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Review

Physiological functions and pathogenic potential of uric acid: A review

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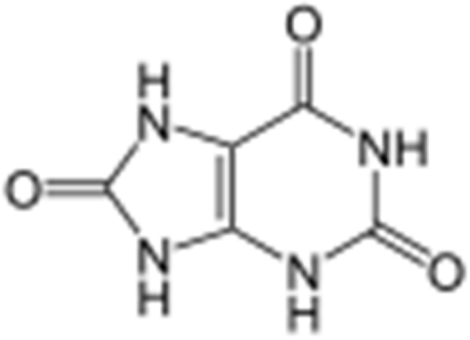
GRAPHICAL ABSTRACT



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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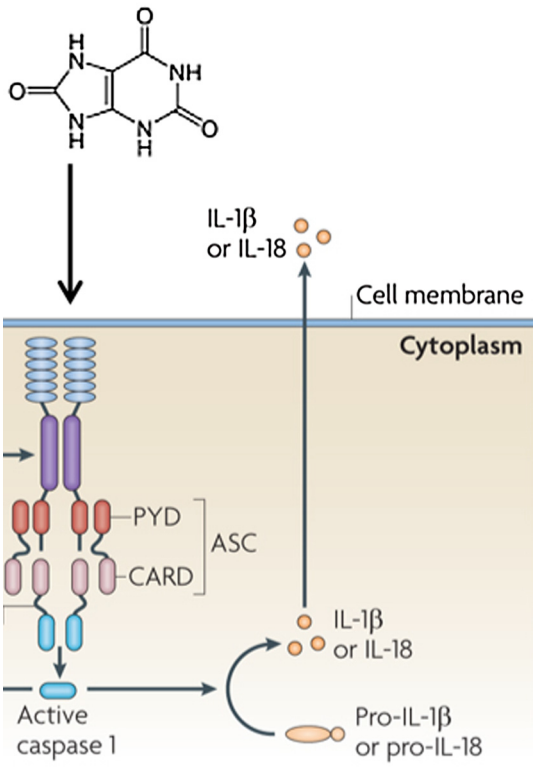

Fig. 1. The most alarming step [80]. Uric acid, $C_5H_4N_4O_3$, 7,9-dihydro-1 H-purine-2,6,8(3 H)-trione, molecular mass 168 Da, is a product of the metabolic breakdown of purine nucleotides (adenine and guanine). Crystals of monosodium urate (MSU) in the joints stimulate the inflammasome, NLRP3. The 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