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REVIEW

Uric acid and inflammation in kidney disease

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Jung SW, Kim SM, Kim YG, Lee SH, Moon JY. Uric acid and inflammation in kidney disease. *Am J Physiol Renal Physiol* 318: F1327–F1340, 2020. First published March 30, 2020; doi:10.1152/ajprenal.00272.2019.—Asymptomatic hyperuricemia is frequently observed in patients with kidney disease. Although a substantial number of epidemiologic studies have suggested that an elevated uric acid level plays a causative role in the development and progression of kidney disease, whether hyperuricemia is simply a result of decreased renal excretion of uric acid or is a contributor to kidney disease remains a matter of debate. Over the last two decades, multiple experimental studies have expanded the knowledge of the biological effects of uric acid beyond its role in gout. In particular, uric acid induces immune system activation and alters the characteristics of resident kidney cells, such as tubular epithelial cells, endothelial cells, and vascular smooth muscle cells, toward a proinflammatory and profibrotic state. These findings have led to an increased awareness of uric acid as a potential and modifiable risk factor in kidney disease. Here, we discuss the effects of uric acid on the immune system and subsequently review the effects of uric acid on the kidneys mainly in the context of inflammation.

immune system; inflammation; kidney disease; uric acid

INTRODUCTION

Uric acid is the end product of purine degradation in humans, but it is further metabolized to allantoin by uricase in other mammals. The level of uric acid in humans (~6.0 mg/dL) is much higher than that in other mammals (<2.0 mg/dL) because of the absence of uricase (49). Loss of the uricase gene in humans could be a result of evolution since uric acid is a powerful antioxidant that accounts for up to 60% of the antioxidant capacity of human plasma (160). Uric acid exerts antioxidant effects by scavenging a free radical and chelating a metal ion (4, 34). Indeed, uric acid is known to exert a protective effect against neurodegenerative diseases such as Parkinson's and Alzheimer's disease (72). The high metabolic rate of the human brain makes it vulnerable to oxidative stress, potentially suggesting that the human body is willing to pay a premium for a potent endogenous antioxidant.

This advantageous feature of uric acid is limited by the fact that it acts as an antioxidant only in the hydrophilic environment of biological fluids, particularly in the presence of ascorbic acid (125). In modern society, an elevated uric acid level seems to be a disadvantageous inheritance. Since Garrod discovered that hyperuricemia is the cause of gout in the 19th century, the deleterious effects of uric acid on cardiovascular and kidney disease have been continuously documented (14, 45, 145).

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Hyperuricemia is defined when the serum uric acid level is >6.8 mg/dL, at which point uric acid reaches saturation at physiological temperature and pH (77). Although an elevated uric acid level is a key factor for monosodium urate (MSU) crystal formation, urate solubility is also influenced by temperature, pH, and various ion concentrations as well as serum, synovial fluid, and cartilage contents (16, 77, 84). This variety of factors involved in MSU crystallization explains why only a minority (~0.5–4.9% annually) of individuals with hyperuricemia develop gout (13). Because hyperuricemia in people without gout does not cause any symptoms and appears to be inert, asymptomatic hyperuricemia had not drawn much attention by the medical community for a few decades. Such asymptomatic hyperuricemia is frequently observed in patients with kidney impairment and thought to be merely a result of decreased renal clearance.

This viewpoint has been challenged since the 2000s, when studies demonstrated that an elevated serum uric acid level is an independent risk factor for kidney function decline in the general population (24, 45, 106, 152). Moreover, in subjects with diabetes mellitus (DM) or established chronic kidney disease (CKD), hyperuricemia was significantly associated with new-onset microalbuminuria or progression of kidney disease (17, 42, 47, 142). Experimentally, oxonic acid-induced hyperuricemia in normal and remnant kidney rats exacerbated the decline in glomerular filtration rate (GFR) and albuminuria in association with various renal damages, such as glomerular hypertrophy, arteriolopathy, and tubulointerstitial nephritis (5, 56, 88, 101, 123). These findings led to a reappraisal of the role

of uric acid from an innocent bystander toward a potentially modifiable risk factor for kidney disease.

Uric acid acts as a danger signal and is capable of eliciting immune and inflammatory reactions at clinically relevant concentrations (62, 86, 127, 156, 162). Hyperuricemia has also been found to trigger or potentiate an inflammatory process in healthy and diseased animal kidneys (56, 87, 89), which could explain worsened kidney outcomes in patients with hyperuricemia. In this review, we will highlight the mechanism by which uric acid activates the immune system and the role of uric acid in inflammation, which is a major biological process in various kidney diseases.

URIC ACID PRODUCTION AND HANDLING

Hyperuricemia is a consequence of overproduction or underexcretion of uric acid or a combination of both processes. The content of urate in the human diet is very low. Most uric acid is endogenously generated primarily in the liver and, to a lesser extent, in the small intestine. The endogenous production of uric acid is affected by the dietary intake of purine, de novo biosynthesis of purine bases, and degradation and recycling of corresponding nucleotides (78). Fructose also leads to the generation of uric acid when ATP is consumed during fructose metabolism. Fructose intake has particularly increased in modern society because of the increased consumption of table sugar (a disaccharide of fructose and glucose) and high-fructose corn syrup (a mixture of fructose and glucose). After its entry into a cell, fructose is converted to fructose-1-phosphate by fructokinase using ATP as the phosphate donor (48). This process leads to the generation of ADP, which is further degraded into inosine monophosphate, hypoxanthine, xanthine, and uric acid. Since these pathways are not regulated by negative feedback, the metabolism of fructose continuously leads to ATP depletion and uric acid accumulation inside cells (48).

The final purine degradation pathway in humans is facilitated by the enzyme xanthine oxidoreductase, which catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid. Xanthine oxidoreductase is present as xanthine dehydrogenase (XDH) and xanthine oxidase (XO), which are two interconvertible forms with different functions related to the transfer of electrons: XDH preferentially uses NAD^+ and produces the stable compound NADH, whereas XO uses O_2 and generates superoxide anion ($O_2^{\cdot -}$) and H_2O_2 (90). Because of this trait of XO, the production of uric acid is coupled with the production of reactive oxygen species (ROS). XDH and XO also differ in their expression patterns: XDH is constitutively expressed, whereas XO is generated by the posttranslational modification of XDH in the setting of hypoxia and inflammation (90). In cases of cell damage, many nucleotides are broken down or released, and their purine bases are subsequently degraded to uric acid with the concomitant generation of ROS by increased activity of XO (44). However, uric acid cannot be considered merely an innocuous coproduct of XO. Uric acid induces oxidative stress via NADPH oxidase activation (120, 126), renin-angiotensin system (RAS) stimulation (20), and mitochondrial dysfunction (11, 62). Importantly, oxidative stress exhibits an interdependent relationship with inflammation in many pathological conditions, including kidney disease (6, 9, 32).

Impaired renal excretion of uric acid is a principal cause of persistent hyperuricemia in ~90% of individuals with this condition (138). In healthy individuals, 60–75% of uric acid is eliminated by the kidneys and the rest is mostly cleared in the small intestine, where it is broken down by gut bacteria. In the kidneys, ~10% of uric acid filtered from the glomeruli is ultimately excreted into the urine, presumably after the following actions in the proximal tubules: *1*) nearly all filtered uric acid is reabsorbed in the S1 segment; *2*) then, 45–50% of the reabsorbed uric acid is secreted in the S1 and S2 segments; and *3*) finally, secreted uric acid is reabsorbed again in the S3 segment (10, 138). In these processes, urate transporter 1 (URAT1), organ anion transporter (OAT)4, and OAT10 in the apical membrane of proximal tubule cells mediate the reabsorption of uric acid into cells, whereas glucose transporter 9 (GLUT9) isoform 1 in the basolateral membrane of these cells is involved in the efflux of uric acid into the interstitium (132, 157). Thus, OAT inhibitors, such as probenecid, increase urinary uric acid excretion, whereas hyperinsulinemia stimulates the reabsorption of uric acid by increasing URAT1 activity (140).

Other cells also take up uric acid through membrane-associated transporters. OAT inhibitors have been shown to decrease the levels of uric acid-induced inflammatory mediators in macrophages (62), endothelial cells (57), and vascular smooth muscle cells (VSMCs) (55). These findings indicate the presence of transporters in these cells. Some studies have been able to detect specific transporters, such as voltage-driven URAT1 and ATP-binding cassette transporter G2 in human umbilical vein endothelial cells (93) and URAT1 in VSMCs (114).

HOW DOES URIC ACID ACTIVATE THE IMMUNE RESPONSE?

Effects of Uric Acid on Innate Immune Cells

The typical example of the proinflammatory effect of uric acid is gout, an inflammatory arthritis caused by the intra-articular deposition of MSU crystals. The inflammatory nature of gout is clearly demonstrated by an increased level of white blood cells in the synovial fluid from patients who experience an acute attack of gout. How MSU crystals actually induce the inflammatory reaction was unknown until 2006, when Martinon et al. (86) discovered that uric acid crystals cause gout by activating the NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome. NLRP3 acts as a cytosolic sensor in innate immune cells. Upon its activation by specific danger stimuli, NLRP3 begins to oligomerize and recruit apoptosis-associated speck-like protein containing a CARD (ASC) and procaspase-1 (85). The assembly of NLRP3 (sensor), ASC (adaptor), and procaspase-1 (effector) forms the NLRP3 inflammasome. In this cytoplasmic multiprotein complex, procaspase-1 is cleaved into its active form, caspase-1, which then converts pro-IL-1β and pro-IL-18 into the biologically active cytokines IL-1β and IL-18, respectively (85). An vitro study has shown that MSU crystals activate intracellular NLRP3 inflammasomes in cultured monocytes and mouse peritoneal macrophages and then induce IL-1β and IL-18 production (86).

Soluble uric acid also activates the NLRP3 inflammasome in macrophages and promotes inflammation according to the results of our research (62). Thus, soluble uric acid has the

potential to be included as an additional inflammatory trigger along with MSU crystals. In our observations, soluble uric acid induced the assembly of NLRP3 and ASC in macrophages (THP-1 cell line) and then increased the production of IL-1β. This effect of soluble uric acid on macrophages was observed at uric acid concentrations as low as 5 mg/dL and was abolished by probenecid and NLRP3 siRNA. Similarly, another study reported that soluble uric acid also stimulated IL-1β secretion from bone marrow-derived macrophages in a NLRP3-dependent pathway under hypoxia (11). Importantly, uric acid-induced mitochondrial ROS were responsible for activation of the NLRP3 inflammasome in both studies. Mitochondria-targeted antioxidants attenuated uric acid-induced NLRP3 activation and IL-1β secretion. These results indicate that soluble uric acid, similar to its crystal form, also acts as an endogenous damage-associated molecular pattern (DAMP) and activates the NLRP3 inflammasome in macrophages.

Kono et al. (68) clearly demonstrated these features of soluble uric acid acting as a DAMP in a mouse study using necrotic lung homogenates. Intraperitoneal injection of necrotic lung tissue collected from uricase transgenic mice, which contained a reduced pool of intracellular uric acid, elicited lower neutrophil and monocyte counts in the peritoneal cavity than injection of tissue from wild-type mice. This finding indicates that uric acid is an essential endogenous trigger for the innate immune cell response induced by cell death. Consideration of all of these results leads to the conclusion that both crystalized uric acid and soluble uric acid are naturally produced danger molecules that send alarm signals via the NLRP3 inflammasome in innate immune cells.

Effects of Uric Acid From Innate to Adaptive Immune Cells

Uric acid modulates the adaptive immune system via innate immune cells, mostly involving dendritic cells (Fig. 1) (19, 69, 127). This feature is well exemplified by the synergistic effect of uric acid on $CD8^+$ T cell priming, during which uric acid induces the expression of costimulatory molecules in dendritic cells. Shi et al. (127) purified low-molecular-weight fractions from ultraviolet-treated 3T3 cells and liver cells by high-performance liquid chromatography and found that these fractions markedly enhanced the cytotoxic T lymphocyte response. The component of the low-molecular-weight fractions not only was degraded by uricase but also exhibited a mass spectrum that matched that of uric acid. Furthermore, the investigators found that uric acid stimulated dendritic cells and macrophages to express the costimulatory molecules CD80 and CD86, thereby enhancing the $CD8^+$ T cell immune response.

In accordance with this experiment, Wang et al. (150) reported that dendritic cell-based antitumor vaccines mixed with uric acid resulted in less tumor growth than those without uric acid in mice challenged with tumor cells. These researchers found that uric acid enhanced the antitumor activity of dendritic cell-based vaccines through $CD8^+$ T cell and natural killer cell activation. These findings indicate that uric acid plays a contributory role in cytotoxic T lymphocyte activation by activating antigen-presenting cells, such as dendritic cells.

Uric acid is also indirectly involved in allergic inflammation. Kool et al. (69) demonstrated that uric acid induced inflammatory dendritic cell ($Ly6C^+CD11b^+$) activation and thereby promoted the T helper (Th)2 cell-mediated immune response responsible for allergic inflammation. The uric acid concentration in bronchoalveolar lavages of mice and humans was significantly increased by intranasal injection or inhalation of allergens (house dust mite, rye, or birch). The number of inflammatory dendritic cells in the draining lymph nodes was significantly reduced by coadministration of allergen and uricase. This effect is associated with a dampened Th2 cell immune response, as represented by decreases in the eosinophil count in bronchoalveolar lavage fluid and a reduction in the pro-Th2 cell cytokine concentration in lung homogenates. The molecular process by which uric acid stimulates a subset of dendritic cells ($Ly6C^+CD11b^+$) involves spleen tyrosine kinase and phosphatidylinositol 3-kinase-δ (signaling downstream of Syk), not NLRP3, ASC, or the IL-1 receptor axis.

Another effect of uric acid on the adaptive immune system includes the Th17 polarization of $CD4^+$ T cells (19). Naïve $CD4^+$ T cells differentiated toward the Th17 lineage when cocultured with uric acid-treated dendritic cells, as evidenced by an increased production of IL-17A in the supernatant. The differentiation of $CD4^+$ T cells toward the Th17 lineage was mediated by IL-1α/β and IL-18, which were produced by uric acid-induced NRLP3 inflammasome activation within dendritic cells in the presence of NF-κB activator (which primes inflammasomes and produces IL-1 and IL-18 precursors).

In addition, some studies have shown that uric acid directly activates T cells in an antigen-independent manner. An experiment using human T cells isolated from healthy human blood samples revealed that uric acid not only increased CD25 expression and NRLP3 inflammasome-dependent IL-1β secretion but also induced T cell proliferation (27–29, 151). When these observations are taken together, it becomes evident that uric acid alarms the immune system by stimulating dendritic cells, macrophages, and T cells (Fig. 1). Given that the biological consequence of immune system activation is inflammation, uric acid clearly contributes to inflammation through immune cell activation. Moreover, the proinflammatory nature of uric acid is currently recognized to impact not only immune cells but also nonimmune cells. These proinflammatory effects of uric acid on the kidneys are described in the next section.

HOW DOES URIC ACID ACTIVATE THE INFLAMMATORY RESPONSE IN THE KIDNEYS?

The kidneys harbor several classes of resident immune cells, such as dendritic cells, macrophages, and lymphocytes, although these cells account for a small population in normal kidneys (144). Upon kidney injury, the inflammatory response is boosted by the concerted interaction of these immune cells with endothelial, mesangial, and tubular epithelial cells (TECs), leading to the recruitment of circulating immune cells. Here, we describe the potential mechanisms by which uric acid is implicated in an inflammatory process according to the kidney compartments (vasculature, glomerulus, and tubulointerstitial area) with a focus on renal parenchymal cells.

Vascular Injury

The kidneys maintain constant renal blood flow and GFR by fine tuning the resistance of afferent and efferent arterioles in response to changes in blood pressure and the tubular fluid flow

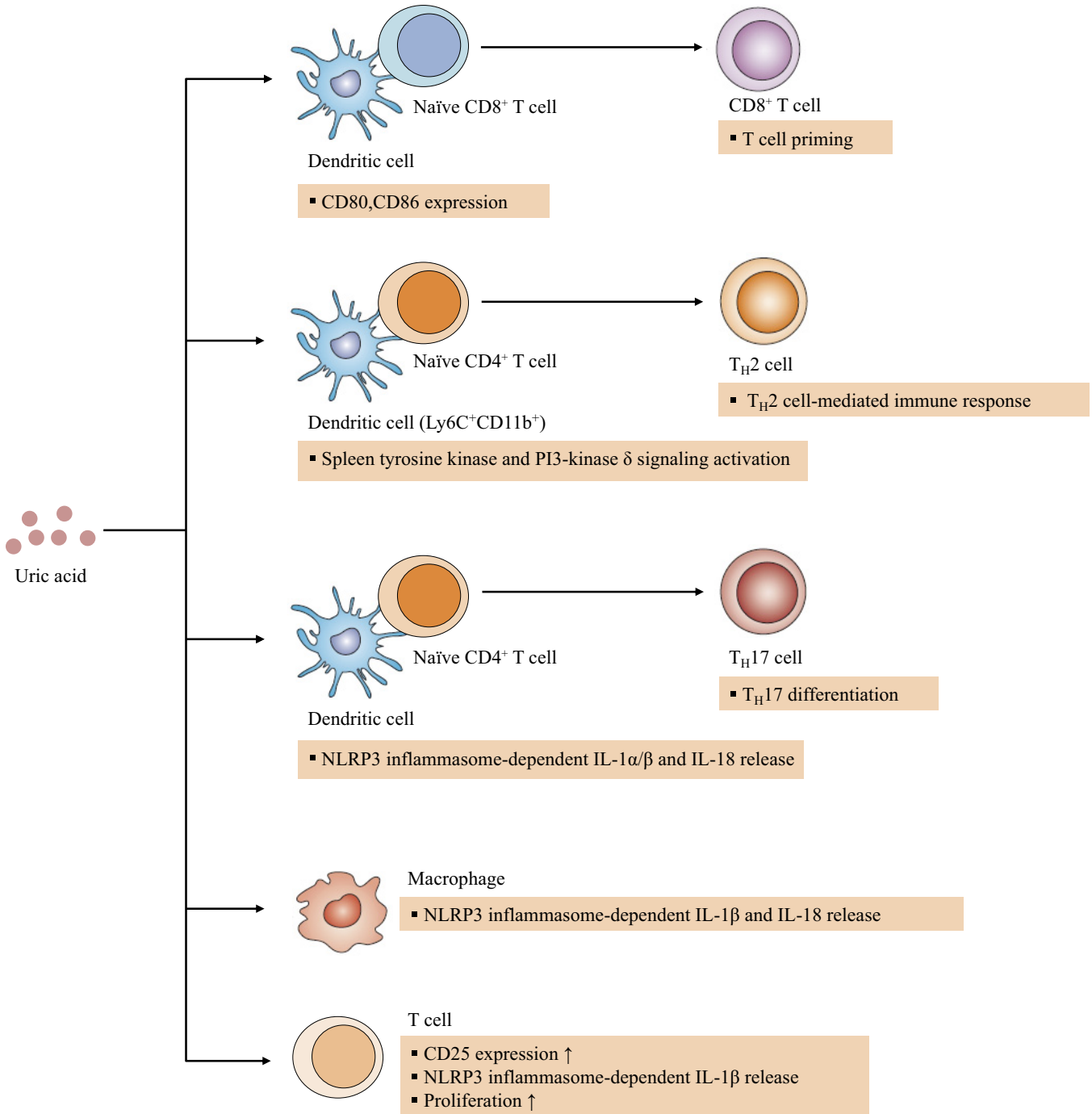

Fig. 1. Proposed mechanism by which uric acid activates the immune system. Uric acid alarms the innate immune system by primarily activating dendritic cells and macrophages. In the cytosol of dendritic cells and macrophages, the NOD-, LRR-, and pyrin domain-containing 3 (NLRP3) inflammasome is assembled and produces IL-1β and IL-18 in response to uric acid. Moreover, uric acid indirectly modulates the adaptive immune system through activated dendritic cells, which manifests as enhanced cytotoxic T cell activity, T helper (Th)2 cell-mediated immune response, and differentiation of naïve T cells toward Th17 cells. Some studies have demonstrated that uric acid also directly activates T cells. PI3-kinase, phosphatidylinositol 3-kinase.

rate. Uric acid alters this physiological balance by inducing vasculopathy characterized by endothelial dysfunction, medial wall thickening, and macrophage infiltration into the vascular wall (56, 60, 87, 88, 121, 123), particularly affecting afferent arterioles.

Renal hemodynamic studies in humans have shown that serum uric acid levels are positively associated with increased renal vascular resistance and decreased renal blood flow (66, 91). This finding was reproduced in elegant micropuncture studies of normal and remnant kidney models, in which hyperuricemia was demonstrated to increase the resistance of both afferent and efferent arterioles, with a greater increase in afferent resistance than in efferent resistance (123). This alteration was coupled with decreased single-nephron GFR result-

ing from a reduced glomerular plasma flow rate and ultrafiltration coefficient (122, 123).

Uric acid-induced vasculopathy could be explained by the direct effects of uric acid on endothelial cells and VSMCs. In in vitro studies, uric acid-treated endothelial cells displayed decreased proliferation, reduced nitric oxide release, and increased adhesion to monocytes, whereas uric acid-treated VSMCs showed increased proliferation and migration (57, 76).

RAS activation is thought to be one of the major causes of vasculopathy caused by uric acid. Hyperuricemia increased renin expression in juxtaglomerular cells and (pro)renin receptor expression in endothelial cells while decreasing nitric oxide synthase-1 expression in the macula densa (87, 159). Importantly, the angiotensin-converting enzyme inhibitor (enalapril) and the angiotensin receptor blocker (losartan) prevented the development of preglomerular arteriolopathy in oxonic acid-induced hyperuricemic rats independent of blood pressure-lowering effects (88).

Another key mechanism regarding the effects of uric acid on endothelial cells and VSMCs lies in its proinflammatory nature. Uric acid induces the expression or release of high-mobility group box 1 (HMGB1) and inflammatory cytokines and chemokines, including C-reactive protein, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1), in endothelial cells and VSMCs (12, 57, 76, 115). Uric acid also increases the expression of adhesion molecules (ICAM-1 and VCAM-1) in endothelial cells, facilitating the adhesion of macrophages (12, 76). Specifically, the following pathways and molecules have been implicated in the uric acid-induced proinflammatory changes in endothelial cells and VSMCs: MAPKs (p38 and ERK 1/2), NF-κB, angiotensin II, Toll-like receptor (TLR)2, TLR4, (pro)renin receptor, and cyclooxygenase-2 (Table 1) (54, 56, 57, 71, 76, 107, 115, 159). Taken together, these results demonstrate that uric acid plays a contributory role in the development of vascular inflammation, further promoting endothelial dysfunction and VSMC proliferation.

Glomerular Injury

A cross-sectional study of human renal biopsy specimens revealed that hyperuricemia was an independent risk factor for segmental glomerulosclerosis (30). In rat kidneys, hyperuricemia was also associated with glomerular hypertrophy, mostly attributed to mesangial cell proliferation, and glomerulosclerosis (101).

In line with these findings, in vitro studies found that uric acid directly induced rat mesangial cell proliferation (75, 163). The mechanisms of uric acid-induced mesangial cell proliferation involve prostaglandin E synthase-1-derived prostaglandin E_2 (75), a potent mediator of inflammation, and NADPH oxidase-originated ROS (163). Uric acid also induces the phenotypic alteration of mesangial cells into antigen-presenting cells. Soluble uric acid enhanced the expression of NLRP3, IL-1β, human leukocyte antigen DR isotype, and CD40 in human mesangial cells in a TLR4-dependent manner (156). In addition, uric acid crystals stimulated ICAM-1 expression in human mesangial cells and thus promoted cell-cell adhesion between human mesangial cells and monocytes (81).

Regarding the direct effect of uric acid on podocyte injury, Kawamorita et al. (59) demonstrated that topiroxostat, an XO inhibitor, attenuated podocyte loss and decreased proteinuria by lowering oxidative stress and the tissue uric acid concentration in puromycin aminonucleoside-induced nephrotic syndrome. Similarly, in hyperuricemic murine models, hyperuricemia caused podocyte damage, as demonstrated by a decrease in podocin and an increase in desmin (5, 116). Although these

Table 1. *Uric acid-induced inflammation in nonimmune cells*

Affected Cells	Effect	Mediator	Reference
Endothelial cells			
Human umbilical vein endothelial cells	CRP	p38, ERK1/2	57
	HMGB1	TLR4, MEK/ERK pathway	115
	Von Willebrand factor, angiopoietin 2, IL-8 release	TLR4, TLR2	71
	MCP-1, IL-8, VCAM-1, ICAM-1, monocyte adhesion	NF-κB	76
	HMGB1, IL-6, TNF-α, VCAM-1, ICAM-1	RAGE, NF-κB	12
	IL-1β, IL-6, ICAM-1, monocyte adhesion	(Pro)renin receptor, angiotensin II, AT_1/AT_2 receptors, ERK1/2	159
Vascular smooth muscle cells			
Human vascular smooth muscle cells	CRP	p38, ERK1/2	57
Primary rat aortic vascular smooth muscle cells	MCP-1	p38, ERK1/2, COX-2, oxidative stress	54
	COX-2	p38, ERK1/2, angiotensin II	107
Rat vascular smooth muscle cells	Thromboxane A_2	COX-2	56
Renal tubular epithelial cells			
HK-2	HMGB1, CXCL12	NF-κB	62
	Soluble ICAM-1		70
NRK-52E	TNF-α, MCP-1, RANTES	NF-κB	162
Mesangial cells			
HBZY-1	Prostaglandin E_2	COX-2, mPGES-1	75
Primary human mesangial cells	NLRP3, IL-1β, HLA-DR, CD40	TLR4	156
Human mesangial cell line	ICAM-1	TLR2, TLR4, ASC, p38	81

HK-2 denotes the human renal proximal tubular epithelial cell line, whereas NRK-52E denotes the rat proximal tubular cell line. HBZY-1 is a mouse mesangial cell line. ASC, apoptosis-associated speck-like protein containing a CARD; AT_1/AT_2 receptors, angiotensin II type 1 and type 2 receptors; COX-2, cyclooxygenase-2; CRP, C-reactive protein; HLA-DR, human leukocyte antigen DR isotype; HMGB1, high-mobility group box-1; MCP-1, monocyte chemoattractant protein-1; mPGES-1, microsomal prostaglandin E synthase-1; RAGE, receptor for advanced glycation end products; RANTES, regulated upon activation, normal T cell expressed and secreted; TLR, Toll-like receptor.

observations provide a tantalizing glimpse into how uric acid affects glomeruli, it warrants further research to better understand its role in this structure.

Tubulointerstitial Inflammation/Fibrosis

Autopsy studies of patients with gout have revealed that urate crystals are deposited in the kidney tubule and interstitium, where they induce inflammation with giant cell reaction (7, 135). This condition has historically been called gouty nephropathy, marked by interstitial inflammation and inflammatory cell infiltration. However, the focal deposition of urate crystals does not sufficiently explain the diffuse interstitial inflammation. In human kidney biopsy studies, serum uric acid levels have been demonstrated to be positively associated with interstitial inflammation/fibrosis and tubular atrophy independent of crystal deposition (30, 100, 161). These findings suggest that soluble uric acid is responsible for the development of tubulointerstitial damage.

The blood supply to the tubulointerstitial area may be reduced by uric acid-induced vasculopathy, potentially causing ischemic damage to this area. More certainly, substantial evidence indicates that uric acid induces these histologic changes by directly affecting TECs (Table 1) (62, 118, 162). We and others have demonstrated that uric acid exerts proinflammatory and profibrotic effects on TECs, as shown by increases in TNF-α, MCP-1, regulated upon activation, normal T cell expressed and secreted (RANTES), and α-smooth muscle actin and a decrease in E-cadherin in response to uric acid in a rat proximal tubular cell line (NRK-52E) (61, 118, 162). This proinflammatory effect of uric acid on TECs works through HMGB1 release and NF-κB signaling activation (62).

Intriguingly, the migratory activity and M1 polarization of macrophages were enhanced by coculture with uric acid-treated TECs (62, 162). This interaction is well explained by the observations that uric acid induces the expression of soluble ICAM-1 and proinflammatory cytokines and chemokines in TECs (62, 70, 162). In accordance with these in vitro findings, macrophage and lymphocyte infiltration was exacerbated by hyperuricemia and lessened by administration of the XO inhibitor in several kidney disease models, including the remnant kidney model (5/6 nephrectomy), diabetic nephropathy, and cyclosporine- and adenine-induced nephropathy (51, 62, 89, 109, 123). Cellular communication among tubular and immune cells in the tubulointerstitium plays a pivotal role in the progression of CKD. In this context, increasing evidence indicates that uric acid expedites the interplay among these cells toward sustained inflammation and progression to tubulointerstitial fibrosis.

URIC ACID AND INFLAMMATION IN KIDNEY DISEASE

Inflammation is a main pathophysiological mechanism in acute kidney injury (AKI) and CKD, including metabolic diseases such as diabetic kidney disease (DKD). Although the inflammatory response to injury is initially aimed at tissue repair and recovery, prolonged and uncoordinated inflammation promotes glomerulosclerosis and tubulointerstitial fibrosis. In this context, we discuss the effects of uric acid on kidney disease in this section.

Uric Acid and Inflammation in DKD

DKD, which affects ~20–40% of people with DM worldwide, is the leading cause of CKD (21). The optimization of glycemic control is essential to preventing the development of DKD (103, 128); however, it is not sufficient to alter the overall clinical course of advanced DKD (2, 153). This gap, which is not explained solely by hyperglycemic insult, can be attributed to additional pathophysiological factors in DKD, including inflammation. Transcriptome analysis of human diabetic kidney biopsies revealed that inflammation-related pathways were highly enriched in the tubulointerstitial compartment (154). This inflammatory nature of DKD is characterized by interstitial infiltration of macrophages and activated lymphocytes in both human and animal diabetic kidneys (18, 95, 104).

We and another group have demonstrated that lowering uric acid levels by XO inhibitors ameliorates macrophage infiltration as well as tubulointerstitial inflammation in diabetic murine models, such as high fructose diet-fed Otsuka Long-Evans Tokushima fatty rats, streptozotocin-induced Sprague-Dawley rats, and *db/db* mice, independent of glycemic control (62, 70, 74). Given that kidney fibrosis is an inevitable consequence of sustained inflammation, fibrosis markers (transforming growth factor-β, collagen, and α-smooth muscle actin) are also improved by the use of XO inhibitors in murine models of DKD (61, 62, 70). These findings are in agreement with the aforementioned in vitro effects of uric acid, which are uric acid-induced macrophage activation and transformation of renal TECs toward the proinflammatory and profibrotic cell phenotypes.

Since intrarenal macrophage accumulation is closely correlated with a rapid loss of kidney function in human and mouse diabetic kidneys (18, 104), these experimental results could be translated into the clinical finding that hyperuricemia is associated with GFR decline in subjects with type 1 or 2 DM who have preserved kidney function (22, 31, 63, 164). An interesting finding in the majority of those studies is that even high-normal levels of serum uric acid (greater than ~5.0–5.5 mg/dL) conferred a risk for kidney function deterioration.

Despite this evidence, a consensus regarding the treatment of asymptomatic hyperuricemia has not yet been reached because of the inconsistent results of clinical trials of uric acid-lowering treatments (Table 2) (65, 67, 97, 130). The Preventing Early Renal Function Loss in Diabetes allopurinol study (83) is a 3-yr randomized clinical trial of allopurinol in patients with type 1 diabetes who had kidney disease on the basis of albuminuria or normoalbuminuria with rapid GFR decline ($\geq$3.0 mL/min/1.73 m^2 per year) (1). The main outcome of the study, which is a measured GFR change, will provide additional clues about the benefit of uric acid-lowering therapy in this population.

Uric Acid and Inflammation in AKI

AKI develops from various harmful stimuli, such as ischemia, nephrotoxic substances, and crystal formation. Regardless of the etiology, kidney damage follows a common cascade of injury characterized by TEC death and infiltrating immune cells, resulting in interstitial inflammation and subsequent fibrosis (15). Uric acid has been proposed to be involved in this

Table 2. *Effects of uric acid-lowering treatment in patients with diabetic kidney disease and chronic kidney disease*

Study Design	Comparison	Study Duration, months	Kidney Function (*P* Value)	Proteinuria (*P* Value)	Reference
Diabetic kidney disease					
Double-blind RCT	Allopurinol ($n = 20$) vs. placebo ($n = 20$)	4	↔	Beneficial (<0.05)	94
Double-blind RCT	Allopurinol ($n = 40$) vs. placebo ($n = 40$)	4	NA	Beneficial (<0.05)	36
Double-blind RCT	Febuxostat ($n = 39$) vs. placebo ($n = 37$)	6	↔	↔	8
Open-label RCT	Febuxostat ($n = 47$) vs. control ($n = 46$)	6	↔	↔	97
Double-blind RCT	Topiroxostat ($n = 43$) vs. placebo ($n = 22$)	7	Beneficial (0.03)	↔	148
Double-blind RCT	Allopurinol vs. placebo (total = 530)	36	Awaiting results	Awaiting results	83
Chronic kidney disease					
Double-blind RCT	Allopurinol ($n = 27$) vs. placebo ($n = 26$)	9	↔	↔	58
Single-blind RCT	Allopurinol ($n = 51$) vs. placebo ($n = 47$)	24	Beneficial (0.02)	↔	37
Post hoc analysis	Allopurinol ($n = 56$) vs. placebo ($n = 51$)	84	Beneficial (0.001)	NA	38
RCT	Allopurinol ($n = 25$) vs. control ($n = 26$)	12	↔	↔	131
Double-blind RCT	Febuxostat ($n = 45$) vs. placebo ($n = 48$)	6	Beneficial (0.05)	NA	130
Double-blind RCT	Febuxostat ($n = 219$) vs. placebo ($n = 222$)	27	↔	NA	65
Open-label RCT	Febuxostat ($n = 21$) vs. control ($n = 19$)	3	↔	Beneficial (0.04)	136
Double-blind RCT	Febuxostat ($n = 32$) vs. placebo ($n = 32$)	12	↔	NA	119
Double-blind RCT	Topiroxostat ($n = 62$) vs. placebo ($n = 60$)	5.5	↔	Beneficial (0.009)	41

n, number of patients. The outcomes, kidney function (estimated glomerular filtration rate or serum creatinine) and/or proteinuria, were compared between uric acid-lowering treatment and the placebo (control) in patients with diabetic kidney disease and chronic kidney disease. These outcomes are shown as no difference (↔) or beneficial in case of improvement with uric acid-lowering treatment. RCT, randomized controlled trial; NA, not available.

process via crystal-dependent and crystal-independent mechanisms (26, 40).

Acute urate nephropathy is a typical example of AKI caused by uric acid crystal deposition and usually occurs as a manifestation of tumor lysis syndrome. The destruction of a high tumor cell burden by chemotherapy induces the release of intracellular nucleotides, which are subsequently metabolized into uric acid by the liver. Accordingly, serum uric acid levels are markedly elevated, usually to levels of >12 mg/dL, and increased renal excretion of uric acid leads to its crystallization inside the tubular lumen. The formation of uric acid crystals causes tubular obstruction, and granulomatous inflammation with macrophage and T cell infiltration ensues (64).

Uric acid crystals also exert direct cytotoxicity to renal TECs. Specifically, cell death of renal TECs in response to MSU crystals involves necroptosis, not pyroptosis or apoptosis, as evidenced by the finding that necrostatin-1 reduced cell death caused by MSU crystals, whereas a pan-caspase inhibitor exerted no effect (98).

In addition to uric acid crystals, soluble uric acid is also adversely involved in experimental models of AKI. In a rat model of cisplatin-induced AKI, hyperuricemia, even at concentrations that do not promote intrarenal crystal deposition, exacerbated cisplatin-induced tubular injury and interstitial inflammation with increased macrophage infiltration and MCP-1 levels (117). Notably, a decrease in the uric acid level by recombinant urate oxidase (rasburicase) ameliorated tubular injury, interstitial inflammation with macrophage infiltration, and elevated MCP-1 levels.

Similarly, febuxostat treatment attenuated renal ischemia-reperfusion injury, as evidenced by less tubular injury and interstitial fibrosis, suppressed macrophage infiltration, and lowered MCP-1 and IL-1β mRNA levels compared with those achieved with vehicle treatment (143). The beneficial effect of febuxostat in this study was determined to be a result of decreased oxidative stress, thereby ameliorating endoplasmic reticulum stress and apoptotic and inflammatory signals. Since XO generates ROS together with uric acid, a decrease in XO-derived ROS production and/or intracellular uric acid contents mediated these beneficial effects.

Clinically, a meta-analysis of observational studies revealed that people with hyperuricemia showed higher incidence rates of AKI after percutaneous coronary intervention and contrast exposure than those without hyperuricemia (52, 158, 165). Furthermore, preoperative elevated serum uric acid levels have been associated with AKI development following cardiovascular surgery (50, 73). Regarding uric acid-lowering treatment, a meta-analysis of randomized controlled trials demonstrated that the prophylactic use of allopurinol may reduce the incidence of contrast-induced AKI in patients undergoing coronary angiography (82), although some studies did not find that allopurinol offered any benefits (35, 43). Collectively, this

evidence indicates that uric acid might exacerbate AKI even in the absence of crystal formation.

The tricky nature of uric acid is that low serum uric acid levels may also be deleterious for the kidneys. Typically, patients with renal hypouricemia due to mutations in URAT1 or GLUT9 have an increased incidence of acute nonmyoglobinuric kidney injury following exercise (23, 137), yet intratubular uric acid crystals are not found in most of these renal biopsies despite high renal uric acid excretion (110, 111). Although the pathogenesis is incompletely understood, one of the mechanisms involves impaired management of exercise-induced oxidative stress due to depletion of uric acid, leading to renal vasoconstriction and ischemia (99, 147). Although hereditary renal hypouricemia is a rare disease entity that may have limited generalizability to commonly encountered cases of hypouricemia, this unique disease provides a lesson that an appropriate level of uric acid may be necessary to properly cope with oxidative stress.

Uric Acid and Inflammation in CKD

Elevated levels of inflammatory cytokines in plasma and intrarenal infiltration of macrophages and T cells (39, 46, 92, 102) represent the systemic and local nature of chronic inflammation in CKD. The pathophysiological mechanisms underlying the inflammatory state in CKD are complex and involve a maladaptive cellular response to injury that leads to persistent activation of proinflammatory and profibrotic signaling (15, 133).

Murine models of CKD have demonstrated that uric acid contributes to these pathophysiological processes. In the remnant kidney model, compared with normouricemic rats, hyperuricemic rats showed higher levels of blood pressure and proteinuria histologically associated with greater glomerulosclerosis, interstitial fibrosis, and vasculopathy (56, 123). Allopurinol prevented the development of these histological features and attenuated the tubulointerstitial infiltration of $CD5^+$ cells in this CKD model (56, 123). Similarly, in a rat model of chronic cyclosporine nephropathy, simultaneous administration of cyclosporine and oxonic acid resulted in increased macrophage infiltration, tubular damage, and collagen deposition compared with cyclosporine alone (89). In these two models, hyperuricemia exerted additional injury and thereby shifted the pathological response to injury toward upregulated inflammation and fibrosis.

Several clinical studies have demonstrated that increases in interstitial macrophages and inflammatory mediators in plasma and urine are closely associated with rapid loss of kidney function in patients with CKD (3, 25, 105, 139). In view of these observations, the proinflammatory effects of uric acid might explain the positive association of hyperuricemia with new-onset CKD or CKD progression observed in prospective cohort studies and a meta-analysis of observational studies (108, 141, 142).

However, interventional studies with XO inhibitors have not always shown uniform results in CKD (Table 2). In recent prospective randomized studies, febuxostat delayed the deterioration of renal function in one study (67), whereas the same medication did not prevent renal function deterioration in another study (65). This discrepancy disrupts the translation of the experimental findings into the management of asymptomatic hyperuricemia in clinical practice (129).

Sato et al. (124) argued that among the trials in which neither the treatment group nor the control group exhibited CKD progression (estimated GFR decline of $\geq$4 mL/min/1.73 m^2 during the study period), the negative result (XO inhibitors were ineffective in slowing CKD progression) was a misinterpretation. They insisted that these trials should be interpreted as having an indeterminate, not negative, result because the effect of any treatment on kidney function would be negative if significant kidney function decline is not observed in both groups.

Another consideration in the interpretation of interventional trials is that the optimal level of serum uric acid is not currently well established. Given that uric acid can act as an antioxidant, lowering uric acid below a certain point may be deleterious to the kidneys. In healthy people, hypouricemia and hyperuricemia were equally associated with decreased renal plasma flow and GFR and increased afferent arteriolar resistance (146). This finding may be attributed to endothelial dysfunction and vasoconstriction under low uric acid levels. Sugihara et al. (134) found that patients with extremely low serum uric acid levels ($<$0.8 mg/dL) had endothelial dysfunction as evidenced by lower flow-mediated dilation than those with normouricemia. In addition, cross-sectional and prospective cohort studies demonstrated that hypouricemia was associated with impaired kidney function in the general population (53, 149), suggesting that low uric acid levels may increase the development and progression of CKD.

Currently, there is a knowledge gap between experimental and clinical studies. To narrow this gap, future research needs to address the several pitfalls observed in present research, which will be discussed in the following section.

FUTURE RESEARCH

This section describes some of the remaining questions in uric acid research and suggests future research directions. One of the difficulties in basic uric acid-related research is the lack of a long-term and stable hyperuricemic animal model. Since most mammals, including rats and mice, can degrade uric acid to allantoin by uricase, hyperuricemia is usually induced in an animal model by providing oxonic acid (uricase inhibitor) or feeding on a fructose diet. There have been continuous attempts to develop a genetic mouse model for human-mimic hyperuricemia, including urate oxidase-deficient mice generated by embryonic stem cell targeting technology (155), GLUT9 knockout mice (113), mice with xanthine oxidoreductase depletion (112), and mice in which urate oxidase is knocked out using the transcription activator-like effector nuclease strategy (80). Intriguingly, the phenotypes of the knockout mouse model for hyperuricemia are mainly related to hypertension, aberrant lipid and glucose metabolism, and inflammatory fibrosis in the kidneys. Since such mice still have limitations in hyperuricemia research because of their high death rate (40–65%) within 5 wk of birth and the wide variation in their uric acid levels from 2.7 to 11.1 mg/dL (79), the development of a new genetically modulated animal model for uric acid research could solve the previously unmet need for such studies.

Present clinical studies evaluating the effect of uric acid-lowering agents in kidney disease have failed to show consis-

tent beneficial effects on preventing kidney disease progression, and we speculate that two reasons might be responsible for these results. First, although uric acid provokes inflammation, oxidative stress, and RAS activation, it is also an end product of unhealthy cell metabolism. Patients with hyperuricemia are likely to have more uric acid-generative metabolic environments, which might be the main harmful reason for kidney disease progression. Because lowering the uric acid level in patients with hyperuricemia does not mean improvement in dysregulated cellular metabolism, it is difficult to consistently show the beneficial effects of uric acid-lowering therapy on kidney diseases in their various stages and in patients with different backgrounds.

Second, we believe that what often hobbles a clinical study on uric acid from the very beginning is the difficulty in selecting appropriate patients. An ideal patient would have asymptomatic hyperuricemia and benefit from uric acid-lowering treatment in terms of uric acid-induced inflammation. In particular, recent clinical trials on DKD have also changed from glucose and blood pressure management to targeting inflammation since there have been no novel and specific therapies and the control of hemodynamic changes in diabetic nephropathy is not sufficient to prevent and regress the disease (2, 96). However, we do not expect that all patients with DKD would benefit from nuclear factor erythroid 2-related factor 2 inducers and inhibitors of the MCP-1/chemokine (C-C motif) receptor 2, IL-1β, and JAK/STAT pathways. Since patients with elevated levels of TNF-α and soluble TNF receptor in plasma and an elevated level of MCP-1 in urine are at high risk for kidney disease progression (3, 25, 33, 105, 139), they might respond better to a treatment that targets the inflammatory pathways. Moreover, the individual susceptibility to hyperuricemia could differ depending on the disease type, sex, and genetic background. In this respect, careful consideration of the factors that are relevant to uric acid-induced inflammation will be helpful in overcoming the discrepancy between experimental and clinical studies.

CONCLUSIONS

Much of the present knowledge on the biological role of uric acid has come from experimental studies that have revealed that uric acid is implicated in immune system activation and inflammation. However, the translation of experimental findings to clinical studies is not always straightforward. Whether the correction of hyperuricemia is beneficial in patients with kidney disease has long been a controversial issue, mostly because of the discordant results in interventional trials of uric acid-lowering therapy.

Uric acid is a double-edged sword in the context of human health, as it has antioxidant and prooxidant properties depending on the surrounding environment. Indeed, the concept of "the lower, the better" is not appropriate for uric acid based on the U-shaped association of uric acid with the measured GFR and loss of kidney function (53, 146). Based on this viewpoint, we hope that future studies will clearly answer the questions regarding the necessity of treatment for asymptomatic hyperuricemia and the level to which uric acid levels should be corrected if necessary.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.-M.K. prepared figures; S.W.J. drafted manuscript; S.-M.K., Y.G.K., S.-H.L., and J.-Y.M. edited and revised manuscript; J.-Y.M. approved final version of manuscript.

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