The Role of Hyperuricemia in the Atherosclerosis

Subjects: Cardiac & Cardiovascular Systems

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Hyperuricemia is related with cardiovascular risks. Reactive oxygen species (ROS) are produced simultaneously with the formation of uric acid by xanthine oxidases. Intracellular uric acid has also been reported to promote the production of ROS. The ROS and the intracellular uric acid itself regulate several intracellular signaling pathways, and alterations in these pathways may result in the development of atherosclerotic lesions.

Hyperuricemia Atherosclerosis

1. Introdution

Hyperuricemia is a common metabolic syndrome. Elevated uric acid levels are risk factors for gout, hypertension, and chronic kidney diseases. Furthermore, various epidemiological studies have also demonstrated an association between cardiovascular risks and hyperuricemia. In hyperuricemia, reactive oxygen species (ROS) are produced simultaneously with the formation of uric acid by xanthine oxidases. Intracellular uric acid has also been reported to promote the production of ROS. The ROS and the intracellular uric acid itself regulate several intracellular signaling pathways, and alterations in these pathways may result in the development of atherosclerotic lesions.

2. The Role of Hyperuricemia in the Pathogenesis of Atherosclerosis

2.1. Oxidative Stress

Oxidative stress is one of the most critical factors in the development of atherosclerosis. Oxidative stress contributes to the pathogenesis of atherosclerosis via induction of the dysfunction of endothelial cells and vasodilation, induction of inflammation in inflammatory cells such as macrophages, aggregation of platelets, and oxidation of LDL.

Reactive oxygen species (ROS) are derived from oxygen molecules (O_2) and are unstable and powerful oxidizing agents. In vivo, they are produced in the process of oxidative phosphorylation (OXPHOS) in mitochondria. In addition, NADPH oxidases, xanthine oxidases, and lipoxygenases are known to produce ROS. There are inherent systems for antioxidant defense in the body. However, if this balance is lost and oxidative stress becomes dominant, atherosclerotic lesions progress.

Uric acid itself is chemically characterized as an antioxidant [1]. However, it is known that intracellular uric acid plays a role in inducing oxidative stress. In the pathogenesis of atherosclerosis, hyperuricemia acts as an inducer of oxidative stress. The mechanisms by which oxidative stress accumulates under hyperuricemic conditions are as follows:

- ROS are produced due to the increased activity of xanthine oxidase in the metabolic process of uric acid;
- The expression and activity of NADPH oxidase increase;
- Mitochondrial ROS (mtROS) are produced due to mitochondrial injury.

2.1.1. Xanthine Oxidoreductase

Xanthine oxidoreductase (XOR) exists in two forms, which are xanthine dehydrogenase (XDH) and xanthine oxidase (XO). XDH oxidizes substrates with NAD+ and produces NADH, while XO oxidizes substrates with O_2 and produces O_2- or H_2O_2. An elevated ratio of XO to XDH was observed in response to oscillatory shear stress in plaques [2]. Furthermore, the expression of XO itself was increased in plaques [3]. ROS derived from XO is involved in a vascular endothelial injury. It has been reported that XOR inhibitors improved endothelial dysfunction in patients with chronic heart disease, diabetes mellitus with mild hypertension, smoking, and sleep apnea syndrome (SAS) [4][5][6][7]. The activity of XO is elevated in pathological conditions such as myocardial infarction and ischemia–reperfusion [8]. Increased XO activity results in a burst of ROS, the attraction of neutrophils, and the induction of tissue injury [9].

The production of ROS by XO induces the migration, proliferation, and production of monocyte chemotactic protein-1 (MCP-1) in arteriolar smooth muscle cells [10] and contributes to the development of atherosclerosis. XOR contributes to foam cell formation. Knock-down of XOR suppressed lipid intake in macrophages and their differentiation into foam cells [11]. XOR was also reported to regulate lipid accumulation and be involved in adipocyte differentiation via activation of the transcription factor PPARγ [12]. XOR regulates inflammatory cytokine secretion. Increased plasma XOR activity was correlated with plasma IL-6 level and NF-kB activity [13]. In mouse macrophages, XOR regulated IL-1β secretion via NLRP3 inflammasome activation [14].

2.1.2. NADPH Oxidase

NADPH oxidase (NOX) is a complex of membrane-bound enzymes. Four members of the NOX family (NOX1, NOX2, NOX4, NOX5) are expressed in vascular smooth muscle cells, and endothelial cells. Activation of NOX is involved in the pro-atherogenic process [15].

It has been reported that uric acid activates NADPH oxidase and produces ROS. Uric acid-activated NADPH oxidase and increased oxidative stress lead to the activation of p38 MAPK and ERK1/2, causing a subsequent decrease in NO bioavailability and increase in protein nitrosylation and lipid oxidation in adipocytes [16]. In the human aorta, uric acid-treated smooth muscle cells increased the cell proliferation and expression of endothelin-1

(ET-1). These effects were suppressed by a NOX inhibitor and siRNA of the NOX subunit (p47phox). ET-1 is a pro-atherogenic molecule derived from vascular endothelium and promotes strong vasoconstriction, the proliferation of smooth vascular cells, and the proliferation of fibroblasts [17]. Uric acid regulates not only the expression level but also the activity level of NOX. Uric acid was observed to promote the phosphorylation of p47phox and the interaction of p-p47phox with p22phox, leading to the assembly of subunits and activation of NOX [18].

2.1.3. Mitochondrial ROS

A high concentration of uric acid caused increased mitochondrial ROS and mitochondrial damage. In hepatocytes, decreased membrane potential, mitochondrial DNA damage, and suppression of OXPHOS due to decreased levels of cytochrome C and succinate dehydrogenase (SDH) were observed [19]. Soluble uric acid-induced endothelial dysfunction in human aortic endothelial cells was related to reduced mitochondria and ATP production. Mitochondrial DNA damage and accumulation of oxidative stress were increased in hyperuricemic rats [20].

The mechanism of mitochondrial injury induced by uric acid remains unclear, but it is assumed that it involves the production of ROS by NADPH oxidase , suppression of AMPK [21], or activation of Rho kinase [22].

2.2. Inflammatory Signaling Pathway

As mentioned above, uric acid induces ROS production. ROS are vital mediators that activate various signaling pathways. Furthermore, uric acid itself may activate several intracellular signaling pathways that result in the production of inflammatory cytokines, adhesion factors, and chemokines and regulate cell proliferation and apoptosis, consequently leading to atherosclerosis development (**Figure 1**).

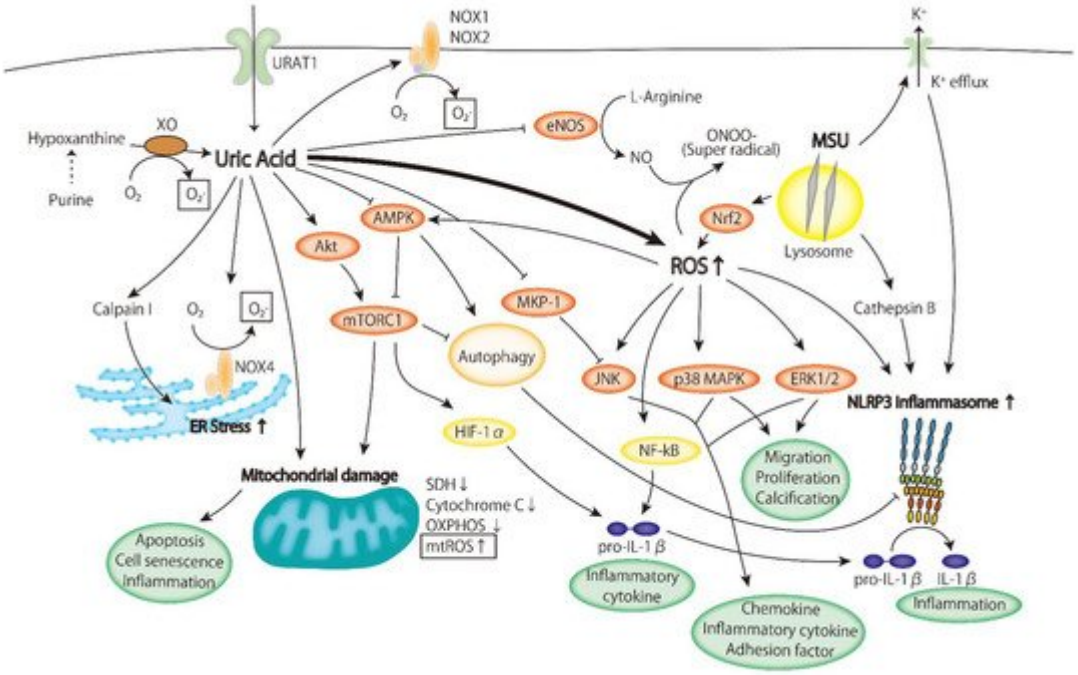

Figure 1. The effect of uric acid on intracellular signaling pathways in the pathogenesis of atherosclerosis. Intracellular uric acid induces reactive oxygen species (ROS) production and activates several inflammatory

signaling pathways. XO, xanthine oxidase; NOX, NADPH oxidase; eNOS, endothelial NO synthase; MSU, monosodium urate; AMPK, AMP-activated kinase; Nrf2, Nuclear factor-erythroid 2-related factor 2; mTORC1, mammalian target of rapamycin complex 1; p38 MAPK, p38 mitogen-activated protein kinase; MKP-1, MAPK phosphatase-1; JNK, Jun N-terminal kinase; ERK, extracellular signaling-regulated kinase; HIF-1α, Hypoxia Inducible Factor 1α; SDH, succinate dehyderogenase; OXPHOS, oxidative phosphorylation; mtROS, mitochondrial ROS.

2.2.1. ERK/p38 MAPK Cascade

The intracellular mitogen-activated protein kinase (MAPK) cascade is crucial for bridging extracellular stimuli to intracellular reactions. The MAPK pathway is composed of three steps of kinase activation: MAPK kinase kinase, MAPK kinase, and terminal MAPK. The main terminal MAPKs are extracellular signal-regulated kinase (ERK) 1/2, Jun N-terminal kinase (JNK), p38 MAPK, and ERK5. ERK, JNK, and p38 have crucial roles in the pathogenesis of atherosclerosis [23].

Several reports have shown that uric acid activates p38 MAPK and ERK. ROS were produced in cardiomyocytes exposed to high uric acid (HUA), and ERK and p38 MAPK were sequentially activated. As a result, the viability of the cardiomyocytes exposed to HUA decreased. In vivo, ERK/p38 MAPK was activated in the heart of a high-uric-acid mouse model, indicating that uric acid induces myocardial damage [24][25]. Activation of ERK1/2 and p38 MAPK was also observed in VSMCs and promoted the expression of MCP-1. This activation of MAPK was also caused by the production of ROS by HUA [26]. In pancreatic β-cells, uric acid activated ERK, decreased cell viability, and induced apoptosis and ROS production. Zurampic, a URAT1 inhibitor, inhibited the ERK pathway and attenuated uric acid-induced cell damage [27]. This observation reflects the effect of intracellular uric acid on MAPK activity. Uric acid also regulates MAPK via phosphatase activity that inhibits the MAPK pathway. In macrophages, febuxostat activated MAPK phosphatase-1 (MKP-1) and deactivated JNK, which led to the suppression of MCP-1 expression [28].

2.2.2. AMPK

AMP-activated protein kinase (AMPK) is a serine/threonine kinase that regulates the intracellular energy state. The suppression of AMPK induced inflammatory responses, such as the production of inflammatory cytokines in macrophages and activation of the NLRP3 inflammasome [29][30]. In a study on the pathogenesis of atherosclerosis, activation of AMPK suppressed the development of atherosclerosis in ApoE-KO mice [31][32].

Uric acid has been reported to suppress AMPK. In a fructose-treated hepatocyte cell line, uric acid suppressed AMPK activity and was involved in gluconeogenesis and insulin resistance [33][34]. This suggests that uric acid is involved in the pathogenesis of metabolic syndrome via the regulation of AMPK. However, several studies reported that AMPK was activated by ROS induced by uric acid [35][36].

In a study of atherosclerosis, it was reported that AMPK was activated in blood cells and plaques, and serum IL-1β or TNFα was decreased in a urate-lowering mouse model fed HFD. In vitro, uric acid attenuated AMPK activity and

led to the activation of the NLRP3 inflammasome and the production of IL-1β [21]. Another study also reported the effect of allopurinol on AMPK. AMPK activity was reduced in rats fed a high-fructose diet, but administration of allopurinol rescued the activation of AMPK [37].

2.2.3. PI3K-Akt Pathway

The PI3K-Akt pathway regulates the migration of monocytes and macrophages, lipid accumulation, cell proliferation, and endothelial dysfunction, which lead to the development of atherosclerotic plaques [38]. In vitro studies suggested that Akt may play a pro-atherogenic role. However, the development of atherosclerosis was aggravated in Akt1 knockout mice [39]. The role of Akt in atherosclerosis is still debated.

In human monocytes, uric acid was observed to phosphorylate Akt, activate mTOR, and subsequently suppress autophagy. These events resulted in the suppressed expression of IL-1R antagonist and increased production of IL-1β [40]. However, uric acid was also reported to suppress Akt. Uric acid was suggested to be involved in the progression of atherosclerosis via insulin resistance induced by the suppression of Akt [41].

2.2.4. Inflammasome

The inflammasome is an innate immune sensor and regulates the activity of caspase-1. The nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3) inflammasome is involved in various infections and inflammatory diseases. NLRP3 assembles and forms a complex with an adaptor protein, ASC, and procaspase-1. Subsequently, procaspase-1 undergoes autolysis and matures to caspase-1. Caspase-1 processes pro-IL-1β and pro-IL-18 to mature IL-1β and IL-18. At the same time, pyroptosis is induced, and IL-1β is released to the extracellular space [42] [43].

Recently, it has become clear that the NLRP3 inflammasome plays an important role in the pathogenesis of atherosclerosis. Canakinumab, an IL-1β inhibitor, suppressed the development of atherosclerosis [44]. Furthermore, colchicine, which inhibits the formation of the NLRP3 inflammasome, also protects against the recurrence of cardiovascular diseases [45].

In atherosclerotic plaques with hyperuricemia, deposition of MSU crystals was reported [46][47]. Monosodium urate (MSU) crystals can be distinguished from calcium crystals by using dual-energy CT, which is useful for the detection of MSU crystals in gout and urolithiasis. Dual-energy CT was performed on 59 patients with gout and 47 controls, and the frequency of cardiovascular MSU deposition was analyzed. The frequency of the deposition in cardiovascular systems was higher among patients with gout (51 [86.4%]) compared with controls (7 [14.9%]), and in coronary arteries, it was higher among patients with gout (19 [32.2%]) compared with controls (2 [4.3%]) [46]. The expression of XO was increased, and there were significantly higher concentrations of uric acid in atherosclerotic plaques [3], which may also affect the deposition of MSU crystals. However, the findings of dual-energy CT may include artifacts [48]. The association between the deposition of MSU crystals and cardiovascular events is not yet clear. Andres et al. reported that MSU deposition in the knee or first metatarsophalangeal joints was related to calcification of coronary arteries [49].

Soluble uric acid, as well as MSU crystals, has been reported to activate the NLRP3 inflammasome [50]. Soluble uric acid induces the production of mitochondrial ROS and leads to the activation of NLRP3 inflammasome complexes. In another report, soluble uric acid suppressed AMPK, led to the production of mitochondrial ROS, and finally activated the NLRP inflammasome [21].

Inflammasome activation in patients with gout or hyperuricemia has been observed in several studies. Serum IL-18, an inflammasome-related cytokine, was reported to be higher in gout patients, and the serum IL-18 level was correlated with the level of C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) [51]. A correlation of the plasma uric acid level with the plasma IL-18 level was also reported [52]. Furthermore, decreasing plasma uric acid levels by administering benzbromarone resulted in decreased plasma IL-18 levels [21].

3. The Impact of Uric Acid

In summary, uric acid plays a pro-atherogenic role in several steps in the progression of plaques as follows. Uric acid promotes oxidative stress and destabilization of NO, which leads to vasoconstriction and endothelial dysfunction. The expressions of chemokines, such as MCP-1, are increased, and monocytes are recruited into the subendothelial layer. Macrophages in subendothelial are differentiated into foam cells depending on oxidative stress by uric acid and the effect of xanthine oxidase. These foam cells or macrophages secrete inflammatory cytokines, and uric acid promotes the production of the cytokines. The inflammatory cytokines attract further inflammatory cells and bring the formation of the necrotic core. Uric acid promotes proliferation and migration of VSMCs via activation of MAPK and oxidative stress, which leads to the progression of atheromatous plaque. Oxidative stress derived from mitochondrial dysfunction by uric acid results in the destabilization of plaques. Inflammation augmented by uric acid via activation of inflammasomes or several inflammatory signaling pathways contributes to the development of atherosclerosis in each atherogenic step (**Figure 2**).

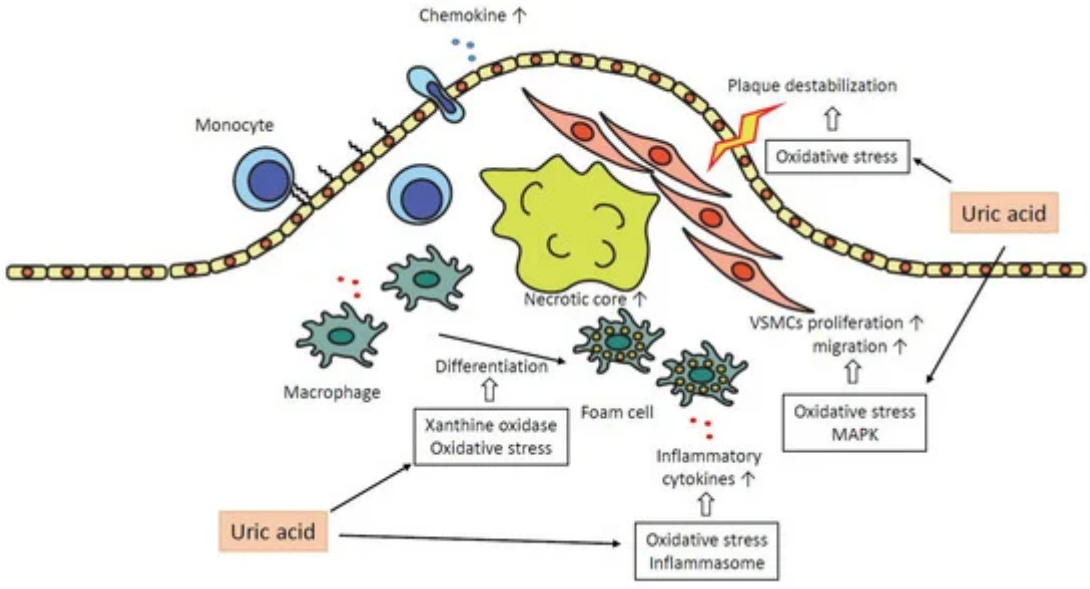

Figure 2. The role of uric acid in the formation of atheroma plaque. Uric acid plays a pro-atherogenic role in several steps in the progression of plaques. MAPK, mitogen-activated protein kinase; VSMCs, vascular smooth muscle cells.

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