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Review

Physiological functions and pathogenic potential of uric acid: A review

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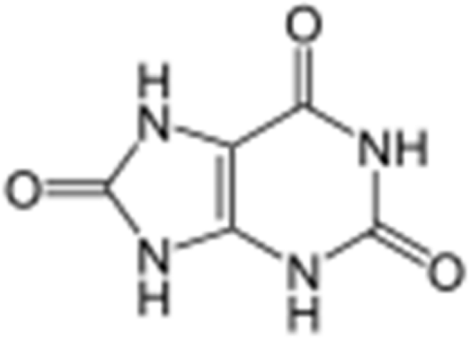
GRAPHICAL ABSTRACT



Uric acid, $C_5H_4N_4O_3$, 7,9-dihydro-1H-purine-2,6,8(3H)-trione, molecular mass 168 Da, is a product of the metabolic breakdown of purine nucleotides (adenine and guanine).

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ABSTRACT

Uric acid is synthesized mainly in the liver, intestines and the vascular endothelium as the end product of an exogenous pool of purines, and endogenously from damaged, dying and dead cells, whereby nucleic acids, adenine and guanine, are degraded into uric acid. Mentioning uric acid generates dread because it is the established etiological agent of the severe, acute and chronic inflammatory arthritis, gout and is implicated in the initiation and progress of the metabolic syndrome. Yet, uric acid is the predominant anti-oxidant molecule in plasma and is necessary and sufficient for induction of type 2 immune responses. These properties may explain its protective potential in neurological and infectious diseases, mainly schistosomiasis. The pivotal protective potential of uric acid against blood-borne pathogens and neurological and autoimmune diseases is yet to be established.

Introduction

Uric acid (Fig. 1) is synthesized mainly in the liver, intestines and other tissues such as muscles, kidneys and the vascular endothelium as the end product of an exogenous pool of purines, derived largely from animal proteins. In addition, live and dying cells degrade their nucleic acids, adenine and guanine into uric acid. Deamination and dephosphorylation convert adenine and guanine to inosine and guanosine, respectively. The enzyme purine nucleoside phosphorylase converts inosine and guanosine to the purine bases, respectively hypoxanthine and guanine, which are both converted to xanthine via xanthine oxidase-oxidation of hypoxanthine

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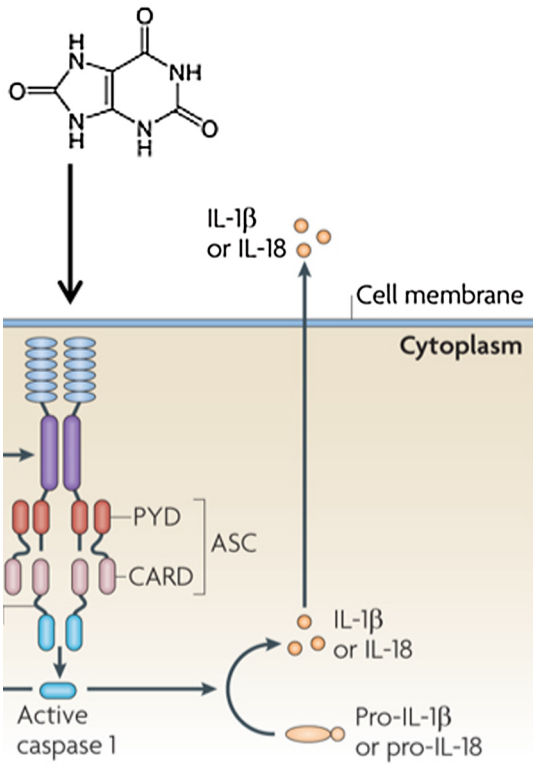

Fig. 1. The most alarming step [80]. Uric acid, $C_5H_4N_4O_3$, 7,9-dihydro-1 H-purine-2,6,8(3 H)-trione, molecular mass 168 Da, is a product of the metabolic breakdown of purine nucleotides (adenine and guanine). Crystals of monosodium urate (MSU) in the joints stimulate the inflammasome, NLRP3. The leucine rich repeat (LRR) at the carboxyl end of NLRP3 is the sensor for pathogen- (PAMP), or danger (DAMP)-associated molecular patterns generated by exposure to MSU. Ligand binding leads to the receptor oligodimerization and allows the amino terminal pyrin (PYD) domain to interact with adaptor ASC, which recruits pro-caspase-1 via its card domain and autoactivates it. The active cysteine peptidase processes the IL-1β precursor (pro-IL-1β), which is then ready to exit the cell as biologically active proinflammatory, 17 kDa IL-1β.

and deamination of guanine by guanine deaminase. Xanthine is further oxidized by xanthine oxidase to uric acid [1,2]. Normally, most daily uric acid disposal occurs via the kidneys. Humans cannot oxidize uric acid to the more soluble compound allantoin due to the lack of uricase enzyme. The enzyme uricase (urate oxidase) can metabolize uric acid to highly soluble 5-hydroxyisourate that is further degraded to allantoic acid and ammonia, easily excreted by the kidneys. However, several primates, including man have lost the functional activity of the enzyme uricase, as uricase mRNA may be detected in human livers but it displays two premature stop codons, and the encoding gene is, thus, a pseudogene [3,4]. Mammals possessing a functional uricase typically display serum uric acid levels of 10–20 μg/mL. In contrast, uric acid levels are 3 to 10 times higher in apes and humans as a result of parallel nonsense mutations that caused a pseudogenization of the uricase gene during the early Miocene era [3,4].

Uric acid in healing and defense: Physiological functions of uric acid

Antioxidant

Most serum uric acid is freely filtered in kidney glomeruli, and approximately 90% of filtered uric acid is reabsorbed, implying that it has a considerable physiological role [2,5]. In humans, over half the antioxidant capacity of blood plasma comes from uric acid [5,6]. Uric acid is a strong reactive oxygen species (ROS) and peroxynitrite scavenger and antioxidant [5–8]. High levels of uric acid are readily detected in the cytosol of normal human and mammalian cells, especially in the liver [9], vascular endothelial cells, and in human nasal secretions, where it serves as an antioxidant [10,11].

Endothelial function

In contrast to studies documenting the ability of uric acid to impair vascular endothelial cells integrity [12], a recent report indicated for the first time that extremely low levels of serum uric acid, attributed to loss-of-function mutations of *SLC22A12* encoding blood vessels and kidney proximal tubular cells transporter, URAT1, cause endothelial dysfunction *in vivo* [13]. This and other reports challenged the view stating that uric acid elicits cardiovascular and kidney diseases via impairing endothelial integrity and function [13–15]. Indeed, uric acid may exert fundamental roles in tissue healing via initiating the inflammatory process that is necessary for tissue repair, scavenging oxygen free radicals, and mobilizing progenitor endothelial cells [15].

Potent mediator of type 2 immune responses

Elevated concentration of uric acid was detected in the peritoneal cavity of mice following injection of the most widely used clinical adjuvant alum (aluminum hydroxide) [16,17]. Experiments involving intraperitoneal injection of mice with the harmless protein, ovalbumin, or ovalbumin + alum, in conjunction with 0 or 50 units uricase demonstrated that uric acid is necessary and sufficient for induction of antibody immune responses to ovalbumin [17]. The alum established T helper 2 (Th2) adjuvanticity was found to be mediated through cell injury leading to the induction of uric acid, which acts as a danger signal promoting the generation of inflammatory monocyte-derived dendritic cells [16,17]. These findings document the pivotal role of uric acid in induction of protective antibody responses to the numerous human vaccines incorporating alum as an adjuvant.

Uric acid release was also demonstrated in the airways of allergen-challenged asthmatic patients and mice, and appeared necessary for mounting Th2 cell immunity, airway eosinophilia, and bronchial hyperreactivity to inhaled harmless proteins and house dust mite allergen. Additionally, administration of MSU crystals together with inhaled harmless proteins elicited vigorous type 2 immunity. Uric acid adjuvanticity was expressed via activating spleen tyrosine kinase (Syk) and the phosphoinositol 3 (PI3)-kinase. Uric acid was thus identified as an essential initiator and amplifier of allergic inflammation *in vivo* [17].

Allergens, which are often proteases, namely cysteine proteases, and the cysteine peptidases papain and bromelain are able to stimulate barrier epithelial cells to produce type 2 cytokines such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33, which are responsible for directing the immune environment to the type 2 axis and hypersensitive inflammation. It was recently shown that allergens and cysteine peptidases, like papain cause stress and damage to the tissue cells, especially the barrier epithelial cells, triggering the release of uric acid. Uric acid was shown to activate epithelial cells for release of TSLP and IL-33, but not IL-25, and was identified as a key player that regulates the development of type 2 immune responses to cysteine peptidase allergens [18]. Human and mouse airway epithelial cells secrete uric acid constitutively; *in vivo* exposure of mice to particulate pollutants and the cysteine peptidase-containing house dust mite triggered increase in uric acid production and release by mucosal cells and mediated allergic sensitization, which was shown to be inhibited by uricase

[19]. Indeed, uric acid is now recognized as an alarmin, like ATP (adenosine triphosphate), the high mobility group box 1 protein (HMGB1), and IL-33, and a prominent and potent mediator of type 2 immune responses involving epithelial cells, innate lymphoid cells, eosinophils, basophils, and mast cells [16–22].

Resistance to parasites

The protective immune response against many helminth parasites is dependent on type 2 immune responses [23]. No information is available regarding the contribution of uric acid in development of protective type 2 immune responses to nematodes. Regarding schistosomiasis, cysteine peptidases, such as papain, *Schistosoma mansoni* cathepsin B1 (SmCB1) and cathepsin L3 (SmCL3) and *Fasciola hepatica* cathepsin L1 (FhCL1) do not induce allergic reactions in mice or hamsters and were shown instead to elicit reproducible and highly significant ($P < 0.0001$) reduction of 50–65% in challenge *S. mansoni* and *Schistosoma haematobium* infection, via generation of polarized (papain, SmCL3, FhCL)- or predominant (SmCB1) type 2 responses involving release of TSLP, IL-4, IL-5, IL-13 and generation of IgG1 antibodies [24–28]. Subcutaneously administered papain or helminth cysteine peptidases interact with epithelial cells, triggering the release of TSLP, the master cytokine of innate and adaptive type 2 immune responses [21,22,24,28]. The generated type 2 cytokines recruit and activate innate lymphoid cells 2, eosinophils, basophils, and mast cells, and support the production of IgG1 antibodies to the cysteine peptidase, thus directing the immune system, at the time of challenge infection, to the type 2 immune arm. Eosinophils, basophils and mast cells-derived basic toxic proteins, proteoglycans, proteases, peroxidases and extracellular trap unite to harm the migrating schistosome larvae, and certainly damage more so the blood capillaries endothelial cells. Injury to the capillary endothelium was shown to trigger release and accumulation of uric acid in the vicinity of the developing blood flukes. These data support the hypothesis stating that endogenous uric acid is necessary for development of type 2 immunity to cysteine peptidases in the absence of adjuvant [16–22]. Detection of elevated concentrations of uric acid in lung and liver of immunized and unimmunized schistosome-infected animals in in entire agreement with documents showing uric acid is constitutively present in normal cells, especially liver, intestine and vascular endothelial cells and increases in concentration when cells are damaged and following release from dying cells [5,9,16–22,29,30].

In the liver sinusoids, when worms begin to grow, ingest blood, and excrete and secrete cysteine peptidases, the type 2 immune effectors and cytokines, damage hepatocytes triggering the release of uric acid. Uric acid has been shown to be associated with non-alcoholic fatty liver disease (NAFLD) and was demonstrated to have a causal role in fatty liver via stimulation increase in fatty acids synthesis and release of unsaturated fatty acids, especially arachidonic acid from lipid depots and cell membrane [31–37]. Due to its powerful anti-oxidant properties, uric acid interferes with the activity of lipoxygenases and serves as a substrate for the enzyme cyclooxygenase. Arachidonic acid is thus allowed to access the parasites and mediate their demise, as arachidonic acid has been shown to be an effective schistosomicide *in vitro* and *in vivo* in mice, hamsters, and in *S. mansoni*-infected children [38–42].

If experiments in independent laboratories support the above scenario and findings, namely the anti-schistosome protective cysteine peptidase-induced type 2 responses/uric acid/arachidonic acid axis, arachidonic acid will be considered not only a safe and effective drug, but even more importantly, a natural schistosomicide [43]. The experiments will also prove, for the first time, that uric acid is an indispensable player in protection against schistosome infection. Since mice and hamsters possess a functional uricase and typically display serum uric acid levels in the 10–20 μg/ml, in contrast to humans where serum uric acid levels are much higher [3,4], it is anticipated, yet remains to be proved, that the cysteine peptidase-based vaccine will achieve considerably higher levels of protection in children than those recorded in mice and hamsters [44].

Defense against neurological and autoimmune diseases

In support, plasma low uric acid levels, leading to decrease in antioxidant molecules, were evident in patients with multiple sclerosis. Peroxynitrites and ROS are believed to be responsible for myelin degradation in multiple sclerosis (MS) and can be blocked by high uric acid levels, while gout patients almost never present with MS disease [45]. Several reports documented association of low uric acid serum levels with MS disease [45–48]. A recent meta-analysis of published data indicated convincingly that patients with MS had lower serum uric acid than healthy controls, and advocated serum uric acid low level as a potential biomarker for multiple sclerosis [49]. Low plasma uric acid levels were also associated with neurological disorders [49–51], Parkinson [52–56], and Alzheimer [57,58] disease, Pemphigus vulgaris, an autoimmune disorder characterized by blistering and sores (erosions) of the skin and mucous membranes [59], and lichen planus, an autoimmune inflammatory disease of the mucocutaneous tissue [60,61], which was also associated with low uric acid levels in saliva [62].

Uric acid dread: Pathogenic potential of uric acid

Gout

Despite its documented protective potential, mentioning uric acid generates apprehension as it is the confirmed aetiological agent of the severe, acute and chronic inflammatory arthritis, gout. However, soluble uric acid is not the culprit as gout is due to deposition of crystals of monosodium urate (MSU) in joints and periarticular tissues [63]. Crystals of MSU do not always elicit inflammation in joints. They must first be coated by serum proteins before interacting with articular cells' surface membrane directly or via receptors, followed by stimulation of a cytosolic molecular platform involved in innate immunity, the cysteine peptidase, caspase 1-activating the NOD-like receptor P3 (NLRP3) inflammasome, which is responsible for proteolytic cleavage of pro-interleukin (IL)-1β and maturation and release of the active IL-1 moiety in the joint [64]. Neutrophils are recruited and activated in response to the spilling of IL-1, producing ROS, proteolytic enzymes, extracellular traps, and pro-inflammatory chemokines and cytokines, which recruit and activate macrophages. Neutrophil extracellular trap (NET) formation is driven by IL-1β, and was shown to contain the alarmin HMGB1 supporting NET pro-inflammatory potential. Accordingly, the pathogenesis of acute gout is the result of a cross-talk between MSU crystals-induced NLRP3 inflammasome activation, IL-1 release, and neutrophil accumulation [64–68].

The alarming steps

Recently, MSU crystals were identified as an endogenous danger signal formed after release of uric acid from dying cells. The injured cells rapidly degrade their RNA and DNA; liberated pyrimidines are catabolized to beta-alanine and beta-aminoisobutyrate and purines are catabolized into uric acid, leading to its accumulation. The cytosol contains around 4 mg/mL uric acid with significant increases following degradation of injured cells nucleic acids [9,69]. Uric acid (Fig. 1) is soluble in biological fluids up to 70 μg/mL, and hence is entirely soluble in human blood, which has constitutive concentration of 40–60 μg/mL. In humans, about

70% of daily uric acid disposal occurs via the kidneys, and in 5–25% of humans, impaired renal (kidney) excretion leads to hyperuricemia (>120 μg/mL). Increase in concentration of uric acid above its solubility level leads to its precipitation as MSU crystals, especially in the joint cavities, evoking severe inflammatory episodes in some persons only, as remarkably, most people with hyperuricemia remain asymptomatic and do not develop gout symptoms [69,30]. It is likely that to elicit gout, hyperuricemia must be associated with defects in the function of the genes regulating urate transport and homeostasis, such as the urate-anion exchanger urate transporter 1 (URAT1) and the glucose transporter, GLUT9 [70–72].

Urate crystals are deposited principally in connective tissues of the joints, tendons, kidney, and rarely in heart valves and pericardium, and readily interact with serum proteins [73]. A group of mouse antibodies of the IgM class were recently shown to facilitate *in vitro* uric acid crystallization and to bind to the MSU crystals [72,74]. Deposited MSU crystals in the joints cavities interact with resident macrophages and mast cells, recruited neutrophils and monocytes, and non- haemopoietic synovial and endothelial cells. All these cells may phago- or endocytose MSU crystals leading to their activation and injury and release of hydrolytic enzymes, reactive oxygen species, and a plethora of danger-associated molecular patterns (DAMP) that might be sensed by the cells surface membrane and cytoplasmic receptors of the innate immune system [75,76].

The crystals of MSU assume a spine structure and expectedly harm the surface membrane of surrounding cells. Injury to body cells is perceived by extracellular receptors of the Toll-like family (TLR), TLR-2 or TLR-4 [75–78]. The response involves generation of pro-IL-1β and tumor necrosis factor. Additionally, the MSU crystals are ingested by resident phagocytes, leading to increase in intracellular sodium content, changes in cell osmomolarity, water influx, and consequent decrease in intracellular potassium concentration. Apparently, this generated danger signal is able to activate a member of the NOD (nucleotide binding and oligomerization domain) subfamily of NOD-, leucine-rich repeat (LRR)-containing receptors (NLR) family members, which include the proteins NLRP1, NLRP3 and NLRC4. The NLRP3 receptor essentially consists of a central NOD domain, LRR ligand sensor domain at the carboxyl terminus, and an effector pyrin (PYD) domain at the amino end. Stimulation of the sensor domain results into oligomerization of the molecule and recruitment of an adaptor protein, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain). The PYD domain of NLRP3 interacts with the PYD domain of ASC, which additionally contains a caspase activating and recruiting domain (card) (Fig. 1). The ASC card domain is able to recruit and autoactivate the cysteine protease caspase-1 which cleaves the inactive, 31 kDa precursor of IL-1β (pro-IL-1β) (and pro-IL-18) into the mature, biologically active, 17 kDa IL-1β, and additionally induces a lytic form of cell death, named pyroptosis [64,79–83].

Of note, the *in vitro* NLRP3- and caspase-1- dependence for MSU crystals-induced IL-1β release was not reproduced in several *in vitro* and *in vivo* situations [77,78]. Moreover, the presence of free fatty acids was necessary for MSU crystals to induce gout-like reactions in mice, via engagement of the TLR-2, activation of ASC and caspase-1, but not NLRP3, and release of IL-1β [77].

The controversy about the mechanism of MSU-induced gout inflammation is not entirely resolved, yet all researchers convene on the MSU-associated release of IL-1β, recruitment and activation of neutrophils, and their inflammatory roles [84]. The functions of IL-1β are multiple and include inducing fever (endogenous pyrogen) via setting the hypothalamic thermostat in the brain, promoting collagenase expression and destruction of muscle and cartilage (catabolin), eliciting inflammation, and recruiting and activating neutrophils [64–69,30,84,85].

Uric acid is also considered a danger signal responsible for increasing osteoarthritis via inflammasome activation as a direct correlation was consistently recorded between severity of knee osteoarthritis and synovial, but not serum, content of uric acid, IL-1β and IL-18 [86,87].

Renal disorders

The kidneys play a major role in the regulation of serum uric acid levels as approximately one third and two-thirds of the uric acid produced in humans is eliminated by the gastrointestinal tract and kidneys, respectively. In the kidney, uric acid undergoes filtration from glomeruli, followed by reabsorption and secretion in the proximal tubules, whereby 90% is reabsorbed into the blood capillaries [2]. Renal tubular handling of uric acid is now shown to be dependent on several proteins belonging to the organic anion transporter (OAT) family. The product of the *SLC22A12* gene, the urate transporter 1 (URAT1) protein on the apical membrane of the renal proximal tubule is highly, if not exclusively, expressed in the kidney, and was the first to be identified as a reabsorptive urate transporter. OAT4 is similar to URAT1 in location and function, namely reabsorption of uric acid. OAT1 and OAT3, encoded by the *SLC22A6* and *SLC22A8* genes, respectively are localized to the basolateral membrane of the renal proximal tubules and form a renal tubular secretory pathway principally involved in luminal excretion of uric acid [2,88]. In addition, recent evidence has demonstrated the instrumental role of the hexose transporter GLUT9 in uric acid reabsorption and interstitial exit as mutations of its encoding gene *SLC2A9* are associated with aberrations of uric acid disposal [70,88].

Increased uric acid production, impaired renal uric acid excretion, or a combination of the two lead to hyperuricemia [2,89]. Hyperuricemia increases the risk of acute kidney injury [90], impairs the contractile activity of the intraglomerular mesangial cells [91], and induces damage to mesangial and proximal tubules epithelial cells probably via TLR 4-dependent up regulation of NLRP3 and IL-1β [92,93]. Hyperuricemia was also shown to be an independent risk factor for chronic kidney disease in type 2 diabetes via injury of the endothelial cells and release of the alarmin HMGB1, stimulating TLR to induce pro-inflammatory and chemotactic cytokines, vascular smooth muscle proliferation, and activation of the NLRP3 inflammasome [94].

Additionally, uric acid may accumulate in the kidney, leading to formation and deposition of stones. Kidney stones and urinary tract infections are the most common urinary tract problems. Uric acid stones occur in 10% of all kidney stones and are the second most-common cause of urinary stones after calcium oxalate and calcium phosphate calculi. The most important risk factor for uric acid crystallization and stone formation is a low urine pH (below 5.5) due to impaired urinary uric acid excretion. Main causes of low urine pH beside high uric acid excretion are chronic diarrhea, severe dehydration, and diabetic ketoacidosis [95].

The metabolic syndrome

Metabolic syndrome is the name for a group of risk factors that raises the threat for heart disease and other health problems, such as diabetes and stroke. Cardiovascular disease (CVD), diabetes type 2, and non-alcoholic fatty liver disease (NAFLD) are manifestations of the metabolic syndrome [95–99].

Cardiovascular diseases

Hyperuricemia was shown to be implicated in development of hypertension and cardiovascular diseases, via induction of growth factors, hormones, cytokines and autacoids [98–100].

Experimental studies have suggested that uric acid may penetrate vascular smooth muscle fibers through an organic anion transport system, followed by activation of multiple signal transduction pathways, which culminate in increased expression of inflammatory mediators. The consequences are a rise of arterial pressure, vascular smooth muscle cell hypertrophy, and hypertension [100,101]. Additionally, soluble uric acid induces vascular endothelial cell dysfunction, namely alteration of cell proliferation and induction of cell senescence and apoptosis, via activating the renin-angiotensin system (a hormone system responsible for regulating plasma sodium concentration and arterial blood pressure) and triggering reactive oxygen and nitrogen species and endoplasmic reticulum stress [102–104].

Insulin resistance and diabetes type 2

An elevated serum uric acid is also one of the best independent predictors of diabetes and commonly precedes the development of both insulin resistance and diabetes type 2, as it was discovered that one quarter of diabetes cases can be attributed to a high serum uric acid level and elevated serum uric acid levels were found to be closely associated with insulin resistance and diabetes mellitus type 2 [105,106]. In response to controversial findings [107], a meta-analysis of prospective cohort studies [108] and a recent critical review [109] concluded that serum uric acid is a strong and independent risk factor for diabetes in middle-aged and older people. Additionally, an increased serum uric acid level was significantly correlated with the severity of albuminuria and diabetic retinopathy in patients with type 2 diabetes mellitus [110].

Rise in consumption of fructose-containing drinks, food and table sugar (sucrose = glucose + fructose) during the last centuries has led to increase in weight gain, visceral and hepatic fat accumulation, resistance to insulin and incidence of diabetes, as well as increase in generation of uric acid, which predisposes to onset of metabolic syndrome, including diabetes. In the liver, the enzyme ketohexokinase phosphorylates fructose, resulting in fall in levels of intracellular phosphates and ATP (adenosine triphosphate). Decrease in intracellular phosphates activates adenosine monophosphate (AMP) deaminase, which catabolizes AMP to inosine monophosphate, and eventually to uric acid via the hypoxanthine-xanthine pathway [111,112]. Elevated amounts of intracellular uric acid are then released in the circulation, inducing inflammation in endothelial cells, kidney and vascular muscle fibers, and pancreas islets of Langerhans [112].

Non-alcoholic fatty acid disease

Numerous clinical and experimental reports have documented association between high serum uric acid levels and non-alcoholic fatty liver disease (NAFLD) [30–35]. The serum uric acid role in producing NAFLD was recently explained via uric acid-mediated generation of ROS and pro-inflammatory cytokines, which lead to increased expression of thioredoxin (TXN)-interacting protein (TXNIP), and ROS-dependent dissociation of TXN from TXNIP, which then interacts with NLRP3, activating the inflammasome in parenchymal and non-parenchymal liver cells, and resulting in release of IL-1β and IL-18. The ROS-TXNIP pathway inflammatory signaling induces deregulation of lipid metabolism-related gene expression and lipid accumulation [31–33], through overexpression of the lipogenic enzyme, acetyl-coenzyme A (COA) carboxylase 1, fatty acid synthase and stearoyl-COA desaturase 1. Another mechanism for uric acid-mediated fat accumulation in liver proposed that uric acid induces oxidative stress in hepatocytes endoplasmic reticulum followed by cleavage into active form and nuclear translocation of the transcription factor, sterol regulatory element-binding protein (SREBP), which regulates the expression and activity of lipogenic enzymes [34]. Of note, analysis of the fatty acid composition of liver phospholipid of patients with NAFLD revealed a significant ($P < 0.05$) elevation of arachidonic acid content and polyunsaturated fatty acid n−6/n−3 ratio compared with control values [35]. Plasma fatty acid composition of people with NAFLD was recently shown to be associated with increase in omega-6 polyunsaturated fatty acids, especially arachidonic acid, compared to healthy controls [36,37].

Conclusions and future perspectives

The contribution of uric acid to development and progress of gout and metabolic syndrome appears to be well-established. The pivotal role of uric acid in preservation of the human species and the individual may be anticipated by the loss of the enzyme uricase in humans and the eagerness of the kidney to retrieve filtered uric acid. Yet, studies are needed to document the paramount importance of uric acid in resistance to infectious, neurological and autoimmune diseases.

Running studies are planned to document a novel and instrumental physiologic function of uric acid in resistance to blood-borne helminthes via providing and publishing solid evidence for the role of type 2 immune responses/uric acid/arachidonic acid axis in innate and acquired protective immunity to infection with *S. mansoni* and *S. haematobium* in rodents.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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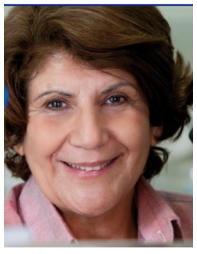

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