ID 7813072, 8 pages, 2016.

[51] Q. Zhang, S. M. Conley, G. Li, X. Yuan, and P. L. Li, “Rac1 GTase inhibition blocked podocyte injury and glomerular sclerosis during hyperhomocysteinemia via suppression of nucleotide-binding oligomerization domain-like receptor containing pyrin domain 3 inflammasome activation,” Kidney & Blood Pressure Research, vol. 44, no. 4, pp. 513–532, 2019.
[52] J. Li, H. Zhang, Y. Dong, X. Wang, and G. Wang, “Omega-3FAs can inhibit the inflammation and insulin resistance of adipose tissue caused by HHcy induced lipids profile changing in mice,” *Frontiers in Physiology*, vol. 12, article 628122, 2021.

[53] Q. S. Xia, F. E. Lu, F. Wu et al., “New role for ceramide in hypoxia and insulin resistance,” *World Journal of Gastroenterology*, vol. 26, no. 18, pp. 2177–2186, 2020.

[54] E. Asgari, G. le Friec, H. Yamamoto et al., “ASC modulates IL-1β secretion in human monocytes by regulating ATP efflux and subsequent NLRP3 inflammasome activation,” *Blood*, vol. 122, no. 20, pp. 3473–3481, 2013.

[55] H. Wen, D. Gris, Y. Lei et al., “Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling,” *Nature Immunology*, vol. 12, no. 5, pp. 408–415, 2011.

[56] C. Wang, Y. Pan, Q. Y. Zhang, F. M. Wang, and L. D. Kong, “Quercetin and alopurinol ameliorate kidney injury in STZ-treated rats with regulation of renal NLRP3 inflammasome activation and lipid accumulation,” *PLoS One*, vol. 7, no. 6, article e38285, 2012.

[57] T. Komada and D. A. Muruve, “The role of inflammasomes in kidney disease,” *Nature Reviews. Nephrology*, vol. 15, no. 8, pp. 501–520, 2019.

[58] Z. Zheng, K. Xu, C. Li et al., “NLRP3 associated with chronic kidney disease progression after ischemia/reperfusion-induced acute kidney injury,” *Cell death discovery*, vol. 7, no. 1, p. 324, 2021.

[59] F. Yi, S. Jin, F. Zhang et al., “Formation of lipid raft redox signaling platforms in glomerular endothelial cells: an early event of homocysteine-induced glomerular injury,” *Journal of Cellular and Molecular Medicine*, vol. 13, no. 9B, pp. 3303–3314, 2009.

[60] C. Zhang, J. J. Hu, M. Xia, K. M. Boini, C. Brimson, and P. L. Li, “Redox signaling via lipid raft clustering in homocysteine-induced injury of podocytes,” *Biochimica et Biophysica Acta*, vol. 1803, no. 4, pp. 482–491, 2010.

[61] S. C. W. Tang and W. H. Yu, “Innate immunity in diabetic kidney disease,” *Nature Reviews. Nephrology*, vol. 16, no. 4, pp. 206–222, 2020.

[62] C. Q. Kleessens, M. Zandbergen, R. Wolterbeek et al., “Macrophages in diabetic nephropathy in patients with type 2 diabetes,” *Nephrology, Dialysis, Transplantation*, vol. 32, no. 8, pp. 1322–1329, 2016.

[63] A. Vilaysane, J. Chun, M. E. Seamone et al., “The NLRP3 inflammasome promotes renal inflammation and contributes to CKD,” *Journal of the American Society of Nephrology*, vol. 21, no. 10, pp. 1732–1744, 2010.

[64] P. Gao, F. F. He, H. Tang et al., “NADPH Oxidase-Induced NALP3 Inflammasome Activation Is Driven by Thioredoxin-Interacting Protein Which Contributes to Podocyte Injury in Hyperglycemia,” *Journal Diabetes Research*, vol. 2015, article 504761, 12 pages, 2015.

[65] P. Gao, X. F. Meng, H. Su et al., “Thioredoxin-interacting protein mediates NALP3 inflammasome activation in podocytes during diabetic nephropathy,” *Biochimica et Biophysica Acta*, vol. 1843, no. 11, pp. 2448–2460, 2014.

[66] Y. Qiao, X. Tian, L. Men et al., “Spleen tyrosine kinase promotes NLR family pyrin domain containing 3 inflammasome-mediated IL-1β secretion via c-Jun N-terminal kinase activation and cell apoptosis during diabetic nephropathy,” *Molecular Medicine Reports*, vol. 18, no. 2, pp. 1995–2008, 2018.

[67] K. Chen, L. Feng, W. Hu et al., “Optineurin inhibits NLRP3 inflammasome activation by enhancing mitophagy of renal tubular cells in diabetic nephropathy,” *The FEBS Journal*, vol. 33, no. 3, pp. 4571–4585, 2019.

[68] H. Yan, J. Xu, Z. Xu, B. Yang, P. Luo, and Q. He, “Defining therapeutic targets for renal fibrosis: exploiting the biology of pathogenesis,” *Biomedicine & Pharmacotherapy*, vol. 143, article 112115, 2021.

[69] Y. Sato and M. Yanagita, “Resident fibroblasts in the kidney: a major driver of fibrosis and inflammation,” *Inflammation and regeneration*, vol. 37, no. 1, p. 17, 2017.

[70] S. M. Conley, J. M. Abais, K. M. Boini, and P. L. Li, “Inflammasome activation in chronic glomerular diseases,” *Current Drug Targets*, vol. 18, no. 9, pp. 1019–1029, 2017.

[71] P. J. Bakker, L. M. Butter, N. Claessen et al., “A tissue-specific role for Nlpr3 in tubular epithelial repair after renal ischemia/reperfusion,” *The American Journal of Pathology*, vol. 184, no. 7, pp. 2013–2022, 2014.

[72] Y. Li, Y. S. Kang, C. Dai, L. P. Kiss, X. Wen, and Y. Liu, “Epithelial-to-mesenchymal transition is a potential pathway leading to podocyte dysfunction and proteinuria,” *The American Journal of Pathology*, vol. 172, no. 2, pp. 299–308, 2008.

[73] C. Kuppe, M. M. Ibrahim, J. Kranz et al., “Decoding myofibroblast origins in human kidney fibrosis,” *Nature*, vol. 589, no. 7841, pp. 281–286, 2021.

[74] H. J. Anders, B. Suarez-Alvarez, M. Grigorescu et al., “The macrophage phenotype and inflammasome component NLRP3 contributes to nephrocalciosis-related chronic kidney disease independent from IL-1-mediated tissue injury,” *Kidney International*, vol. 93, no. 3, pp. 656–669, 2018.

[75] K. F. Hua, S. M. Yang, T. Y. Kao et al., “Osthole mitigates progressive IgA nephropathy by inhibiting reactive oxygen species generation and NF-κB/NLRP3 pathway,” *PLoS One*, vol. 8, no. 10, article e77794, 2013.

[76] W. Han, Q. Ma, Y. Liu et al., “Huangkui capsule alleviates renal tubular epithelial-mesenchymal transition in diabetic nephropathy via inhibiting NLRP3 inflammasome activation and TLR4/NF-κB signaling,” *Phytotherapy*, vol. 57, pp. 203–214, 2019.

[77] S. Song, D. Qi, F. Luo et al., “Knockdown of NLRP3 alleviates high glucose or TGFβ1-induced EMT in human renal tubular cells,” *Journal of Molecular Endocrinology*, vol. 61, no. 3, pp. 101–113, 2018.

[78] S. Martin-Rodriguez, C. Caballo, G. Gutierrez et al., “TLR4 and NALP3 inflammasome in the development of endothelial dysfunction in uraemia,” *European Journal of Clinical Investigation*, vol. 45, no. 2, pp. 160–169, 2015.

[79] W. Yu, B. Gao, N. Li et al., “Sirt3 deficiency exacerbates diabetic cardiac dysfunction: role of Foxo3A-Parkin-mediated mitophagy,” *Biochimica et Biophysica Acta - Molecular Basis of Disease*, vol. 1863, no. 8, pp. 1973–1983, 2017.

[80] M. L. Chen, X. H. Zhu, L. Ran, H. D. Lang, L. Yi, and M. T. Mi, “Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-miROS signaling pathway,” *Journal of the American Heart Association*, vol. 6, no. 9, 2017.

[81] S. Kapetanaki, A. K. Kumawat, K. Persson, and I. Demirel, “The fibrotic effects of TMAO on human renal fibroblasts is mediated by NLRP3, caspase-1 and the PERK/Akt/mTOR pathway,” *International Journal of Molecular Sciences*, vol. 22, no. 21, p. 11864, 2021.
[82] J. J. Yoon, H. K. Lee, H. Y. Kim et al., "Saquinavir protects renal mesangial cell dysfunction against angiotensin II by improving renal fibrosis and inflammation," *International Journal of Molecular Sciences*, vol. 21, no. 19, p. 7003, 2020.

[83] W. Wang, X. Wang, J. Chun et al., "Inflammasome-independent NLRP3 augments TGF-β signaling in kidney epithelium," *Journal of Immunology*, vol. 190, no. 3, pp. 1239–1249, 2013.

[84] S. M. Kim, Y. G. Kim, D. J. Kim et al., "Inflammasome-independent role of NLRP3 mediates mitochondrial regulation in renal injury," *Frontiers in Immunology*, vol. 9, p. 2563, 2018.

[85] Y. G. Kim, S. M. Kim, K. P. Kim, S. H. Lee, and J. Y. Moon, "The role of inflammasome-dependent and inflammasome-independent NLRP3 in the kidney," *Cell*, vol. 8, no. 11, 2019.

[86] C. Nathan and A. Ding, "Nonresolving inflammation," *Cell*, vol. 140, no. 6, pp. 871–882, 2010.

[87] H. Yaribeygi, M. T. Mohammadi, R. Rezaee, and A. Sahbekkar, "Fenofibrate improves renal function by amelioration of NOX-4, IL-18, and p53 expression in an experimental model of diabetic nephropathy," *Journal of Cellular Biochemistry*, vol. 119, no. 9, pp. 7458–7469, 2018.

[88] E. Kickstein, S. Krauss, P. Thornhill et al., "Biganuine metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 107, no. 50, pp. 21830–21835, 2010.

[89] Y. M. Cho and T. J. Kieffer, "New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitizer," *Diabetologia*, vol. 54, no. 2, pp. 219–222, 2011.

[90] S. Ravindran, V. Kuruvilla, K. Wilbur, and S. Munusamy, "Nephroprotective effects of metformin in diabetic nephropathy," *Journal of Cellular Physiology*, vol. 232, no. 4, pp. 731–742, 2017.

[91] C. Bulcao, F. F. Ribeiro-Filho, A. Sanudo, and S. G. Roberta Ferreira, "Effects of simvastatin and metformin on inflammation and insulin resistance in individuals with mild metabolic syndrome," *American Journal of Cardiovascular Drugs*, vol. 7, no. 3, pp. 219–224, 2007.

[92] H. M. Lee, J. J. Kim, H. J. Kim, M. Shong, B. J. Ku, and E. K. Jo, "Upregulated NLRP3 inflammasome activation in patients with type 2 diabetes," *Diabetes*, vol. 62, no. 1, pp. 194–204, 2013.

[93] S. Bhansali, A. Bhansali, P. Dutta, R. Walia, and V. Dhawan, "Metformin upregulates mitophagy in patients with T2DM: a randomized placebo-controlled study," *Journal of Cellular and Molecular Medicine*, vol. 24, no. 5, pp. 2832–2846, 2020.

[94] G. Tang, F. Duan, W. Li et al., "Metformin inhibited Nod-like receptor protein 3 inflammasomes activation and suppressed diabetes-accelerated atherosclerosis in apoE−/− mice," *Bio-medicine & Pharmacotherapy*, vol. 119, article 109410, 2019.

[95] T. A. Zelniker, S. D. Wiviott, I. Raz et al., "SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials," *Lancet*, vol. 393, no. 10166, pp. 31–39, 2019.

[96] D. Kawanami, K. Matoba, Y. Takeda et al., "SGLT2 inhibitors as a therapeutic option for diabetic nephropathy," *International Journal of Molecular Sciences*, vol. 18, no. 5, p. 1083, 2017.

[97] V. Perkovic, M. J. Jardine, B. Neal et al., "Canagliflozin and renal outcomes in type 2 diabetes and nephropathy," *The New England Journal of Medicine*, vol. 380, no. 24, pp. 2295–2306, 2019.

[98] F. Prattichizzo, P. de Candia, and A. Ceriello, "Diabetes and kidney disease: emphasis on treatment with SGLT-2 inhibitors and GLP-1 receptor agonists," *Metabolism*, vol. 120, article 154799, 2021.

[99] S. R. Kim, S. G. Lee, S. H. Kim et al., "SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease," *Nature Communications*, vol. 11, no. 1, p. 2127, 2020.

[100] E. Benetti, R. Mastrococca, G. Vitarelli et al., "Empagliflozin protects against diet-induced NLRP-3 inflammasome activation and lipid accumulation," *The Journal of Pharmacology and Experimental Therapeutics*, vol. 359, no. 1, pp. 45–53, 2016.

[101] H. Hussain, G. Abbas, I. R. Green, and I. Ali, "Dipeptidyl peptidase IV inhibitors as a potential target for diabetes: patent review (2015-2018)," *Expert Opinion on Therapeutic Patents*, vol. 29, no. 7, pp. 535–553, 2019.

[102] Y. G. Kim, S. H. Min, S. Hahn, T. J. Oh, K. S. Park, and Y. M. Cho, "Efficacy and safety of the addition of a dipeptidyl peptidase-4 inhibitor to insulin therapy in patients with type 2 diabetes: a systematic review and meta-analysis," *Diabetes Research and Clinical Practice*, vol. 116, pp. 86–95, 2016.

[103] N. Wang, T. Yang, J. Li, and X. Zhang, "Dipeptidyl peptidase-4 inhibitors as add-on therapy to insulin in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials," *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, vol. 12, pp. 1513–1526, 2019.

[104] S. H. Min, J. H. Yoon, S. Hahn, and Y. M. Cho, "Efficacy and safety of combination therapy with an α-glucosidase inhibitor and a dipeptidyl peptidase-4 inhibitor in patients with type 2 diabetes mellitus: a systematic review with meta-analysis," *Journal of diabetes investigation*, vol. 9, no. 4, pp. 893–902, 2018.

[105] Y. Birnbaum, M. Bajaj, H. C. Yang, and Y. Ye, "Combined SGLT2 and DPP4 inhibition reduces the activation of the Nlrp3/ASC inflammasome and attenuates the development of diabetic nephropathy in mice with type 2 diabetes," *Cardiovascular Drugs and Therapy*, vol. 32, no. 2, pp. 135–145, 2018.

[106] Y. Birnbaum, M. Bajaj, J. Qian, and Y. Ye, "Dipeptidyl peptidase-4 inhibition by saxagliptin prevents inflammation and renal injury by targeting the Nlrp3/ASC inflammasome," *BMJ Open Diabetes Research & Care*, vol. 4, no. 1, article e000227, 2016.

[107] D. S. Ghorpade, L. Ozcan, Z. Zheng et al., "Hepatocyte-secreted DPP4 in obesity promotes adipose inflammation and insulin resistance," *Nature*, vol. 555, no. 7698, pp. 673–677, 2018.

[108] E. M. Varin, E. E. Mulvihill, J. L. Beaudy et al., "Circulating levels of soluble dipeptidyl peptidase-4 are dissociated from inflammation and induced by enzymatic DPP4 inhibition," *Cell Metabolism*, vol. 29, no. 2, pp. 320–334.e5, 2019.

[109] in LiverTox, *clinical and research information on drug-induced liver injury*, Bethesda (MD), 2012.

[110] M. Olcum, B. Tastan, I. Ercan, I. B. Eltutan, and S. Genc, "Inhibitory effects of phytochemicals on NLRP3 inflammasome activation: a review," *Phytomedicine*, vol. 75, article 153238, 2020.

[111] A. Y. Berman, R. A. Motchen, M. Y. Wiesenfeld, and M. K. Holz, "The therapeutic potential of resveratrol: a review of clinical trials," *NPJ precision oncology*, vol. 1, no. 1, 2017.
[112] E. Öztürk, A. K. K. Arslan, M. B. Yerer, and A. Bishayee, “Resveratrol and diabetes: a critical review of clinical studies,” *Biomedicine & Pharmacotherapy*, vol. 95, pp. 230–234, 2017.

[113] C. C. Chang, C. Y. Chang, J. P. Huang, and L. M. Hung, “Effect of resveratrol on oxidative and inflammatory stress in liver and spleen of streptozotocin-induced type 1 diabetic rats,” *The Chinese Journal of Physiology*, vol. 55, no. 3, pp. 192–201, 2012.

[114] P. Brasley, G. A. Molnár, M. Mohás et al., “Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients,” *The British Journal of Nutrition*, vol. 106, no. 3, pp. 383–389, 2011.

[115] M. Kitada and D. Koya, “Renal protective effects of resveratrol,” *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 568093, 7 pages, 2013.

[116] J. F. Saldanha, O. Leal Vde, P. Stenvinkel, J. C. Carraro-Eduardo, and D. Mafra, “Resveratrol: why is it a promising therapy for chronic kidney disease patients?” *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 963217, 6 pages, 2013.

[117] Y. P. Chang, S. M. Ka, W. H. Hsu et al., “Resveratrol inhibits NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy,” *Journal of Cellular Physiology*, vol. 230, no. 7, pp. 1567–1579, 2015.

[118] Y. D. Xiao, Y. Y. Huang, H. X. Wang et al., “Thioredoxin-interacting protein mediates NLRP3 inflammasome activation involved in the susceptibility to ischemic acute kidney injury in diabetes,” *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 2386068, 17 pages, 2016.

[119] L. A. Zenewicz, "IL-22: there is a gap in our knowledge," *Immunohorizons*, vol. 2, no. 6, pp. 198–207, 2018.

[120] G. Asadikaram, H. Akbari, Z. Safi et al., “Downregulation of IL-22 can be considered as a risk factor for onset of type 2 diabetes,” *Journal of Cellular Biochemistry*, vol. 119, no. 11, pp. 9254–9260, 2018.

[121] M. Cheng, Y. Zhou, B. Wang et al., "IL-22: a potential mediator of associations between urinary polyyclic aromatic hydrocarbon metabolites with fasting plasma glucose and type 2 diabetes," *Journal of Hazardous Materials*, vol. 401, article 123278, 2021.

[122] S. Wang, Y. Li, J. Fan et al., "Interleukin-22 ameliorated renal injury and fibrosis in diabetic nephropathy through inhibition of NLRP3 inflammasome activation," *Cell Death & Disease*, vol. 8, no. 7, article e2937, 2017.

[123] Y. Shen, W. Chen, L. Han et al., "VEGF-B antibody and interleukin-22 fusion protein ameliorates diabetic nephropathy through inhibiting lipid accumulation and inflammatory responses," *Acta Pharmacaceuta Sinica B*, vol. 11, no. 1, pp. 127–142, 2021.

[124] C. Y. Tan, Q. Weiier, Y. Zhang, A. J. Cox, D. J. Kelly, and R. G. Langham, "Thioredoxin-interacting protein: a potential therapeutic target for treatment of progressive fibrosis in diabetic nephropathy," *Nephron*, vol. 129, no. 2, pp. 109–127, 2015.

[125] Z. Z. Tang, Y. M. Zhang, T. Zheng, T. T. Huang, T. F. Ma, and Y. W. Liu, "Sarsasapogenin alleviates diabetic nephropathy through suppression of chronic inflammation by down-regulating PAR-1: In vivo and in vitro study," *Phytomedicine*, vol. 78, article 153314, 2020.

[126] Y. W. Liu, Y. C. Hao, Y. J. Chen et al., "Protective effects of sarsasapogenin against early stage of diabetic nephropathy in rats," *Phytotherapy Research*, vol. 33, no. 9, p. 2470, 2019.