Insights into the relationship between serum uric acid and pulmonary hypertension (Review)

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Abstract. Pulmonary hypertension (PH) is a progressive lethal disease, which is characterized by abnormal vascular remodeling and persistently elevated pulmonary artery pressure, eventually leading to right heart failure and even death. Although great progress has been made in treating PH, the mortality rate remains high. Metabolic disorders are one of the important hallmarks of PH. Obesity, lipids, glucose tolerance and insulin resistance are risk factors for numerous cardiovascular diseases and are often accompanied by a considerable increase in serum uric acid (SUA) concentrations. Uric acid (UA) is the end product of purine nucleotide metabolism and is closely related to cardiovascular diseases including PH. Hyperuricemia promotes the development and progression of PH through endothelial dysfunction, oxidative stress, inflammatory responses and activation of the renin-angiotensin system. In the present review, the advancements in knowledge about UA metabolism and PH, and the current understanding of the potential interactions and mechanisms of SUA in PH were systematically summarized, which may provide new insights into the pathogenesis of PH.

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Key words: serum uric acid, hyperuricemia, metabolic disorder, pulmonary hypertension, cardiovascular disease

Contents

1. Introduction

Pulmonary hypertension (PH) is a serious health problem that affects ~1% of the global population (1). In the United States and Europe, pulmonary arterial hypertension (PAH) is found in 15-50/million individuals (2). Among them, idiopathic, heritable and anorexigen-induced PH account for 52.6% of total PH cases, of which 6-10% of patients have a family history of PH (3,4). Furthermore, >70% of patients with PAH are women aged 20-40 years, and its incidence is twice as high as that in men (5-7). Although the advancement of medical treatments has improved the survival rate, the prognosis of PH is still poor, and its mortality rate remains high (8). The 5-year mortality rates of patients diagnosed with idiopathic pulmonary arterial hypertension (IPAH) or familiar PH were 31.8 and 46.3%, respectively in China as of 2014 (9). Increasing evidence has shown that a variety of systemic metabolic derangements are associated with PH with a number of studies on this topic focused on the role of obesity, dyslipidemia, insulin resistance (IR), glucose intolerance and metabolic disorder in the progression of pulmonary circulation diseases (10-13). Hyperuricemia is an important metabolic syndrome and is closely associated with gout, coronary heart disease, hypertension, heart failure and atrial fibrillation through oxidative stress, endothelial

dysfunction, inflammatory reactions and activation of the renin-angiotensin-aldosterone system (14-17). These conditions may directly lead to the occurrence or development of these diseases (18-25). Whether hyperuricemia is an independent risk factor of PH and how hyperuricemia promotes the occurrence of PH remains to be determined. To the best of our knowledge, there has been no systematic analysis of these issues to date. In the present review, the complex relationship between hyperuricemia and PH is focused on providing a novel viewpoint and strategy for the prevention and treatment of PH.

2. Search strategy

PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (webofscience.com/) and Science Direct (https://www.sciencedirect.com/) databases were searched for PH and uric acid (UA; hyperuricemia) relevant studies and systematic reviews without language or time restrictions. The search subject terms included: Pulmonary hypertension, pulmonary arterial hypertension, IPAH, secondary PH, cardiovascular disease, UA, serum UA (SUA), hyperuricemia, metabolic, inflammatory responses, oxidative stress, renin-angiotensin system, endothelial dysfunction, smooth muscle cell proliferation. No artificial intelligence tools were used in the preparation of the reviews or manuscripts.

3. Pathophysiological basis of PH

PH is a chronic progressive disease, which is related to metabolic processes (26). PH is characterized by rising pulmonary artery pressure and vascular remodeling, which eventually lead to right heart failure and death (27). According to the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension, PH is defined on the basis of right heart catheterization hemodynamic assessment. Pre-capillary PH is defined as mean pulmonary arterial pressure (mPAP) >20 mmHg at rest, pulmonary arterial wedge pressure (PAWP) <15 mmHg and pulmonary vascular resistance (PVR) >2 Wood units at rest. Postcapillary PH is defined as mPAP >20 mmHg and PAWP ≥15 mmHg at rest. Exercise PH is defined as an mPAP/cardiac output slope >3 mmHg/l/min between rest and exercise (28,29). Currently, the clinical classification of PH follows the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH (30,31) and the Proceedings of the 6th World Symposium on PH (32). PH is divided into five categories according to the etiology and hemodynamic parameters (33) as follows: i) PAH, including idiopathic and hereditary PH; ii) PH caused by left heart disease, including heart failure and valvular heart disease with a maintained or decreased ejection fraction; iii) PH caused by pulmonary diseases and/or hypoxia, including chronic obstructive pulmonary disease, interstitial lung disease and other pulmonary diseases with mixed restrictive and obstructive modes; iv) chronic thromboembolic PH and other pulmonary artery obstructions; and v) PH with unclear and/or multifactorial mechanisms, including blood and systemic disease (31,34). PH is not a disease isolated to pulmonary circulation but is considered a systemic disease associated with notable metabolic dysfunction (35). Among these, PH caused by left heart disease, lung disease and/or hypoxia and connective tissue disease may be closely related to metabolic disorders of the pulmonary circulation (36-38). When pulmonary circulation metabolism is disordered, circulating metabolic substances can induce dysfunction of pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs), and stimulate excessive proliferation and anti-apoptosis of pulmonary vascular cells (26). These conditions eventually lead to pulmonary vascular remodeling and provide conditions for the development of PH (39,40). UA, which is one of the products of purine metabolism, can be affected in certain pathological states, resulting in abnormal UA concentrations in the pulmonary circulation. Although, increased UA in the pulmonary circulation deteriorates PH, the associated molecular mechanisms remain unclear (41). Before determining the effect of UA on PH, the sources, metabolic pathways and biological properties of UA need to be understood.

4. Metabolism and biological characteristics of UA

Source and metabolism of UA. UA can be derived exogenously and endogenously. Exogenous UA, which accounts for 20% of the total UA, originates from exogenous foods rich in purine compounds, nucleic acids and nucleoproteins, such as animal viscera, seafood, mushrooms, beans, wine and meat (42). Endogenous UA accounts for 80% of the total sources and is derived from purine products formed by the transformation, decomposition and metabolism of amino acids, phosphoribosyl and nucleic acids in the body (43,44).

There are numerous enzymes involved in the conversion of adenine and guanine to UA. Xanthine oxidase is the key rate-limiting enzyme in this process and it plays an important role in purine metabolism. Xanthine oxidase is involved in two important stages in the conversion of purines to UA: i) The conversion of hypoxanthine to xanthine; and ii) the conversion of xanthine to UA (45). Hypoxanthine nucleotides (inosine monophosphate) and guanine nucleotides are converted to xanthine by oxidation of xanthine oxidase-hypoxanthine and deamination of guanine by guanine deaminase (46). Finally, xanthine is further oxidized to UA by xanthine oxidase (46-48). In most mammals, uricase further oxidizes UA to allantoin, but humans cannot convert UA into allantoin, which is more soluble owing to the lack of uricase (Fig. 1) (49-51). Therefore, human purine catabolism ends in the UA stage.

The metabolism of SUA *in vivo* requires an important transporter called human urate transporter 1 (URAT1), which is encoded by the gene, *SLC22A12* (52). It is expressed in the mural membrane of proximal renal tubular cells (53,54). Human URAT1 acts as a urate/anion exchanger and is involved in the reabsorption of urate in the kidneys (55). At a physiological pH, UA mainly exists in the form of urate (46). Reportedly, ~70% of UA is metabolized in the kidney, and after filtration by the glomerulus, more than 90% of UA is reabsorbed and secreted by the renal tubules, with ~10% excreted in the urine (46,56). In addition, ~30% of UA is metabolized in the intestine (42). Adenosine triphosphate binding cassette transporter 2, which is another urate transporter, is widely expressed on the surface of intestinal lumen cells and plays a major role in intestinal excretion (Fig. 2) (57-60). Therefore, UA excretion occurs mainly in the kidneys and intestines.

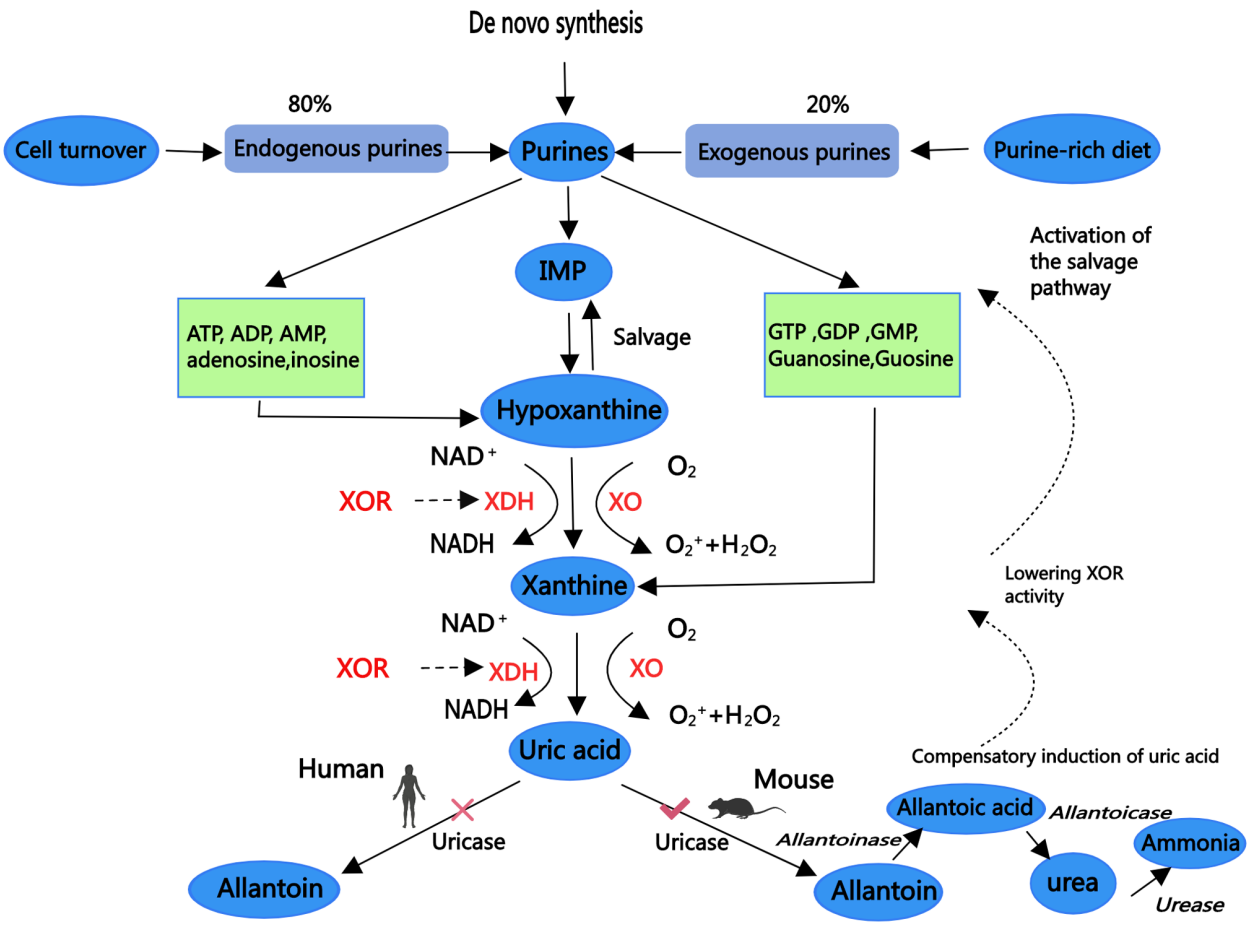

Figure 1. Sources and metabolism of UA. Endogenous and exogenous purines are metabolized to UA by XO through the *de novo* and remedial synthesis pathways of purines. Purine metabolism terminates at the UA stage owing to the absence of uricase in the human body. However, rodents have the enzyme allantoinaise, which metabolizes UA into the more soluble allantoin, and further breaks it down into urea and ammonia. XO, xanthine oxidase; UA, uric acid; IMP, inosine monophosphate; XDH, xanthine dehydrogenase; XOR, xanthine oxidoreductase.

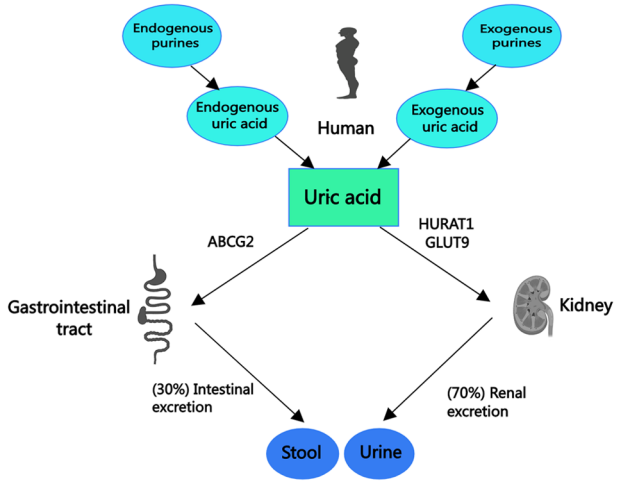

Figure 2. Excretion routes of UA. Endogenous and exogenous purines are ultimately synthesized into UA through a variety of metabolic pathways. A total of 30% of the body's UA is excreted through the intestines and 70% in the kidneys. UA, uric acid; ABCG2, ATP-binding cassette superfamily G member 2; HURAT1 human uric acid transporter 1; GLUT1, glucose transporter 1.

Normal SUA concentrations are 89-357 μmol/l (1.5-6.0 mg/dl) in women and 149-417 μmol/l (2.5-7.0 mg/dl) in men (46). However, impaired purine metabolism in the body, such as excessive purine food intake and disease (e.g., obesity, diabetes and tumor), can lead to increased UA production and/or decreased excretion, which further results in an increase in SUA concentrations and even hyperuricemia (61). Hyperuricemia is usually defined as an SUA concentration >417 μmol/l (7.0 mg/dl) in men and postmenopausal women, or ≥357 μmol/l (6.0 mg/dl) in premenopausal women with a normal purine diet (46). When the average SUA concentration in humans is higher than its solubility limit of 405 μmol/l (6.8 mg/dl), urate crystals are formed and deposited in the kidneys, tissues and joints (62), leading to renal calculi, gout and other diseases (e.g., gouty arthritis).

The variability of SUA concentrations is multifactorial, and it is also affected by genetic and non-genetic factors (63). Genome-wide association studies have shown that the polymorphism and mutations of genes encoding SLC22A12, SLC2A9 and adenosine triphosphate binding cassette transporter 2 are related to hyperuricemia (64). In addition, the transporters URAT1, glucose transporter 9 (GLUT9) and breast cancer resistance protein are associated with hyperuricemia and gout (64-67). The concentration of UA is influenced by non-genetic factors, mostly caused by excessive intake and decreased excretion.

Physiological characteristics of UA. Biologically, UA can have not only pro-oxidative but also anti-oxidative properties (68-72).UA has antioxidant effects under physiological conditions. The antioxidant mechanism of UA is mainly driven by the fact that UA is an oxygen radical scavenger, scavenging superoxide anions, hydroxyl groups, singlet oxygen and other reactive substances *in vivo* (73,74). This protects the cardiovascular system from oxidative stress damage. UA acts as a pro-oxidant in states with high levels of UA or low levels of other antioxidants (68). The oxidative effects of UA mainly manifest in mediating the immune response after cell injury (75), increasing pro-inflammatory immune activation (76) and promoting low-density lipoprotein oxidation (77), the proliferation of smooth muscle cells and activation and the adhesion of platelets (78). In the presence of Cu^{2+} in the *in vitro* environment, UA is susceptible to antioxidant-oxidant interconversion (79,80). In addition, UA can react with other oxidants ($ONOO^-$, OH^-) and form pro-oxidants, which participate in lipid metabolism and cause a chain reaction of lipophilic radical oxidation (81,82). Therefore, UA exerts oxidative and antioxidant effects at different concentrations (83,84). In cardiovascular disease, UA is considered a 'double-edged sword' with beneficial and detrimental effects on cardiovascular disease (17,85). So, is there a similar association between UA and PH?.

5. Interaction of UA and PH

PH affects the level of UA metabolism. Hyperuricemia is commonly found in patients with secondary PH. Patients with PH and hemolytic diseases, such as thalassemia (86), sickle cell anemia (87), spherocytosis (88) and paroxysmal sleep hemoglobinuria (89,90), can develop erythrocyte lysis, adenosine deaminase release (91), tissue and organ hypoxia, reduced oxygen-carrying capacity and increased UA metabolism (92). In patients with PH and metabolic syndrome (93), hyperinsulinemia enhances the reabsorption of urate in the proximal tubules and UA concentrations increase (94). Inflammation, hypoxia and endothelial damage caused by connective tissue disease-related PH, such as systemic sclerosis, systemic lupus erythematosus and Sjogren's syndrome, also play an important role in the increase in UA concentrations (95). After inflammation is activated, the release of cytokines promotes pulmonary artery vessel remodeling and cell proliferation, resulting in insufficient lung perfusion, tissue ischemia and hypoxia (96,97). These findings suggest that patients with secondary PH are closely associated with abnormal UA metabolism, and the SUA concentration reflects the severity of the illness to a certain extent. Therefore, UA may be useful as a potential biological marker of PH and may be able to be applied to the clinical setting and therefore, the importance of the application of UA in clinical treatment is discussed in the present review.

UA as a potential biomarker of PH. The relationship between SUA and IPAH was first discovered in 1999 (98). Nagaya *et al* (98) found that patients with IPAH have considerably elevated SUA concentrations and the degree of SUA increase was positively correlated with the severity of New York Heart Association (NYHA)classification (99), negatively correlated with cardiac output, positively correlated with total pulmonary resistance, and correlated with the severity of IPAH, which was also an independent risk factor for poor prognosis of IPAH (98). The logarithm of SUA concentration was closely related to MPAP and right atrial pressure (100-102). When SUA concentrations are >339 μmol/l (5.7 mg/dl), SUA concentrations predict right ventricular dysfunction in patients with IPAH (102,103). Baseline hyperuricemia and high variability in SUA concentrations at the first follow-up are strongly associated with 5-year mortality in patients with IPAH (104). Elevated SUA concentrations shorten the survival of patients with IPAH, whereas low SUA concentrations improve survival and delay clinical deterioration (105). Therefore, in the long term, high SUA concentrations may be a good predictor of survival in patients with IPAH. Close monitoring of UA concentrations may be useful in assessing the disease severity, clinical prognosis of patients with PH and early detection of patients at high risk of death from IPAH.

Similar to IPAH, UA has high clinical value in connective tissue disease-associated PH. In patients with PH secondary to systemic sclerosis, elevated SUA concentrations are negatively correlated with the 6-min walk test distance and linearly correlated with pulmonary artery pressure (106-109). Serum uric acid concentrations were significantly elevated in patients with systemic lupus erythematosus (SLE) secondary to PH and were significantly correlated with plasma NT-pro-B natriuretic peptide (NT-pro-BNP) levels and resting pulmonary systolic pressure (sPAP), as well as responding to the severity of SLE disease (110). When SUA is above the critical concentration of 6.5 mg/dl, the incidence of PH in patients with SLE can be reasonably and accurately predicted. Therefore, SUA concentrations can be used as an alternative marker to screen for PH in patients with SLE (111). When the baseline SUA concentration is ≥416 μmol/l (7 mg/dl), future development of PH secondary to SLE can be predicted (112). A multifactorial analysis showed that high UA concentrations were not only associated with all-cause mortality from disease but also strongly associated with death from PH and thus, UA concentrations may serve as an independent predictor of survival in patients with connective tissue-related PH (113). Therefore, dynamic observation of SUA concentrations may be useful for assessing the severity of the condition and serve as a predictor of prognosis in connective tissue disease-associated PH.

In conclusion, UA is not only a marker of metabolism but also a representative independent risk factor and predictor of PH. The aforementioned evidence suggests that UA is closely associated with PH (114-117). However, the specific mechanisms involved in hyperuricemia promoting the development and progression of PH is unclear. In the present review, the effects of high UA concentrations on PH and the molecular mechanisms of the effects of high UA concentrations on endothelial cells, smooth muscle cells and renin-angiotensin system (RAS) activation are described.

6. Hyperuricemia promotes the development of PH

Hyperuricemia can mediate the development of cardiovascular disease by inducing endothelial dysfunction, oxidative stress, inflammatory responses and activation of the RAS (Fig. 3) (118-122). On a pathophysiological basis, UA also

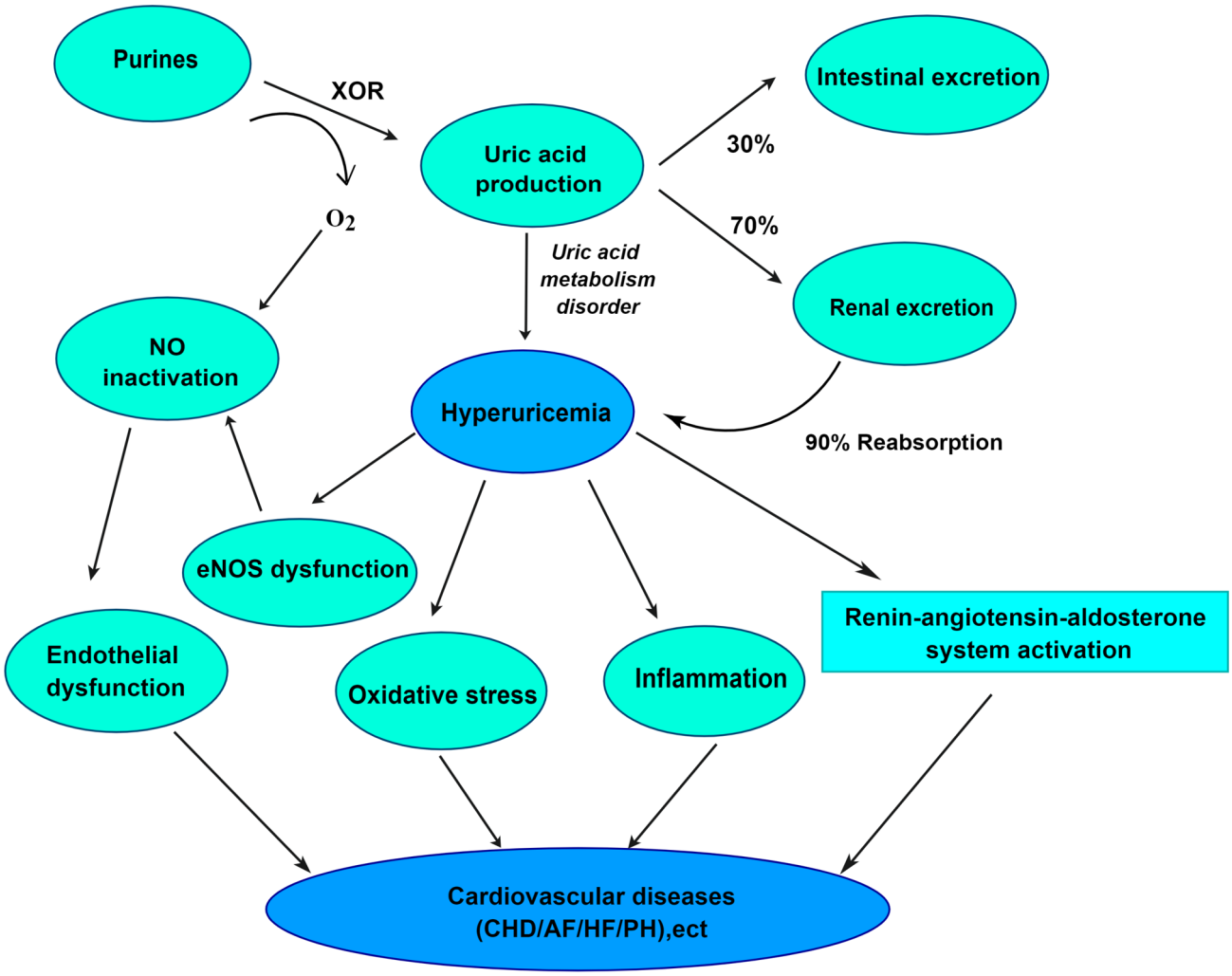

Figure 3. High UA affects the development of cardiovascular disease through endothelial dysfunction, oxidative stress, inflammation and activation of the RAS system. Disturbances in UA metabolism can cause hyperuricemia, which affects the development and progression of cardiovascular diseases through endothelial dysfunction, oxidative stress, inflammation and activation of the RAS system. Pre-capillary PH: mPAP >20 mmHg, PAWP <15 mmHg and PVR >2 Wood units at rest. Post-capillary PH: mPAP >20 mmHg and PAWP ≥15 mmHg at rest. PH, pulmonary hypertension; CHD, coronary heart disease; AF, atrial fibrillation; HF, heart failure; RAS, renin-angiotensin system; UA, uric acid; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; NO, nitric oxide; eNOS, endothelial NO synthase; XOR, xanthine oxidoreductase.

induces pulmonary vascular endothelial dysfunction and promotes the transformation of smooth muscle cell proliferation (123,124), thereby possibly promoting the development of PH. The series of molecular mechanisms whereby UA affects the course of PH through a series of molecular mechanisms are described in the present review.

UA induces endothelial dysfunction. Endothelial cells are in direct contact with blood flow and act as a permeability barrier to maintain the exchange between the tissues of the vessel wall and blood (125,126). Furthermore, endothelial cells secrete vasoactive substances and cytokines, which also play an important role in regulating vasoconstriction, vascular inflammation, platelet aggregation and adhesion (127). Therefore, the integrity of endothelial function plays a major role in maintaining cardiovascular homeostasis.

Endothelial dysfunction is one of the main pathological features of PH (128-130). Numerous studies have shown that hyperuricemia causes endothelial dysfunction and may play an important role in the vascular remodeling of PH (131). However, the specific mechanisms by which UA affects endothelial dysfunction are not fully understood.

Nitric oxide (NO) is an endothelium-derived relaxing factor and it regulates vascular tension, inhibits platelet activation and causes intimal hyperplasia (132). High UA concentrations are hypothesized to result in endothelial dysfunction by affecting the production of NO, which may contribute to PH (133). UA may affect the formation of NO in two ways. Firstly, UA can be directly oxidized with NO to form superoxide anion, which consumes high levels of NO. Secondly, there are various pathways by which UA inhibits NO production which are described in the present review.

Endothelial NO synthase (eNOS) is a key enzyme for NO synthesis in endothelial cells. This enzyme catalyzes the hydrolysis of L-arginine to produce NO (134). UA can enter endothelial cells through URAT1 on the cell membrane (135), inducing intracellular reactive oxygen species production, endoplasmic reticulum stress and protein kinase C activation (136). Activated protein kinase C inactivates the inhibitory site of eNOS, Thr495, by phosphorylating it and rendering it

unable to bind calmodulin and catalyzes NO synthesis (136). In addition to regulating glucose homeostasis, insulin activates the signal of phosphatidylinositol 3-kinase (PI3K)-protein kinase B (Akt), which promotes the activation of eNOS phosphorylation and NO production, thus inducing vasodilation (137). Hyperuricemia antagonizes insulin receptor substrates and blocks insulin-dependent eNOS phosphorylation in the PI3K/Akt/eNOS pathway, thereby inhibiting NO production (137,138). Elevated UA concentrations in patients with metabolic syndrome (MS) can trigger endothelial dysfunction by decreasing endothelial NO bioavailability, while reduced NO production in this pathway may be associated with hyperinsulinemia and insulin resistance (IR) (139), which lead to increased monocyte adhesion and impaired cellular energy metabolism (140,141).However, allopurinol may restore the effect of insulin on NO production and vasodilation by reducing SUA concentrations, thereby improving the associated clinical symptoms (142,143).

UA also increases the expression of the inflammatory cytokines interleukin-6 and interleukin-8, tumor necrosis factor-α and miR-155 by activating nuclear factor-κB (NF-κB) (144,145). Overexpression of miR-155 leads to decreased eNOS stability, reduced NO production and endothelial dysfunction (146). By contrast, the use of NF-κB inhibitor II can prevent the UA-induced decrease in NO and the inflammatory reaction (145). Furthermore, arginase competes with eNOS to bind L-arginine and catalyze its hydrolysis to ornithine and urea (147). However, UA reduces NO production in endothelial cells by increasing arginase activity and promoting competition between arginine and eNOS for L-arginine (41,147). Mitochondrial damage is also a major feature of endothelial dysfunction. UA can trigger mitochondrial calcium overload and reactive oxygen species production by activating the mitochondrial Na^+/Ca^{2+} exchanger (148). This process can inhibit the tricarboxylic acid cycle and damage mitochondrial DNA, thus leading to endothelial dysfunction (149). These findings suggest that UA induces reduced NO production and vascular endothelial dysfunction, which in turn causes abnormal pulmonary vasoconstriction and provides a pathophysiological basis for the development of PH.

UA promotes smooth muscle cell proliferation. UA can enter vascular smooth muscle cells (VSMCs) via URAT1 (SLC22A12, a member of the organic anion transporter superfamily) (150,151), stimulating specific mitogen-activated protein kinases (MAPKs), ERK 1/2 and p38 MAPK (152,153). This stimulation induces cyclooxygenase-2 production and local coagulation, promotes platelet-derived growth factor (PDGF)-A and PDGF-C chain secretion and upregulates PDGF-A receptor mRNA expression, promotes VSMC proliferation, increases cell survival and reduces apoptosis (123,153-159). However, angiotensin II (Ang II) type I receptor inhibits UA-induced activation of p38 MAPK and ERK 1/2, thereby blocking the proliferative pathway of VSMCs (153,160). In addition, UA may also regulate the proliferation of smooth muscle cells by inducing inflammatory responses and activation of the chemokine monocyte chemoattractant protein 1, transcription factor activator protein-1, NF-κB and inflammasome NOD-like receptor protein 3 (153,161,162). Xanthine oxidase and URAT1 were up-regulated in remodeled pulmonary artery walls in patients of IPAH, monocrotaline (MCT) and Sugen-hypoxia rats, increasing intracellular UA production, which promotes the proliferation of pulmonary artery smooth muscle cells, leading to further deterioration of PH (163). Thus, UA promotes smooth muscle cell proliferation and may play an important role in vascular remodeling in PH.

Activation of the RAS by UA aggravates pulmonary artery pressure. The RAS is an important and complex endocrine system in the body. It not only plays an important role in regulating blood pressure and maintaining extracellular fluid homeostasis, but also affects the normal development of the cardiovascular system and maintains homeostasis of cardiovascular function (164). Several studies have shown that elevated SUA concentrations may be associated with activation of the RAS (121,161,165-168). In animal studies, high UA concentrations inhibited NOS-1 activity in glomerular dense plaques, downregulated NO production and activated the RAS (157,160,169-171), leading to elevated blood pressure. These findings are consistent with human studies suggesting that UA activates the RAS to mediate an elevation in blood pressure (172,173). Usually, the activation of RAS begins with the decrease of blood flow through renal artery (174). The production of angiotensin peptides is first initiated by the synthesis and processing of preprorenin in juxtaglomerular cells neighboring the renal glomerulus with subsequent proteolytic cleavage of the signal peptide, intracellular sorting of prorenin to dense-core secretory vesicles, and cleavage of the prosegment, producing catalytically active renin that is secreted in the systemic circulation (164,175,176). Renin hydrolyzes angiotensinogen secreted by the liver to produce angiotensin I (Ang I) (177). In PAECs, Ang I is cleaved to Ang II by angiotensin-converting enzyme (178). In the mechanism of high UA-induced endothelial dysfunction, excess UA can be rapidly taken up by vascular smooth muscle cells, and intracellular UA upregulates angiotensinogen mRNA expression, thereby promoting Ang II production and Ang II type 1 receptor (main effector peptide of RAS) expression (179). These findings suggest that UA upregulates Ang II expression, activates the RAS system, produces oxidative stress, and leads to endothelial cell senescence and apoptosis (179,180). Ang II, which is a pleiotropic endocrine and paracrine hormone, upregulates vasopressin released by the central nervous system and induces VSMC contraction in the pulmonary circulation and systemic arterial and venous circulation (176,181). In addition, Ang II stimulates the release of aldosterone, which stimulates mineralocorticoid receptors in PAECs, inducing hypertrophy of PASMCs and pulmonary artery vascular remodeling (182-185). However, the vascular remodeling effects caused by UA and Ang II stimulation of VSMC proliferation and hypertrophy is inhibited by losartan [an angiotensin receptor blocker (ARB)] and captopril [an angiotensin-converting enzyme inhibitor (ACEI)] (157,186). Ang II also promotes vasoconstriction, proliferation, inflammation and fibrosis in the pulmonary vascular system and lung parenchyma by stimulating ANG II type 1 receptor (187,188). All of these studies suggest that UA mediates the relationship between the RAS and PH, promoting pulmonary vascular remodeling, enhancing

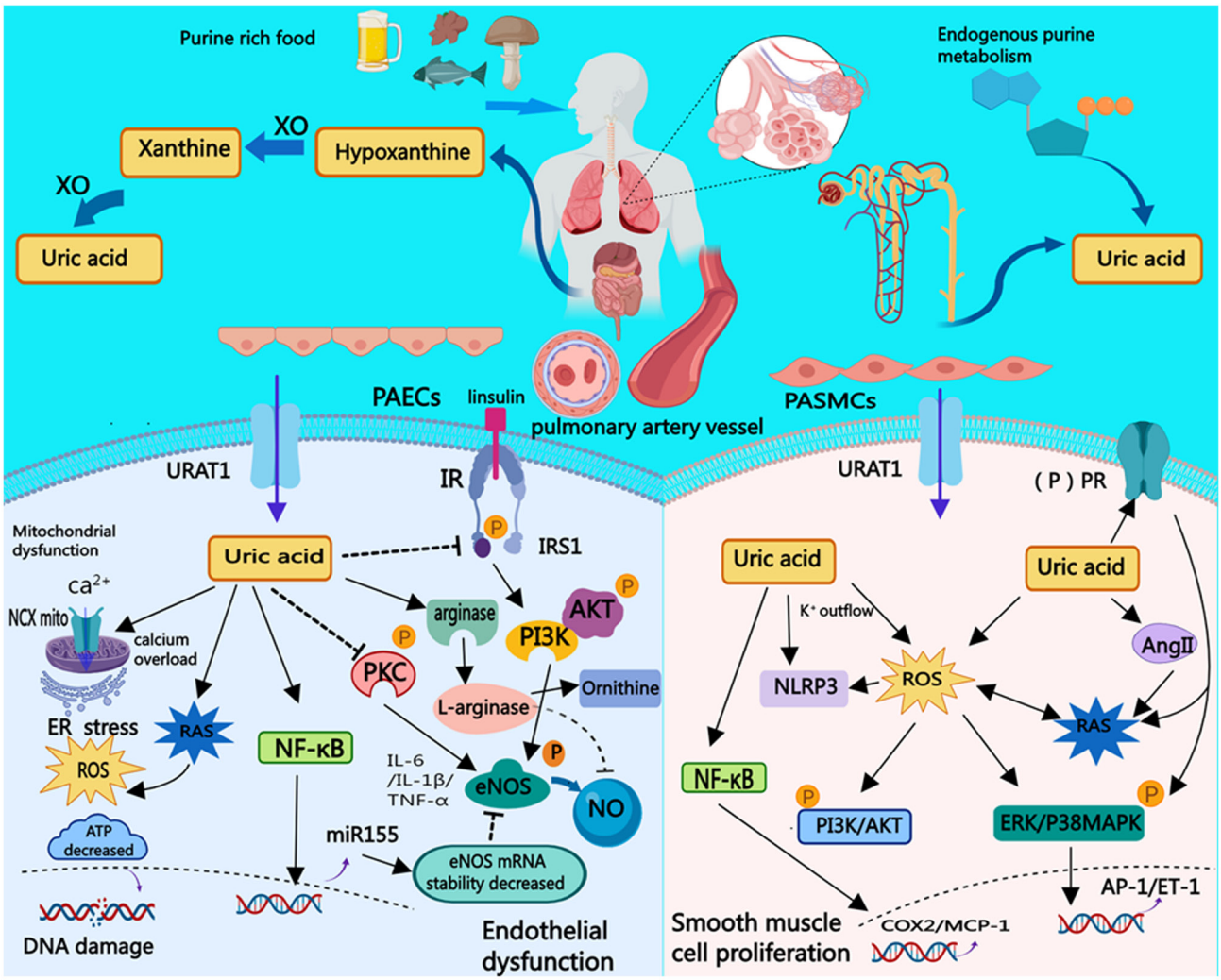

Figure 4. Investigation of the molecular mechanisms of the potential association between high UA concentrations and PAECs and PASMCs. After entering endothelial cells, UA induces the production of ROS, activates mitochondria to trigger calcium overload and affects NOS activity or stability through various pathways. The activation of these pathways causes reduced NO production and an inflammatory response, which leads to endothelial dysfunction and abnormal pulmonary vascular constriction. UA can also directly act on smooth muscle cells, promoting smooth muscle cell proliferation. NO, nitric oxide, NO; PAECs, pulmonary artery endothelial cells; PASMCs, pulmonary arterial smooth muscle cells; XO, xanthine oxidase; RAS, renin-angiotensin system; URAT1, urate transport protein 1; GLUT-9, glucose transporter-9; NLRP3, NOD-like receptor protein 3; eNOS, endothelial NO synthase; NCX mito, mitochondrial Na^+/Ca^{2+} exchanger; NF-κB, nuclear factor-κB; PKC, protein kinase C; ER, endoplasmic reticulum; ROS, reactive oxygen species; IR, insulin receptor; IRS1, insulin receptor substrate 1; MCP-1, monocyte chemoattractant protein 1; (P)PR, renin (pro)receptor.

pulmonary vasoconstriction and ultimately exacerbating the progression of PH.

7. Potential mechanisms by which PH affects UA concentrations

PH affects UA concentrations in two main ways. First, an elevation in SUA concentrations in patients with PH is mainly due to tissue ischemia/hypoxia and oxidative stress (30,189,190). When oxygen metabolism is abnormal in the body, tissue ischemia or hypoxia and oxidative stress can lead to elevated UA concentrations (191,192). For example, PH is associated with chronic heart failure and chronic obstructive pulmonary disease, tissue hypoxia, increased anaerobic metabolism, decreased adenosine triphosphate synthesis and accelerated purine degradation, leading to increased uric acid production (193-195). In addition, patients with heart failure are often associated with renal insufficiency or even renal failure, which can reduce UA excretion and lead to increased UA concentrations (196). As SUA concentrations rise, free radicals released by xanthine oxidase may activate inflammatory cells (197). When UA concentrations exceed the threshold, hyperuricemia enhances intracellular urate accumulation via down-regulation of cell-surface BCRP/ABCG2 expression in vascular endothelial cells (198), leading to endothelial dysfunction, leukocyte recruitment, cytokine release, and stimulation of activation and proliferation of VSMCs, as well as vasoconstriction and diastolic dysfunction (199) and ultimately, exacerbates tissue hypoxia (200). Moreover, hyperuricemia is involved in oxidative metabolism, platelet adhesion, blood rheology and platelet aggregation (201,202). These processes can increase platelet adhesion and make patients with PH more susceptible to pulmonary vascular thrombosis (203). Hypoxia also leads to impaired pulmonary vascular perfusion, and the release of additional cytokines further accelerates vascular remodeling and fibrosis (191,204,205). The effect of the use of drugs, such

as diuretics in the setting of heart failure, on UA concentrations should not be overlooked. Borghi *et al* (206) reported that tab diuretics, thiazides and aspirin may increase SUA concentrations. When PH is combined with underlying diseases, such as renal insufficiency, hypermetabolic syndrome, obesity, hyperlipidemia, hypertension, coronary artery disease and diabetes mellitus, it can also result in hyperuricemia (11,93,131). These diseases mainly cause dysfunction of UA excretion/increased UA synthesis (199). Additionally, the use of clinical medications in these conditions can interfere with UA concentrations. Examples of these medications include calcium channel blockers (e.g., amlodipine and cilnidipine) (207), angiotensin-converting enzyme inhibitors (e.g., captopril, enalapril and ramipril) (208,209), angiotensin-converting enzyme II receptor antagonists (e.g., losartan) (210), lipid-lowering agents (e.g., atorvastatin, simvastatin, ezetimibe and fenofibrate) (211), weight loss medications (e.g., orlistat) (212) and hypoglycemic agents (e.g., metformin) (213). Additionally, sodium glucose transporter protein 2 reduces UA concentrations (214,215). Therefore, PH with hypoxia leads to elevated UA concentrations. However, UA, as a risk marker, exacerbates the severity of PH and increases the risk of death due to PH.

8. Protective effect of UA-lowering drugs on PH

Currently, UA-lowering drugs mainly include the following categories: i) Drugs that inhibit UA production (xanthine oxidase inhibitors, such as allopurinol and febuxostat) (216,217); ii) drugs that promote UA excretion (drugs that inhibit the production of the UA reabsorption proteins URAT1 and GLUT9, such as benzbromarone and probenecid) (218,219); iii) drugs that promote UA catabolism (UA enzymes, such as rasburicase and pegloticase) (220,221); and iv) antihypertensive drugs (ACEIs such as enalapril, and ARBs such as irbesartan and losartan) (208,210). Based on the role of UA in PH, some of these drugs (e.g., allopurinol and benzbromarone) have been shown to reduce SUA concentrations and has a certain protective effects against arterial hypertension (163,222-224). Therefore, lowering SUA concentration has the potential to serve as a target for the treatment of PH.

9. Conclusions and prospects

Increasing evidence has shown that UA is inextricably associated with PH and may serve as a circulating marker of PH (189) (Fig. 4). UA may be involved in PH by mediating inflammatory responses, oxidative stress, RAS activation and endothelial dysfunction (131). PH leads to tissue ischemia/hypoxia and oxidative stress, and impaired UA metabolism, which lead to an increase in SUA concentrations (225,226). However, the causal relationship between UA and PH is not completely clear. Hyperuricemia may be considered a risk factor/independent risk factor for PH and a predictor of disease onset, progression and prognosis (115,116,227), but whether SUA can be used as a circulating marker for PH needs to be validated by additional clinical and basic research. In addition, to determine whether lowering SUA concentrations improves the clinical symptoms of PH, further investigation and clinical studies are required.

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Availability of data and materials

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Authors' contributions

YZ and WL conceived and designed the entire review and wrote the paper. YZ assisted with the figures. MC, JZ, YH, HL, XS and WL reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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