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SPECIFIC ROLE OF IL-1B IN URIC ACID-RELATED INFLAMMATION : A NARRATIVE REVIEW

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ABSTRAK

Kondisi peradangan dalam hiperurisemia disebabkan oleh kristal monosodium urate yang merangsang pelepasan IL-1β, menandai tonggak penting dalam patogenesis hiperurisemia. Beberapa penelitian telah mengaitkan hubungan antara kadar asam urat dalam serum dan pelepasan IL-1β. IL-1β memainkan peran kunci dalam patogenesis rematik asam urat. Sinyal IL-1β saat ini dianggap sebagai peristiwa perangsang yang memicu peradangan asam urat dan mempromosikan rekrutmen sejumlah besar neutrofil ke situs peradangan. Aktivasi neutrofil yang disebabkan oleh kristal mengakibatkan inhibisi apoptosis, degranulasi, pelepasan reactive oxygen species (ROS), TNF-α, IL-1β, dan PGE2, serta pembentukan jaringan neutrofil ekstraseluler, yang lebih memperkuat proses peradangan. Penelitian terkini menunjukkan bahwa pasien hiperurisemia memiliki kadar IL-1β yang signifikan lebih tinggi. Penelitian lain menyarankan bahwa peningkatan kadar IL-1β berkorelasi dengan patologi anatomi yang lebih parah pada jaringan sendi pergelangan kaki tikus, termasuk hiperplasia sinovial, kerusakan kartilago, dan erosi tulang.

ABSTRACT

The specific role of IL-1β in uric acid-related inflammation: A Narrative Review. Inflammatory conditions in hyperuricemia are caused by monosodium urate crystals that induce the release of IL-1β, marking a crucial milestone in the pathogenesis of hyperuricemia. Several studies have linked the relationship between serum uric acid levels and the release of IL-1β. IL-1β plays a key role in the pathogenesis of gout. The IL-1β signaling is currently considered an initiating event that triggers uric acid inflammation and promotes the recruitment of a large number of neutrophils to the inflammatory site. Neutrophil activation caused by crystals results in the inhibition of apoptosis, degranulation, the release of reactive oxygen species (ROS), TNF-α, IL-1β, and PGE2, as well as the formation of extracellular neutrophil tissue, further reinforcing the inflammatory process. Recent research indicates that hyperuricemia patients have significantly higher levels of IL-1β. Other studies suggest that elevated IL-1β levels correlate with a more severe anatomical pathology in the joint tissues of rat ankles, including synovial hyperplasia, cartilage damage, and bone erosion.

INTRODUCTION

In ancient times, humans had long suffered from hyperuricemia without understanding why and how it occurred. It wasn't until the late 17th century that they began to have a better understanding of the cause of hyperuricemia, namely the increase in uric acid (C5H4N4O3), discovered by Carl Wilhelm Scheele. Uric acid is the end product of purine catabolism.[1] Typically, the uric acid levels in the serum of healthy adults range from 1.5 to 6.0 mg/dL for women and 2.5 to 7.0 mg/dL for men. Excessive concentration of uric acid can lead to the formation of monosodium urate crystals. Generally, individuals can be diagnosed with pathological hyperuricemia when their levels exceed the normal values.[2,3]

Sufferers of hyperuricemia abroad are predominantly men above 34 years old. The prevalence of hyperuricemia in the United States is 5.9% for men (6.1 million) and 2% for women (2.2 million).[4] In 2015, there was an increase in the prevalence of hyperuricemia in the United States to 14.6% (32.5 million people).[5] The prevalence in Indonesia is approximately 1.6–13.6% of 100,000 people and continues to increase with age. According to the Basic Health Research (Riskesdas) in 2018, the prevalence of joint diseases in Indonesia by province based on doctor diagnoses in the population aged ≥ 15 years is around 7.3%, with the highest age group being ≥ 65 years.[4,6] Studies have suggested that inflammatory elements like interleukin (IL)-1β, IL-17, and IL-8, as well as NOD-like receptor protein 3 (NLRP3) inflammasome and tumor necrosis factor-alpha (TNF-α), alongside anti-inflammatory factors such as IL-10 and IL-37, are all involved in the inflammatory process of gout induced by monosodium urate (MSU).[2] Gout is fundamentally instigated by the exclusive release of IL-1β in response to the formation of monosodium urate (MSU) crystals during instances of hyperuricemia, thus offering an auspicious opportunity to investigate the contributory factors influencing IL-1β secretion.[1,2] This literature review aims to gather important literature regarding the role of interleukin (IL)-1β in the hyperuricemia process and connect the dots among them, enabling critical review and evaluation of available evidence, and providing information about the role of interleukin (IL)-1β in the hyperuricemia process that needs to be strengthened.

METHOD

We reviewed the available evidence and summarized data sources on examining the relationship and seeking available evidence on interleukin (IL)-1β in the process of hyperuricemia, the role of interleukin (IL)-1β in gout arthritis, the association of interleukin (IL)-1β with uric acid and MSU crystals. Additionally, we searched for research on changes in interleukin (IL)-1β levels after management, or comparison of control groups.

A comprehensive literature review on the role of interleukin (IL)-1β in hyperuricemia was conducted from September 2023 to November 2023. The following keywords were used ((interleukin (IL)-1β OR "role of interleukin (IL)-1β" OR "hyperuricemia") AND Gout arthritis) OR (("Uric Acid OR "Monosodium Urate" OR "interleukin (IL)-1β, role in inflammatory process") AND "hyperuricemia") in PubMed. The role of interleukin (IL)-1β in the inflammatory process by uric acid, the role of interleukin (IL)-1β in the process of hyperuricemia, changes in interleukin (IL)-1β levels in various management intervention groups were used in Google and local journals. We imposed a decade time limit on our search, and all articles identified from September 2023 to November 2023 were included. Additional articles were identified from the references in the

retrieved literature.

Hyperuricemia

Hyperuricemia or gout is a clinical condition characterized by an elevation in the serum uric acid (SUA) levels in the blood. In premenopausal women, SUA levels ≥ 6 mg/dl are considered, while in men and postmenopausal women, SUA levels ≥ 7 mg/dl. The pathological threshold for hyperuricemia is 6.8 mg/dl.[7] This increase in uric acid levels is also associated with diabetes, cardiovascular, and kidney diseases.[8] Hyperuricemia is a major contributing factor to gout. When uric acid levels exceed the threshold, crystallization of monosodium urate (MSU) occurs, depositing in peripheral joints and surrounding tissues, leading to gout or gouty arthritis.[2] If left untreated over an extended period, it can result in joint damage, soft tissue damage, and kidney tissue.[9]

Etiology of Hyperuricemia

The etiology of hyperuricemia involves the excess production of uric acid through the purine degradation pathway, primarily in the liver, and low uric acid excretion in the kidneys through reuptake transporters, including Uric Acid Transporter 1 (URAT1), Glucose Transporter 9 (GLUT 9), and secretory transporters such as ATP-binding cassette subfamily G member 2 (ABCG2).(10)Additionally, low uric acid excretion in the intestines through ABCG2 contributes to hyperuricemia. Other causes include mutations in hypoxanthine-guanine phosphoribosyl transferase (HGPRT), which convert hypoxanthine into IMP and guanosine into GMP. Reduced HPGRT activity leads to increased levels of hypoxanthine and results in hyperuricemia. HPGRT deficiency causes Lesh-Nyhan syndrome or Kelly-Seegmiller syndrome.[10,11]

There are risk factors for hyperuricemia, such as a diet rich in purine-containing foods like meat and seafood. Furthermore, a high intake of beverages and foods containing high amounts of fructose (alcohol and beer) is a contributing factor.[11] Obstructive sleep apnea- hypopnea syndrome (OSAHS), chronic kidney disease (CKD), and medications such as acetylsalicylic acid, cyclosporine, theophylline, mycophenolate, beta- and alpha-1-adrenergic agents, and angiotensin-converting enzyme (ACE) inhibitors can elevate uric acid levels in the blood. On the other hand, vitamin C, cherries, coffee, folic acid, low-fat milk, physical activity, lactobacillus, urate-lowering therapy (ULT), and medications such as losartan, atorvastatin, calcium channel blockers, sodium-glucose co-transporter (SGLT-2) inhibitors, phenobarbital, sevelamer, metformin, and angiotensin-II/neprilysin inhibitors can lower uric acid levels in the blood.[12,13]

IL-1β (Interleukin-1 β) is a Specific Cytokine in Hyperuricemia

The formation of urate crystals in hyperuricemia triggers gout attacks primarily through the activation of monocytes and macrophages, leading to the release of interleukin (IL)-1β through NLRP3 inflammasome vesicles. This process induces both local and systemic high-level pro-inflammatory responses and the influx and activation of neutrophils in the joints. Hyperuricemia or gout is a disease entirely caused by the secretion of IL-1β in response to monosodium urate (MSU) crystals formed during hyperuricemia, providing an opportunity to study factors contributing to IL-1β secretion.[1]

Genetic mutations in uricase and URAT1, as well as a diet rich in purines and fructose, dramatically increase human susceptibility to developing hyperuricemia. Elevated uric acid conditions can induce epigenetic reprogramming in monocytes, resulting in a more pro- inflammatory state. Altered microbiota in gout leads to a deficiency of anti-inflammatory short-chain fatty acids.

Within cells, MSU crystals induce various effects, including mitochondrial damage, increased xanthine oxidase (XO) activity, reactive oxygen species (ROS) production, decreased intracellular ATP (ATP), inhibition of AMP-dependent protein kinase (AMPK), and Nrf2 nuclear translocation. All these effects have been shown to induce NLRP3 inflammasome activation and subsequent caspase-1 and pro-IL-1β activation.[14,15]

The role of mitochondrial ROS in MSU-induced IL-1β production is also relevant in a study reporting that NF-kB negatively regulates NLRP3 activation by increasing p62 expression, a crucial autophagy receptor. Stimulated by NLRP3 activators, p62, LC3-II, and Parkin are recruited to damaged mitochondria, initiating their clearance through autophagy (mitophagy). Therefore, the induced NF-kB expression of p62 negatively regulates NLRP3 activation by inhibiting the release of DNA and ROS from damaged mitochondria.(14–16)Conversely, other studies suggest that p62 accumulates in lysosomal damage induced by MSU crystals and disrupts autophagy. They show that MSU crystals cause p62 to bind to Kelch-like ECH-associated 1 (keap-1), which typically acts as a transcriptional repressor by binding to nuclear factor E2-related factor 2 (Nrf2), a transcription factor involved in oxidative stress responses. The release of Nrf2 from keap-1 facilitates its translocation to the nucleus and induces the transcription of heme oxygenase-1 and superoxide dismutase, both proven necessary for MSU-induced NLRP3 activation. Another study observes a positive feedback loop between MSU-induced ROS production and p62 expression, both mediating increased caspase-mediated apoptosis and IL-1β production. Thus, NLRP3 inflammasome regulation can be negatively controlled by p62 when damaged mitochondria are effectively removed through mitophagy, while excess p62 can also stimulate NLRP3 activation through Nrf2- mediated transcription and ROS production.[14,16]

Another crucial intracellular sensor for the pathogenesis of gout is AMP-activated protein kinase (AMPK). Recent studies show that MSU crystals inhibit AMPK activity, and AMPKa knockout mice exhibit significantly higher inflammatory responses in the MSU crystal air pouch model. Additionally, it is known that colchicine induces AMPK phosphorylation in vitro, identifying a new molecular target for this ancient drug in the treatment of gout. Although it is important to validate these findings in human cells and patient groups, these discoveries provide a basis for further research to explore the potential use of AMPK activators in treating inflammation in gout.[14,16]

Uric acid induces the production of reactive oxygen species (ROS). ROS serves as a crucial mediator that activates various signaling pathways. Additionally, uric acid itself can activate several intracellular signaling pathways that generate inflammatory cytokines, adhesion factors, and chemokines, while also regulating cell proliferation and apoptosis, ultimately contributing to the development of atherosclerosis.[13,17]

ERK/p38 MAPK Cascade

The intracellular mitogen-activated protein kinase (MAPK) cascade is crucial for connecting extracellular stimuli to intracellular responses. Several reports have shown that uric acid activates p38 MAPK and ERK. ROS is generated in cardiomyocytes exposed to uric acid, and ERK and p38 MAPK are sequentially activated. Uric acid also regulates MAPK through phosphatase activity inhibiting the MAPK pathway.[13,18]

AMPK

AMP-activated protein kinase (AMPK), a serine/threonine kinase, regulates intracellular energy status. AMPK is activated by decreased intracellular ATP concentrations and an increased

ATP to ADP or AMP ratio. AMPK activation promotes glycolysis and oxidative phosphorylation (OXPHOS), leading to ATP production. Currently, research is focused on AMPK as a key molecule connecting metabolism to inflammation. AMPK suppression induces inflammatory responses, such as the production of inflammatory cytokines in macrophages and NLRP3 inflammasome activation.[13,18,19]

Uric acid is reported to suppress AMPK. In hepatocytes treated with fructose, uric acid suppresses AMPK activity, contributing to gluconeogenesis and insulin resistance. This suggests that uric acid is involved in the pathogenesis of metabolic syndrome through AMPK regulation. However, some studies report that AMPK is activated by uric acid-induced ROS. In vitro, uric acid reduces AMPK activity, leading to NLRP3 inflammasome activation and IL-1β production.[13]

PI3K-Akt Pathway

Phosphatidylinositol-3 kinase (PI3K) catalyzes phosphorylation at position 3 of the inositol ring of phosphatidylinositol, a cell membrane component, and also has serine/threonine protein kinase activity. Under PI3K, the most important effector molecule is Akt. Akt is a serine/threonine kinase and a key molecule involved in various signaling pathways, including cell proliferation, differentiation, apoptosis, and cell migration. Moreover, Akt is involved in the cell cycle and glucose metabolism through GSK3b, as well as cell growth and survival through mTORC1. In human monocytes, uric acid is observed to phosphorylate Akt, activate mTOR, and subsequently suppress autophagy. This event results in the suppression of IL-1R antagonist expression and increased IL-1β production. However, it is also reported that uric acid suppresses Akt. Uric acid is suspected to be involved in the development of atherosclerosis through insulin resistance induced by Akt suppression can be seen in Figure 1.[13,19,20]

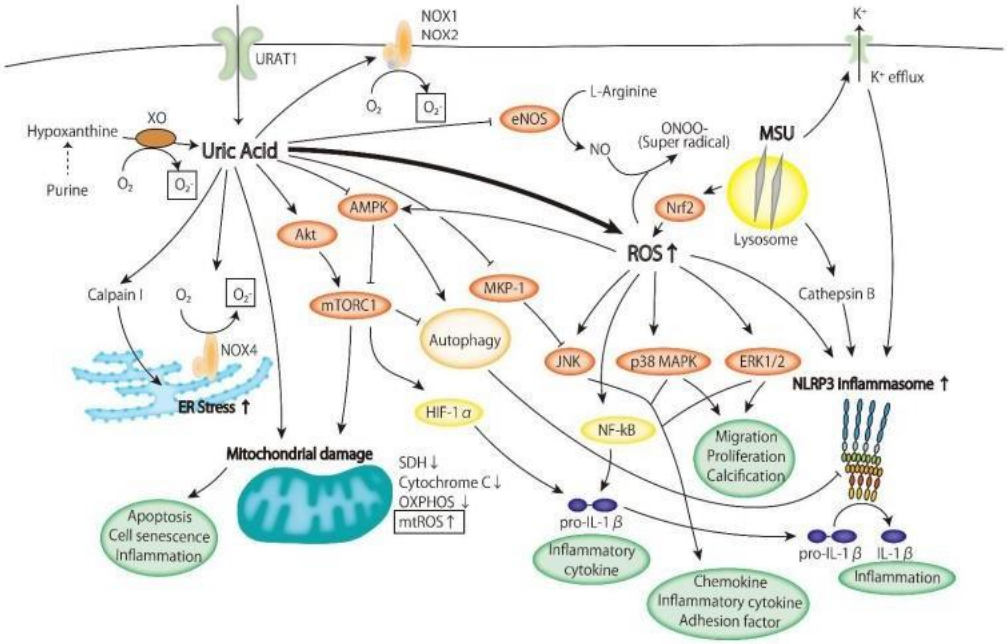

Figure 1. Intracellular uric acid induces ROS production and activates several inflammatory signaling Pathways[13]

Inflammasome

The inflammasome is an innate immune sensor that regulates caspase-1 activity. Inflammasome activation is induced after the recognition of pathogen-associated molecular

patterns (PAMPs) derived from microorganisms and damage-associated molecular patterns (DAMPs) from dying or dead host cells. The nucleotide-binding and leucine-rich repeat protein-3 (NLRP3) inflammasome is involved in various infections and inflammatory diseases.(21,22)NLRP3 expression is induced by NF-kB activation. Subsequently, it assembles and forms a complex with the adaptor protein ASC and procaspase-1. Then, procaspase-1 undergoes autolysis and becomes caspase-1. Caspase-1 processes pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18. At the same time, pyroptosis is induced, and IL-1β is released into the extracellular space.[13,23,24]

Sterile crystals activate the NLRP3 inflammasome. In uric acid-related diseases, monosodium urate (MSU) crystals activate the NLRP3 inflammasome, inducing IL-1β release and promoting arthritis development. The mechanism of NLRP3 inflammasome activation by MSU crystals involves phagocytes such as macrophages or neutrophils; these cells engulf the crystals, leading to lysosome rupture and the release of cathepsin B into the cytosol.(24–26) K+ efflux or ROS production is also induced, triggering NLRP3 inflammasome activation.[13,27,28] Recently, MSU crystals have been shown to induce Nrf2 translocation to the nucleus and alter intracellular ROS levels, promoting NLRP3 inflammasome activation.[13,29,30]

CONCLUSION

IL-1β plays a crucial role in the pathogenesis of uric acid. The IL-1β signal is currently considered an initiating event that triggers uric acid inflammation and promotes the recruitment of a large number of neutrophils to the inflammatory site. Neutrophil activation caused by crystals results in the inhibition of apoptosis, degranulation, the release of reactive oxygen species (ROS), TNF-α, IL-1β, and PGE2, as well as the formation of extracellular neutrophil tissue, further reinforcing the inflammatory process. It would be beneficial to conduct future research in animal models to examine IL-1β levels during hyperuricemia.

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