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Review Article

Xanthine oxidoreductase in digestive diseases: A context-dependent redox switch linking inflammation, metabolism and carcinogenesis

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ABSTRACT

Xanthine oxidoreductase (XOR) is a molybdenum-containing enzyme that catalyzes the final steps of purine catabolism, generating uric acid and, under specific conditions, reactive oxygen species (ROS) and reactive nitrogen species. Due to its high expression in the liver and gastrointestinal tract, XOR has emerged as an important regulator of redox homeostasis, innate immunity and metabolic adaptation in digestive diseases. This review examines the role of XOR in hepatic disorders, intestinal ischemia–reperfusion (I/R) injury and inflammatory bowel disease (IBD), focusing on oxidative stress, tissue injury, host–microbiome interactions and carcinogenesis. Evidence indicates increased XOR activity in inflammatory and fibrotic liver diseases, where ROS generation contributes to hepatocellular damage, fibrosis and disease progression. In intestinal I/R injury, XOR links ATP depletion and hypoxanthine accumulation to reperfusion-associated oxidative stress, barrier dysfunction, bacterial translocation and systemic inflammation. In IBD, XOR participates in cytokine amplification, redox imbalance, thiopurine metabolism and inflammation-associated colorectal carcinogenesis. Emerging evidence also supports bidirectional interactions between XOR/urate metabolism and the gut microbiota, suggesting a broader role for XOR in regulating intestinal immune homeostasis. However, the biological significance of XOR is strongly context dependent. Whereas increased XOR activity promotes inflammatory tissue injury, advanced gastrointestinal malignancies are frequently characterized by reduced XOR expression, loss of cellular differentiation and enhanced de novo purine synthesis. Overall, XOR emerges as a central, but highly plastic, regulator at the interface between metabolism, inflammation and host-microbiome interactions in digestive diseases. Its clinical exploitation will depend on the ability to understand, rather than oversimplifying, this complexity.

1. Introduction

The oxidation of hypoxanthine to xanthine and of xanthine to uric acid (UA) represents the terminal part of purine catabolism in all living beings and, in multicellular organisms, is catalyzed by xanthine dehydrogenase (XDH) [1], which in mammals becomes xanthine oxidoreductase (XOR). In fact, the enzyme produced by mammalian cells is an NAD^+-dependent dehydrogenase, but it can be converted into an oxidase (XO), which uses oxygen and produces the reactive oxygen species (ROS) hydrogen peroxide (H_2O_2) and superoxide anion ($O_2\bullet$-). This conversion can be reversible, when driven by the oxidation of two specific sulfhydryl residues, or irreversible, when caused by limited proteolysis of the protein area in which they are included [2].

In humans, *XOR* expression is relatively low in most cell types and predominantly localized in the liver, gut and lactating mammary cells [3]. Human endothelial cells also express endogenous XDH, although generally at relatively low basal levels. Endothelial XOR expression and activity can be increased by inflammatory cytokines, hypoxia and other vascular stressors. In addition, circulating XO, mainly released from the liver, binds with high affinity to sulfated glycosaminoglycans on the endothelial surface and may subsequently be internalized, thereby further increasing endothelial XOR content and activity [4–6].

XOR belongs to the molybdenum–iron–sulfur flavin enzyme family and forms a homodimer of approximately 300 kDa, which contains two

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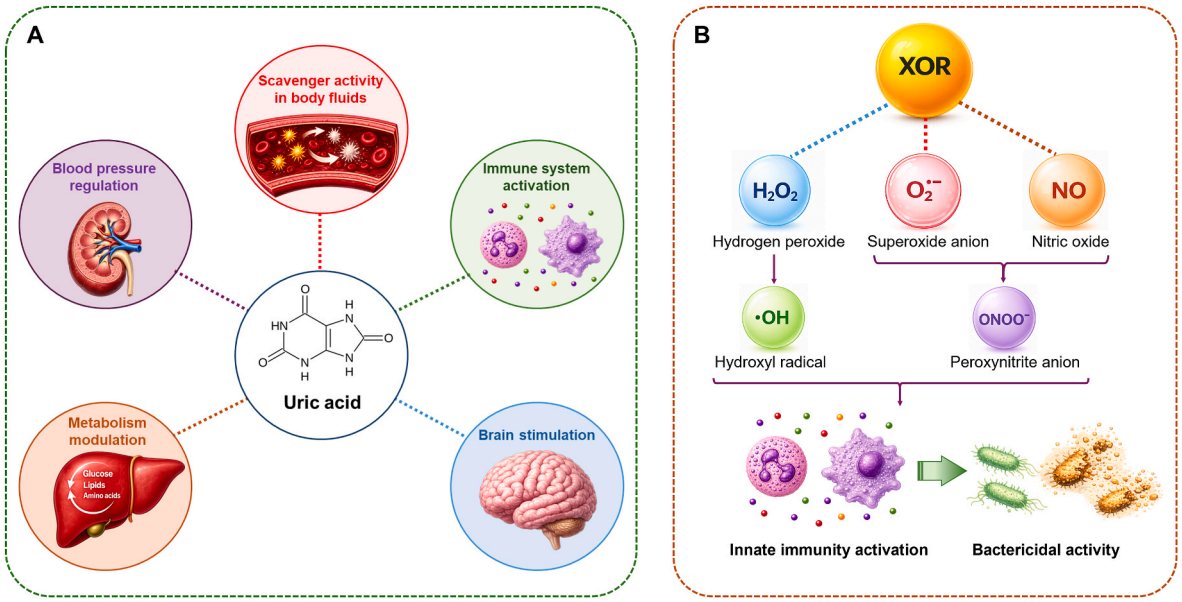

Fig. 1. Physiological roles of xanthine oxidoreductase (XOR) products. (A) Main physiological activities associated with uric acid (UA). UA is the final product of purine metabolism in higher primates and it exerts multiple biological activities in different organs and tissues. In circulation, UA scavenges free radicals, acting as a non-enzymatic antioxidant in body fluids. In the kidney, UA participates in the regulation of blood pressure through renal-associated mechanisms involved in sodium handling and endothelial function. Within the immune system, UA contributes to innate immune activation by stimulating macrophages and promoting cytokine-mediated inflammatory signaling pathways. In the liver, UA influences metabolic homeostasis through modulation of pathways related to glucose, lipid and amino acid metabolism. In the central nervous system, UA has been associated with neuronal activity, neurostimulation and potential neuroprotective effects linked to its antioxidant activity. **(B)** Role of reactive oxygen species (ROS) and reactive nitrogen species (RNS) produced by XOR in innate immunity. XOR-derived cytotoxic radicals are essential in innate immunity both during the cytocidal phase of phagocytosis and in controlling the mucosal microbiome.

flavin molecules, eight iron atoms, eight sulfur atoms and two molybdenum atoms, which are essential for the catabolism of purines [7]. In higher primates, including humans, the end-products of the purine degradation pathway are xanthine and UA, which are irreversibly formed; so, XOR activity prevents the salvage pathway of purine nucleotides [8]. In these beings, the UA serum level is higher than in ureotelic mammals and UA has different roles: i) it acts as an important antioxidant by scavenging ROS and contributing to redox homeostasis in body fluids [9], ii) it contributes to blood pressure and vascular tone regulation by increasing cyclooxygenase-2 expression and activating the renin-angiotensin system [10], iii) it enhances the innate immune response by activating macrophages through the production of damage associated molecular patterns (DAMPs) and by inducing NLRP3 inflammasome activation, thus promoting cytokine-mediated inflammatory signaling pathways [11], iv) it influences metabolism by promoting fat accumulation and hepatic gluconeogenesis, thereby increasing blood glucose levels [12], v) it stimulates brain activity, similarly to other purines [13] (Fig. 1A).

However, UA, particularly when accumulated intracellularly, can also contribute to oxidative stress by activating NADPH oxidase or by reacting with free radicals and producing urate free radicals that can propagate a free radical chain reaction [9].

Beyond purine catabolism, XOR is able to catalyze other endogenous and exogenous substrates, including some drugs [14]. Additionally, XOR has other activities, being also able to act as nicotinamide adenine dinucleotide (NADH) oxidase, which produces ROS [15], as well as nitrate reductase, which produces nitric oxide (NO), particularly under conditions of hypoxia and low pH [16]. Reduced transition metals (like Fe^{2+}) catalyze the breakdown of H_2O_2 giving rise to hydroxyl radical (•OH) through the Fenton and the Fenton-like reactions [17]. In addition, peroxynitrite ($ONOO^-$) is formed in biological systems through the reaction between NO and O_2•-. The ability of XOR to produce both ROS and NO, which can generate both •OH and $ONOO^-$, justifies the defensive function of XOR during the cytocidal activity of leukocytes in innate immunity [18]. Furthermore, these cytotoxic radicals may contribute to exerting protective activity against opportunistic infections on the mucosal surface, while preserving the commensal microbiota [19] (Fig. 1B).

The improved health outcomes associated with breastfeeding compared to formula feeding may be due, at least in part, to the presence of hypoxanthine and xanthine in infant saliva, but not in adult saliva. During suckling, these substrates enable XO from breast milk to produce ROS in amounts sufficient to: i) inhibit the growth of some opportunistic pathogens, ii) act as substrate for lactoperoxidase present in human milk, which exerts bactericidal activity [20]. However, the ability of XOR to produce ROS and reactive nitrogen species (RNS), and consequently cytotoxic radicals, also highlights its pathological potential due to the proinflammatory and oxidative stress-promoting action of such products and derivatives [19].

Given the prevalent localization of XOR in the liver and intestine together with its ability to produce both oxidant and antioxidant substances and their proinflammatory action, in this review we investigate XOR role in the course of digestive tract diseases. In particular, we considered liver diseases, intestinal ischemia-reperfusion (I/R) injury and inflammatory bowel disease (IBD), since a noteworthy amount of literature suggests that XOR activity and its products play a crucial role in the pathogenesis and development of such diseases.

2. Hepatic diseases

The catabolism of purines introduced with the diet occurs mainly in the liver, which represents the primary source of UA circulating in the plasma. About two-thirds of UA is eliminated by kidney [21], while the remainder by intestine.

During viral hepatitis, an increase in XOR activity has been reported both in liver tissue [22] and in serum [23–26] of patients. Cytokines produced during viral infections, such as interferon (IFN)-γ, may account for the increased hepatic expression of XOR [27,28]. The rise in serum XOR levels may result from the release of XOR from dead hepatocytes during the acute phase of hepatitis together with the level

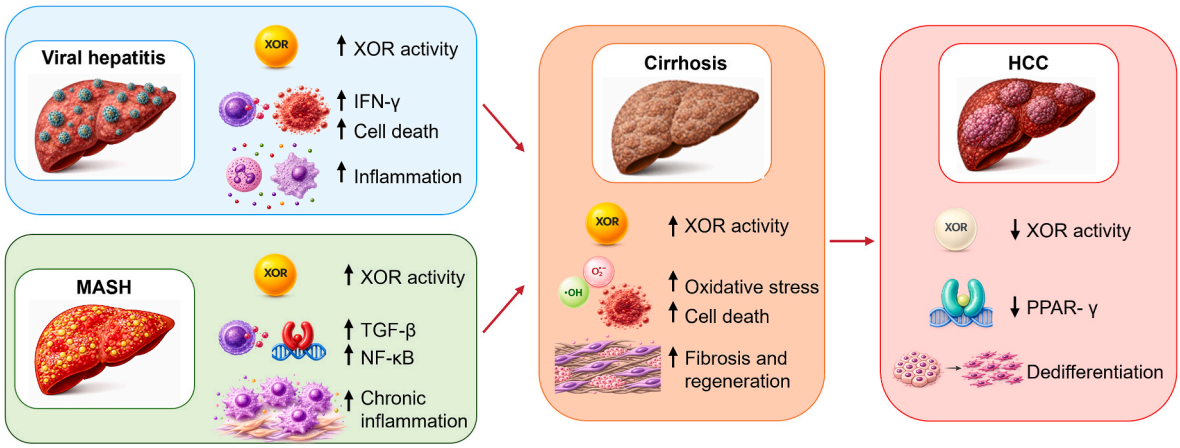

Fig. 2. Role of xanthine oxidoreductase (XOR) activity in chronic liver disease progression and hepatocellular carcinoma (HCC). In chronic viral hepatitis, increased XOR activity is associated with enhanced interferon-γ (IFN-γ)-related immune responses and increased hepatocyte cell death, accompanied by persistent inflammatory activation. Viral infection promotes recruitment and activation of inflammatory immune cells, including macrophages and neutrophils, contributing to chronic liver injury and progression toward cirrhosis. In metabolic dysfunction-associated steatohepatitis (MASH), increased XOR activity contributes to activation of pro-inflammatory and pro-fibrotic pathways, including transforming growth factor-β (TGF-β) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. These pathways sustain chronic inflammation, activation of fibroblasts and extracellular matrix remodeling, thereby promoting progressive liver fibrosis and cirrhosis development. At the cirrhotic stage, persistent XOR activation enhances oxidative stress through increased production of reactive oxygen species (ROS), including superoxide anion (O_2•-) and hydroxyl radical (•OH), resulting in additional hepatocyte injury and cell death. Simultaneously, chronic tissue damage induces cycles of fibrosis and compensatory liver regeneration characterized by fibroblast activation, collagen deposition and formation of regenerative hepatocyte nodules. After progression to HCC, XOR activity decreases in association with decreased peroxisome proliferator-activated receptor gamma (PPAR-γ) signaling and the acquisition of dedifferentiated tumor phenotypes.

increase of other liver enzymes in the serum [25,29]. Similarly, intoxication with hepatotoxic substances and cholestatic conditions may lead to increased serum XOR levels [26,30]. Consistently, regardless of the etiology, serum XOR activity increases in close correlation with liver transaminase levels in the active phase of liver disease [31].

The XOR competitive inhibitor allopurinol prevented in rat the secondary biliary cirrhosis induced by common bile duct ligation and the experimental cirrhosis induced by carbon tetrachloride chronic treatment. These findings suggest a role for XOR in the pathogenesis of cirrhosis through the induction of oxidative stress, transforming growth factor (TGF)-β production and translocation of nuclear factor kappa B (NF-κB) [32,33]. Consistently, in Wistar rats, the treatment with the XOR non-competitive inhibitor febuxostat significantly improved liver function and lipid profiles in metabolic dysfunction-associated steatosis (MASH) induced by a high-sucrose and high-fat diet. XOR inhibition reduced hepatic steatosis, intralobular inflammation and hepatocellular ballooning. It also decreased serum levels of inflammatory, fibrotic and cell death markers and reduced cell death [34]. Additionally, increased XOR activity has been reported in liver during the progression from steatohepatitis associated with metabolic dysfunction to cirrhosis. Moreover, XOR activity inhibition may attenuate inflammation associated with liver damage [35]. These results, obtained from animal experiments, suggest that the increased activity of XOR, observed in these liver diseases, contributes to the progression towards cirrhosis, probably through the pro-inflammatory action of its products.

However, the further evolution to cancer is associated with a strong decrease of XOR activity in liver tissue [22,36–38]. Indeed, it should be considered that human XOR gene (*hXOR*) transcription is normally downregulated in most tissues [39], except in the liver, the gastrointestinal tract and the lactating mammary gland [40,41]. In these organs, cell differentiation is associated with a high level of XOR, while a low concentration of XOR corresponds to a lack of differentiation, as observed in malignant neoplasms. In fact, XOR activates the Peroxisome Proliferator-Activated Receptor (PPAR)-γ, thus promoting differentiation, growth inhibition and apoptosis of tumor cells [42] (Fig. 2). Moreover, low levels of XOR and its reduced activity are associated with increased de novo purine biosynthesis, providing an additional advantage to tumor growth.

Recent in vitro evidence has provided additional mechanistic insight into the biological consequences of XOR downregulation in cancer. In breast cancer cells, intracellular XOR-derived UA was shown to chelate redox-active iron, thereby limiting the size of the labile iron pool and restraining cell proliferation and metastatic potential. Consequently, reduced XOR expression decreases intracellular UA availability, increases iron bioavailability and favors tumor progression. Consistently, the urate exporter ABCG2 is highly expressed in breast cancer cells, whereas its pharmacological inhibition increases intracellular UA levels and attenuates cancer cell proliferation. Although this mechanism has been characterized primarily in breast cancer models, it provides a possible additional explanation for the selective loss of XOR in other malignancies that arise from normally XOR-rich tissues, including hepatocellular and gastrointestinal cancers, suggesting that the XOR-UA-

Table 1
XOR activity in experimental and clinical liver pathology.

Disease	XOR activity	Site of observation	Proposed mechanism	Human evidence	Animal evidence	XOR inhibition effect
Hepatitis[a]	↑	Serum, liver	IFN-induced XOR upregulation and XO-derived ROS promote hepatocellular injury and inflammation	Yes [22–26, 31,46]	Yes [24,27,28, 30,34,35,47]	Protection [34, 35,47]
Cirrhosis	↑	Serum, liver	XOR-derived ROS promote oxidative stress and fibrogenic signaling (NF-κB/TGF-β), leading to hepatocellular injury and collagen deposition	Yes [22]	Yes [32,33,35]	Protection [32, 33]
HCC	↓	Tumor tissue	Reduction of XOR activity is associated with hepatocellular dedifferentiation and altered purine metabolism	Yes [22,36, 37]	Yes [48,49]	Not established

[a] Viral hepatitis, steatohepatitis, cholestasis, intoxication with hepatotoxic substances.

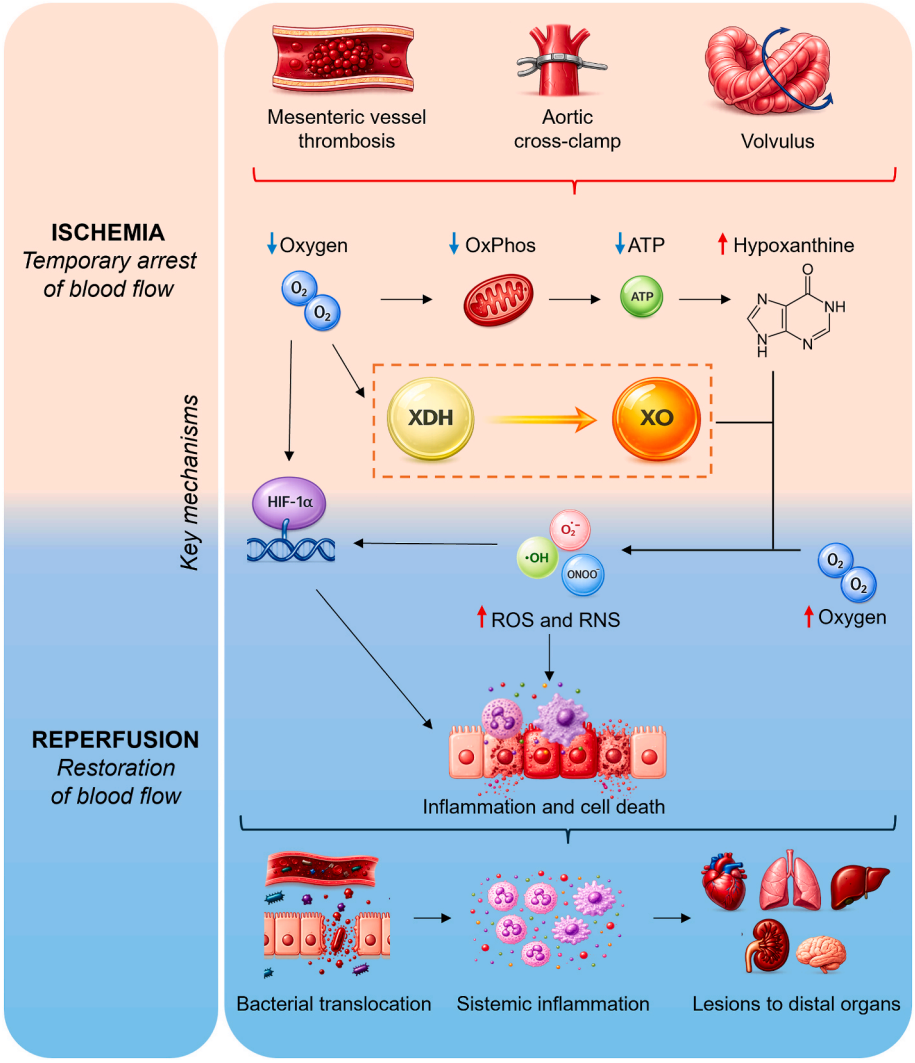

Fig. 3. Mechanisms linking intestinal ischemia/reperfusion (I/R), xanthine oxidoreductase (XOR) activation, oxidative stress and systemic inflammation. Intestinal ischemia may result from mesenteric vessel thrombosis, aortic cross-clamping during surgical procedures or volvulus, all of which can cause a temporary interruption of intestinal blood flow. Reduced oxygen availability inhibits mitochondrial oxidative phosphorylation (OxPhos), leading to depletion of intracellular ATP and accumulation of hypoxanthine through ATP catabolism. Ischemia and hypoxia also promote conversion of xanthine dehydrogenase (XDH) to xanthine oxidase (XO), while simultaneously activating hypoxia-inducible factor 1 alpha (HIF-1α)-dependent hypoxic signaling pathways. During reperfusion, restoration of oxygen supply enhances the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), including superoxide anion (O_2•-), hydroxyl radical (•OH) and peroxynitrite ($ONOO^-$), partly through XO-mediated hypoxanthine metabolism. ROS/RNS production contributes to epithelial injury, intestinal inflammation and cell death, resulting in disruption of the intestinal mucosal barrier. Damaged enterocytes release damage-associated molecular patterns (DAMPs), further amplifying inflammatory responses. Loss of epithelial barrier integrity promotes bacterial translocation from the intestinal lumen into the bloodstream, thereby inducing systemic inflammation characterized by activation and recruitment of inflammatory immune cells. Sustained systemic inflammation contributes to lesions in distal organs, including the heart, lung, liver, kidney and brain, potentially leading to multiple organ dysfunction.

iron axis may represent an additional mechanism linking loss of XOR expression to tumor aggressiveness [43]. All together, these findings may explain why a low XOR level has been associated with a high grade of malignancy and a worse prognosis in cancer patients [44]. Consistently, a study enrolling 400 people from India (58.5% male with a mean age of 62.1 ± 12.61 years) reported deficiency in molybdenum (an important XOR cofactor) in patients with esophageal cancer compared to healthy subjects [45].

Increased XOR activity has been found in several liver diseases, while reduced XOR activity has been observed in hepatocellular carcinoma in both experimental and clinical pathology (Table 1).

Overall, available evidence consistently indicates that XOR appears to have a role in amplifying acute inflammatory responses and promoting oxidative stress during the chronicization of pathological processes, through the action of its products and their derivatives. Instead, the collapse of XOR activity in tissues that normally express it intensely represents a sign of tissue dedifferentiation, characteristic of neoplastic transformation.

However, whether increased XOR activity acts as a primary driver of disease progression or reflects ongoing hepatocellular injury remains incompletely resolved.

3. Intestinal ischemia-reperfusion injury

An abundant presence of XOR in the intestinal lumen is ensured by frequent enterocyte turnover. This large amount of XOR contributes to strengthening innate immune defenses in intestinal tissue, which is particularly exposed to pathogenic agents. XOR-derived ROS and RNS are effective against opportunistic infections [18] while sparing the commensal microbiota [19,20]. However, when produced in excessive

amounts, these reactive species can also contribute to inflammation and oxidative stress, which in turn lead to pathological conditions.

Intestinal perfusion blockage can result from thrombosis of the afferent or efferent mesenteric vessels. It also occurs following volvulus and transplant procedures that require temporary arrest of blood flow in the aorta [50]. The consequences of I/R begin when oxygen and nutrient deprivation cause the dropping of ATP levels by blocking mitochondrial oxidative phosphorylation. The depletion of cell energy stores drives ATP catabolism, resulting in accumulation of hypoxanthine [51]. Ischemia and hypoxia also induce the conversion of XDH to XO and trigger the hypoxic response through the activation of hypoxia-inducible factor 1 (HIF-1). HIF-1 promotes inflammatory and apoptotic processes that damage the intestinal mucosal barrier and facilitate bacterial translocation, leading to systemic inflammation [52]. These effects worsen during the reperfusion phase by inducing microvascular dysfunction with protein leakage and edema formation due to ROS formation, at least in part caused by the conversion of XDH to XO [53,54]. However, this conversion is not essential because XDH can also produce $O_2\bullet$- in the presence of a low NAD^+/NADH ratio, which occurs during and after tissue ischemia [55].

In addition, intestinal I/R induces the release of DAMPs, which in turn stimulate the production of inflammatory mediators that cause systemic inflammatory response syndrome. Furthermore, multiple organ dysfunction syndrome can develop with a high mortality rate. In particular, lesions to distal organs often involve the lung, thus reducing survival [56,57] (Fig. 3).

In a rat model of intestinal I/R, a significant increase in XO activity was observed [58]. Furthermore, adult male Wistar rats subjected to I/R showed marked histopathological changes in the intestine and significantly increased plasma and intestinal lactate concentrations and lactate dehydrogenase activity. Also, intestinal XO and UA levels, as well as TNF-α, interleukin-1beta (IL-1β) and NF-κB were significantly increased in I/R-treated rats compared to sham-operated animals [59].

Circulating XO activity, plasma leukotactic activity for neutrophils and pulmonary neutrophil retention were acutely increased in rats subjected to intestinal I/R compared to controls or animals fed a diet enriched with allopurinol or tungsten, the latter inhibiting XO by competing with molybdenum during the enzyme synthesis [60]. In these experiments, intestinal I/R was induced in normal and XO-inactivated rats by 5 min of superior mesenteric artery occlusion followed by 6 h of reperfusion. The procedure increased leukocyte level not only in the gut but also in the lung and provoked distant lung leak in normal but not in XO-inactivated rats, suggesting a role for XO in the pathogenesis of this remote organ injury [61,62].

XOR activity level doubled in patient plasma 7 min after reperfusion following an aortic cross-clamp procedure in the superior mesenteric, celiac and right renal artery beds [63].

Experimental intestinal I/R resulted in an alteration of the gut microbiota, which in turn influenced outcomes. Pretreatment of animals with beneficial bacteria reduced the release of inflammatory cytokines, enterocytes apoptosis and tight junction disruption, thus preventing bacterial translocation and systemic consequences [64]. Specifically, mice with a relative abundance of *Lactobacillus murinus* were more resistant to intestinal ischemia/reperfusion injury than mice with a different microbiome and treatment with this bacterium significantly prevented I/R-induced intestinal damage and improved mouse survival. In vitro experiments suggest that these results are dependent on M2 macrophage activation through TLR2 and the subsequent release of IL-10 [65].

Several Lactobacillus species have been shown to reduce serum uric acid levels, as discussed in the next chapter. This raises the possibility that the intestinal microbiota may influence the progression of intestinal I/R injury through mechanisms involving XOR activity and uric acid metabolism. If so, it would strengthen the hypothesis that XOR-derived products play a significant role in both the local and systemic manifestations of intestinal I/R.

Flap transplantation is commonly used to repair skin or deeper tissue damaged by trauma, burns or surgery. In most cases, damage to microcirculation occurs as a consequence of I/R, which can compromise the graft survival. Pretreatment with allopurinol for one week significantly improved skin flap survival in dogs. XOR inhibition resulted in reduced inflammation in grafts and a more preserved tissue architecture on histopathology one week after surgery compared to untreated specimens [66].

Collectively, experimental studies support a mechanistic role for XOR in the pathogenesis of intestinal I/R injury. Importantly, XOR occupies a unique position among redox enzymes because it directly couples purine catabolism to reperfusion-associated oxidative stress, thereby acting as one of the earliest amplifiers of tissue injury.

4. Inflammatory bowel disease (IBD)

IBD are a group of autoimmune diseases, whose main forms are ulcerative colitis and Crohn's disease. Ulcerative colitis predominantly affects the colon and rectum whereas Crohn's disease primarily affects the terminal ileum, but can occur anywhere along the gastrointestinal tract, from the mouth to the anus [67]. The thiopurines azathioprine and 6-mercaptopurine are widely used in the treatment of IBD and are effective in two-thirds of patients [68]. Improved outcomes have been reported by combining thiopurine therapy with allopurinol [69]. In fact, XOR is able to catabolize thiopurines, thus reducing its efficacy in antitumor and immunosuppressive treatments [38]. However, XOR inhibition by febuxostat was able to attenuate experimental ulcerative colitis in mice through decreased NF-κB expression and reduced level of the proinflammatory cytokines TNF-α, IL-1β, IL-6 and IFN-γ. Febuxostat-treated animals also showed increased levels of reduced glutathione and superoxide dismutase activity together with decreased levels of malondialdehyde, carbonyl protein, NO, myeloperoxidase and XO in colon tissue in comparison with untreated mice [70]. These findings suggest that XOR plays a role in autoimmune diseases of the gut because its products promote inflammation and oxidative stress.

Over the past decades, an increasing number of publications have suggested that IBD can be improved through the modulation of the gut microbiome, which can exert antioxidant and anti-inflammatory effects and regulate XOR activity and UA metabolism. For example, administration of *Limosilactobacillus fermentum* M5e to hyperuricemic mice inhibited XO activity and promoted fecal urate excretion by upregulating the transport proteins ABCG2 and SLC2A9, thereby reducing systemic inflammation [71]. Furthermore, Chinese patients with end-stage renal disease (10 men and 6 women) undergoing continuous ambulatory peritoneal dialysis were included in a 12-week placebo-controlled crossover study with inulin-type prebiotics. Serum UA concentration decreased by approximately 10% in the treated group compared to the control group. Greater fecal degradation of UA was observed in the treated group, likely due to an enrichment of purine-degrading species in the gut microbiota [72]. On the other hand, hyperuricemia is often associated with increased levels of pro-inflammatory markers and alterations in the intestinal microbiome. In fact, the intestinal microbiota plays a significant role in the catabolism of UA [73]. Various bioactive substances derived from plant foods have demonstrated their potential in alleviating chronic diseases and reducing hyperuricemia by modulating the intestinal microbiota [74–76]. Furthermore, obesity-related gut microbiota-induced hyperuricemia has been shown to contribute to alveolar bone destruction in experimental periodontitis, while allopurinol administration reversed the worsening of UA-associated bone destruction [77]. Recent experimental evidence demonstrates that modulation of gut microbiota can directly reduce hyperuricemia by restoring short-chain fatty acid production, strengthening intestinal barrier integrity, and regulating urate transporters such as ABCG2, GLUT9 and URAT1 [78].

Compared to wild-type mice, hyperuricemic ones, obtained using a urate oxidase knockout model, showed: i) abundance of inflammation-

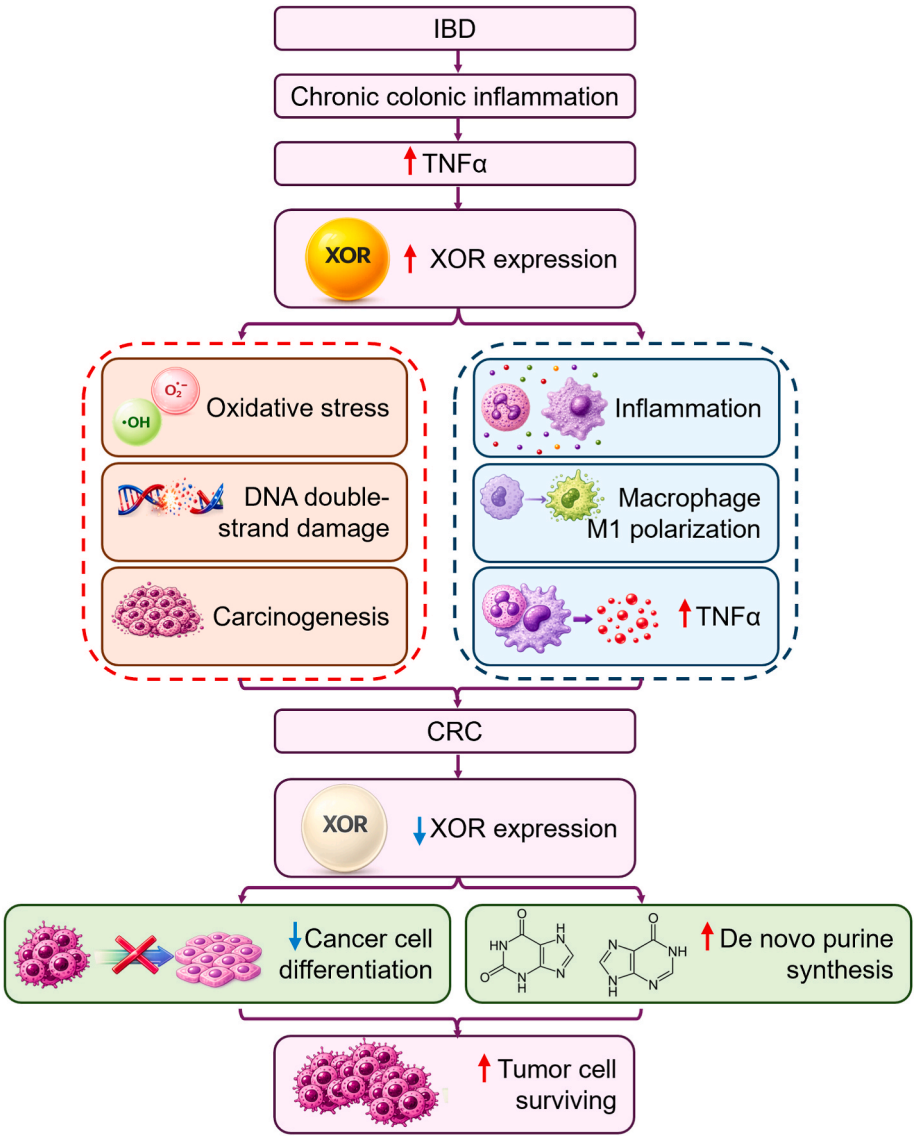

Fig. 4. Role of xanthine oxidoreductase (XOR) during inflammation-associated colorectal carcinogenesis in inflammatory bowel disease (IBD). Chronic intestinal inflammation in IBD promotes sustained production of tumor necrosis factor alpha (TNF-α), which contributes to increased XOR expression and activity in the colonic mucosa. Elevated XOR activity enhances oxidative stress through generation of reactive oxygen species (ROS), including superoxide anion (O_2•-) and hydroxyl radical (•OH), resulting in oxidative DNA damage and DNA double-strand breaks. These events contribute to genomic instability and carcinogenesis. In parallel, increased XOR activity amplifies inflammatory signaling by promoting recruitment and activation of immune cells, including neutrophils and macrophages, and by favoring macrophage M1 polarization. Activated inflammatory cells further increase TNF-α production, sustaining a positive inflammatory feedback loop that supports progression from chronic colonic inflammation to colorectal cancer (CRC). At later stages of CRC progression, XOR expression becomes reduced. Decreased XOR expression is associated with impaired cancer cell differentiation and increased de novo purine synthesis, thereby supporting tumor cell survival and maintenance of a more aggressive tumor phenotype.

associated microbiota that is indicative of gut dysbiosis, ii) intestinal lymphocyte infiltration, increased expression of Toll-like receptor 2, 4 and 5 and elevated levels of the pro-inflammatory cytokines IL-1β and TNF-α, indicating intestinal immune dysregulation, iii) high levels of circulating lipopolysaccharide (LPS) suggesting that a compromised intestinal barrier allows microbial influx into the circulatory system [79].

Autoimmune diseases are associated with gut dysbiosis because the gut microbiota influences regulatory T-cell homeostasis, promoting tolerance to symbiotic microorganisms. In addition, both microbial derived-short chain fatty acids, generated by the fermentation of dietary fibers, and bio-transformed bile acids can modify the host immune system [80]. In fact, short-chain fatty acids derived from the normal intestinal microbiota have anti-inflammatory and antioxidant effects, also promoting the improvement of the intestinal barrier and constituting an energy source for colonocytes. Furthermore, the intestinal microbiota provides metabolic benefits such as vitamin synthesis and fermentation of complex carbohydrates. Healthy microbiota is favored by a Mediterranean-type diet rich in vegetables [81]. Enterohepatic circulation promotes the biotransformation of bile acids by the intestinal microbiota, which is essential for controlling the proliferation of harmful bacteria and is depleted in IBD-related dysbiosis, thus representing a predictive marker of early remission. In addition, biotransformed bile acids can regulate the balance between proinflammatory T_H17 lymphocytes and anti-inflammatory T_{reg} lymphocytes [82].

A microbiome study was conducted on pediatric patients from the PROTECT (Predicting Response to Standardized Colitis Therapy) cohort with 95 participants (43 women, 52 men) aged 4 to 17 years. Refractory ulcerative colitis, which often leads to colectomy, is predominantly

Table 2
XOR activity in experimental and clinical intestinal pathology.

Disease	XOR activity	Site of observation	Proposed mechanism	Human evidence	Animal evidence	XOR inhibition effect
I/R	↑	Plasma, intestine	Hypoxanthine accumulation and XDH→XO conversion drive reperfusion-associated ROS generation, promoting epithelial injury, barrier dysfunction, bacterial translocation, systemic inflammation and remote organ damage	Yes [63]	Yes [58–60]	Protection [54,60]
IBD	↑	Colon tissue/ disease models	XOR-derived ROS promote oxidative stress, NF-κB activation, cytokine amplification, and mucosal inflammation	Limited [68,69]	Moderate [70,87]	Protection [70,87]
CRC	↑ early inflammatory phase ↓ advanced tumor	Colorectal tumor tissue	Reduced XOR expression is associated with tumor dedifferentiation and altered purine metabolism	Yes [88]	Yes [86,87]	Not established (indirect evidence [86,87])

associated with enrichment of typical oral bacteria and is also associated with depletion of some specific bacteriophages. Notably, the expansion of *Veillonella parvula*, an inflammation-associated oral bacterium expressing the xanthine dehydrogenase gene *xdhA*, was linked to the metabolism of both endogenous purines and thiopurine drugs, suggesting a potential interaction between gut dysbiosis, purine metabolism, and therapeutic response in ulcerative colitis [83].

The above reported studies suggest that the positive action developed by microbiota on autoimmune diseases affecting gut may depend at least in part on the microbiota ability of modulating XOR activity and uricemia level.

IBD-associated oxidative stress and chronic inflammation have been implicated in multistep colorectal tumorigenesis and may lead to colorectal cancer (CRC), particularly in the case of ulcerative colitis [84]. It has been suggested that modulating the intestinal microbiota and correcting dysbiosis could represent an effective remedy in the prevention and treatment of CRC [73]. In fact, not only some bacteria can act as biomarkers, but others are able to modulate chemotherapy and immunotherapy through their metabolites [85].

CRC progression has been associated with increased XOR expression, detected by immunohistochemical staining in a mouse model of colitis-associated colon carcinogenesis. TNF-α induced XOR expression in colon tissues and colon cancer epithelial cells in a time- and dose-dependent manner, whereas specific mitogen-activated protein kinase inhibitors completely blocked the XOR up-regulation. TNF-α also induced the increase in γH2AX, indicating oxidative DNA damage, that can be inhibited by knocking down XOR gene expression in colon tumor cells or by inhibiting it with allopurinol. These findings suggest that XOR contributes to DNA damage. LPS induced XOR expression in cultured macrophage cell lines and caused their M1 polarization, thereby inducing TNF-α transcription. TNF-α transcription was abolished by inhibiting XOR expression or with allopurinol, demonstrating that M1 polarization was mediated by XOR [86].

XOR inhibition alleviated ulcerative colitis in a mouse model using dextran sulfate sodium. Furthermore, in colonic epithelial cells, hypoxic conditions increased expression of XOR, which accumulates in the nucleus and upregulates HIF-1α levels, causing oxidative DNA damage, which can be prevented with allopurinol. These findings suggest a significant role for XOR during the early stages of CRC [87] (Fig. 4).

XOR expression was significantly reduced or even undetectable in tissue samples from 478 CRC patients, and the level of expression was associated with the degree of tumor differentiation. Thus, XOR proved to be a significant prognostic factor associated with the histological degree of differentiation, regardless of established parameters [88].

Current evidence supports a role for XOR in intestinal inflammation, oxidative stress, thiopurine metabolism and inflammation-associated colorectal carcinogenesis (Table 2). However, the specific contribution of XOR activity remains sometimes difficult to distinguish from downstream effects mediated by urate and inflammatory signaling.

5. Conclusions

In liver disease, intestinal I/R, and IBD, XOR activity appears to follow a consistent pattern: under conditions of hypoxia, inflammation, and metabolic stress, activity shifts toward pro-oxidant and pro-inflammatory processes, amplifying tissue damage. Conversely, down-regulation of XOR in advanced malignancies reflects cellular dedifferentiation and metabolic reprogramming rather than protection. This duality emphasizes XOR as a dynamic node rather than a unidirectional determinant of disease.

Interestingly, the literature reviewed demonstrates a convergence of biochemical, preclinical, and clinical data. In liver disease, increased serum XOR activity robustly correlates with hepatocellular damage, while pharmacological inhibition attenuates steatosis, fibrosis, and inflammation in experimental models, supporting a causal contribution. In intestinal I/R, the sequence linking ATP depletion, hypoxanthine accumulation, alteration of the redox state of XOR, and generation of ROS/RNS is mechanistically robust and experimentally validated. In IBD, XOR integrates oxidative stress, cytokine amplification, thiopurine metabolism and microbiota dysregulation, providing a unifying framework linking mucosal inflammation to systemic metabolic alterations and carcinogenesis. In particular, the bidirectional interaction between XOR/urate metabolism and the gut microbiota represents a major conceptual advance. In short, XOR seems to represent a context-dependent redox switch linking inflammation, metabolism and carcinogenesis, thus showing a dual face from oxidative injury to tumor differentiation in diseases of the digestive system. In particular, XOR appears as the interface between redox signaling and host–microbiome interactions, by regulating redox homeostasis and disease progression in the digestive tract. However, some critical limitations constrain these conclusions. Some evidence is based on animal models that only partially mimic human chronic disease. Pharmacological studies, predominantly using allopurinol, do not fully distinguish the specific effects of XOR from systemic alterations in urate metabolism. Future research should prioritize longitudinal studies in humans to validate circulating XOR as a biomarker and to clarify its temporal dynamics across different stages of disease. Importantly, therapeutic strategies should go beyond global inhibition, focusing on selective modulation that preserves antimicrobial and metabolic functions while limiting oxidative damage.

In summary, XOR emerges as a central, but highly plastic, regulator at the interface between metabolism, inflammation and host-microbiome interactions in digestive diseases. Its clinical exploitation will depend on the ability to understand, rather than oversimplifying, this complexity.

Conceptual Perspective: The biological effects of XOR are determined not only by its catalytic activity but also by several contextual factors. Tissue differentiation influences basal XOR expression, inflammatory stimuli regulate transcriptional activation, oxygen availability determines the balance between dehydrogenase and oxidase activities, substrate availability controls ROS generation, while the gut microbiota modulates purine metabolism and urate homeostasis. Together, these

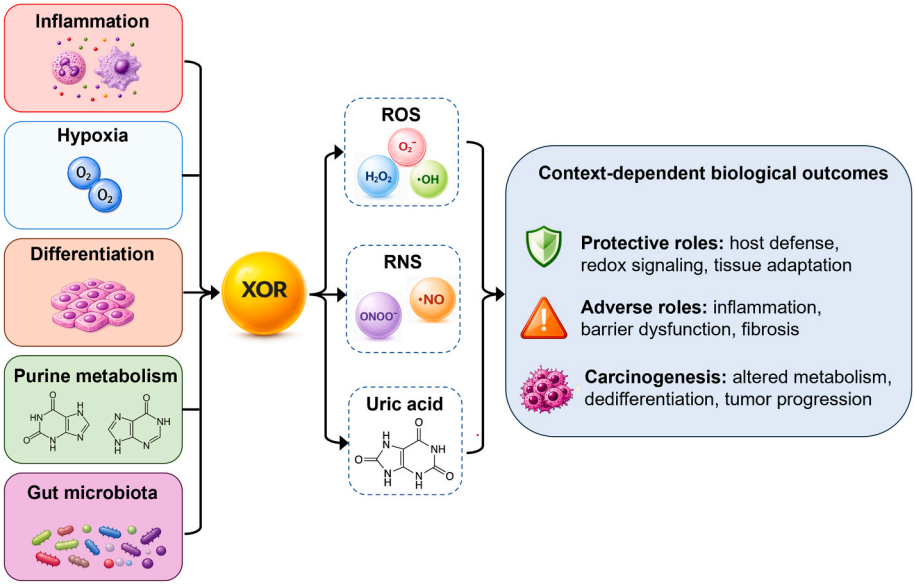

Fig. 5. Xanthine oxidoreductase (XOR) as a context-dependent redox switch. The biological functions of XOR are determined by the interplay of multiple contextual factors rather than by its enzymatic activity alone. Inflammatory stimuli, hypoxia, tissue differentiation, purine metabolism and host–microbiota interactions modulate XOR expression and activity, thereby influencing the relative production of reactive oxygen species (ROS), reactive nitrogen species (RNS) and uric acid. Depending on the pathological context, these metabolites may exert either protective or detrimental biological effects. Physiological functions include host defense, redox signaling and tissue adaptation, whereas persistent activation contributes to oxidative stress, chronic inflammation, epithelial barrier dysfunction and fibrosis. Conversely, reduced XOR expression is associated with altered purine metabolism, loss of cellular differentiation and tumor progression.

determinants explain why identical enzymatic activities may produce either protective or detrimental biological outcomes depending on the pathological context (Fig. 5).

Declaration of generative AI use

During the preparation of figures the authors used ChatGPT Edu in the workspace Alma Mater Studiorum - Università di Bologna - EDU. The AI has been used in order to develop an outline and editing to make figures as clear as possible. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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CRediT authorship contribution statement

Maria Giulia Battelli: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Massimo Bortolotti:** Visualization, Writing – review & editing. **Andrea Bolognesi:** Investigation, Writing – review & editing. **Letizia Polito:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M. Terao, E. Garattini, M.J. Romão, S. Leimkühler, Evolution, expression and substrate specificities of aldehyde oxidase enzymes in eukaryotes, J. Biol. Chem. 295 (2020) 5377–5389, https://doi.org/10.1074/jbc.REV119.007741.

[2] T. Nishino, XDH and XO research and drug discovery-personal history, Molecules 28 (2023) 4440, https://doi.org/10.3390/molecules28114440.

[3] P. Xu, P. LaVallee, J.R. Hoidal, Repressed expression of the human xanthine oxidoreductase gene. E-box and TATA-like elements restrict ground state transcriptional activity, J. Biol. Chem. 275 (2000) 5918–5926, https://doi.org/10.1074/jbc.275.8.5918.

[4] T. Adachi, T. Fukushima, Y. Usami, K. Hirano, Binding of human xanthine oxidase to sulphated glycosaminoglycans on the endothelial-cell surface, Biochem. J. 289 (1993) 523–527, https://doi.org/10.1042/bj2890523.

[5] M. Houston, A. Estevez, P. Chumley, M. Aslan, S. Marklund, D.A. Parks, B. A. Freeman, Binding of xanthine oxidase to vascular endothelium. Kinetic characterization and oxidative impairment of nitric oxide-dependent signaling, J. Biol. Chem. 274 (1999) 4985–4994, https://doi.org/10.1074/jbc.274.8.4985.

[6] E.E. Kelley, T. Hock, N.K. Khoo, G.R. Richardson, K.K. Johnson, P.C. Powell, G. I. Giles, A. Agarwal, J.R. Lancaster Jr., M.M. Tarpey, Moderate hypoxia induces xanthine oxidoreductase activity in arterial endothelial cells, Free Radic. Biol. Med. 40 (2006) 952–959, https://doi.org/10.1016/j.freeradbiomed.2005.11.008.

[7] R. Hille, J. Hall, P. Basu, The mononuclear molybdenum enzymes, Chem. Rev. 114 (2014) 3963–4038, https://doi.org/10.1021/cr400443z.

[8] M. Furuhashi, New insights into purine metabolism in metabolic diseases: role of xanthine oxidoreductase activity, Am. J. Physiol. Endocrinol. Metab. 319 (2020) E827–E834, https://doi.org/10.1152/ajpendo.00378.2020.

[9] M.P. Pinz, I. Medeiros, L.A.D.C. Carvalho, F.C. Meotti, Is uric acid a true antioxidant? Identification of uric acid oxidation products and their biological effects, Redox Rep. 30 (2025) 2498105, https://doi.org/10.1080/13510002.2025.2498105.

[10] D.H. Kang, T. Nakagawa, L. Feng, S. Watanabe, L. Han, M. Mazzali, L. Truong, R. Harris, R.J. Johnson, A role for uric acid in the progression of renal disease, J. Am. Soc. Nephrol. 13 (2002) 2888–2897, https://doi.org/10.1097/01.asn.0000034910.58454.fd.

[11] L.A.B. Joosten, T.O. Crişan, P. Bjornstad, R.J. Johnson, Asymptomatic hyperuricaemia: a silent activator of the innate immune system, Nat. Rev. Rheumatol. 16 (2020) 75–86, https://doi.org/10.1038/s41584-019-0334-3.

[12] C. Cicerchi, N. Li, J. Kratzer, G. Garcia, C.A. Roncal-Jimenez, K. Tanabe, B. Hunter, C.J. Rivard, Y.Y. Sautin, E.A. Gaucher, R.J. Johnson, M.A. Lanaspa, Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids, FASEB J. 28 (2014) 3339–3350, https://doi.org/10.1096/fj.13-243634.

[13] R.G. Cutler, S. Camandola, K.F. Malott, M.A. Edelhauser, M.P. Mattson, The role of uric acid and methyl derivatives in the prevention of age-related neurodegenerative disorders, Curr. Top. Med. Chem. 15 (2015) 2233–2238, https://doi.org/10.2174/1568026615666150610143234.

[14] M.G. Battelli, L. Polito, M. Bortolotti, A. Bolognesi, Xanthine oxidoreductase in drug metabolism: beyond a role as a detoxifying enzyme, Curr. Med. Chem. 23 (2016) 4027–4036, https://doi.org/10.2174/0929867323666160725091915.

[15] S.A. Sanders, R. Eisenthal, R. Harrison, NADH oxidase activity of human xanthine oxidoreductase–generation of superoxide anion, Eur. J. Biochem. 245 (1997) 541–548, https://doi.org/10.1111/j.1432-1033.1997.00541.x.

[16] N. Cantu-Medellin, E.E. Kelley, Xanthine oxidoreductase-catalyzed reduction of nitrite to nitric oxide: insights regarding where, when and how, Nitric Oxide 34 (2013) 19–26, https://doi.org/10.1016/j.niox.2013.02.081.
[17] Z. Zhao, Hydroxyl radical generations form the physiologically relevant Fenton-like reactions, Free Radic. Biol. Med. 208 (2023) 510–515, https://doi.org/10.1016/j.freeradbiomed.2023.09.013.
[18] H.M. Martin, J.T. Hancock, V. Salisbury, R. Harrison, Role of xanthine oxidoreductase as an antimicrobial agent, Infect. Immun. 72 (2004) 4933–4939, https://doi.org/10.1128/IAI.72.9.4933-4939.2004.
[19] M. Bortolotti, L. Polito, M.G. Battelli, A. Bolognesi, Xanthine oxidoreductase: one enzyme for multiple physiological tasks, Redox Biol. 41 (2021) 101882, https://doi.org/10.1016/j.redox.2021.101882.
[20] S.S. Al-Shehri, C.L. Knox, H.G. Liley, D.M. Cowley, J.R. Wright, M.G. Henman, A. K. Hewavitharana, B.G. Charles, P.N. Shaw, E.L. Sweeney, J.A. Duley, Breastmilk-saliva interactions boost innate immunity by regulating the oral microbiome in early infancy, PLoS One 10 (2015) e0135047, https://doi.org/10.1371/journal.pone.0135047.
[21] L. Polito, M. Bortolotti, M.G. Battelli, A. Bolognesi, Chronic kidney disease: which role for xanthine oxidoreductase activity and products? Pharmacol. Res. 184 (2022) 106407 https://doi.org/10.1016/j.phrs.2022.106407.
[22] F. Stirpe, M. Ravaioli, M.G. Battelli, S. Musiani, G.L. Grazi, Xanthine oxidoreductase activity in human liver disease, Am. J. Gastroenterol. 97 (2002) 2079–2085, https://doi.org/10.1111/j.1572-0241.2002.05925.x.
[23] M.H. Shammaa, S. Nasrallah, T. Chaglassian, A.K. Kachadurian, U.A. Al Khalidi, Serum xanthine oxidase: a sensitive test of acute liver injury, Gastroenterology 48 (1965) 226–230.
[24] C. Ramboer, F. Piessens, J. De Groote, Serum xanthine oxidase and liver disease, Digestion 7 (1972) 183–195, https://doi.org/10.1159/000197273.
[25] S. Giler, O. Sperling, S. Brosh, I. Urca, A. De Vries, Serum xanthine oxidase in jaundice, Clin. Chim. Acta 63 (1975) 37–40, https://doi.org/10.1016/0009-8981(75)90375-7.
[26] M.G. Battelli, S. Musiani, M. Valgimigli, L. Gramantieri, F. Tomassoni, L. Bolondi, F. Stirpe, Serum xanthine oxidase in human liver disease, Am. J. Gastroenterol. 96 (2001) 1194–1199, https://doi.org/10.1111/j.1572-0241.2001.03700.x.
[27] M. Terao, G. Cazzaniga, P. Ghezzi, M. Bianchi, F. Falciani, P. Perani, E. Garattini, Molecular cloning of a cDNA coding for mouse liver xanthine dehydrogenase, regulation of its transcript by interferons in vivo, Biochem. J. 283 (1992) 863–870, https://doi.org/10.1042/bj2830863.
[28] Y. Moriwaki, T. Yamamoto, J. Yamakita, S. Takahashi, Z. Tsutsumi, K. Higashino, Effect of interferon-gamma on purine catabolic and salvage enzyme activities in rats, Biochim. Biophys. Acta 1427 (1999) 385–391, https://doi.org/10.1016/s0304-4165(99)00038-0.
[29] M.G. Battelli, A. Bolognesi, L. Polito, Pathophysiology of circulating xanthine oxidoreductase: new emerging roles for a multi-tasking enzyme, Biochim. Biophys. Acta 1842 (2014) 1502–1517, https://doi.org/10.1016/j.bbadis.2014.05.022.
[30] M.G. Battelli, L. Buonamici, L. Polito, A. Bolognesi, F. Stirpe, Hepatoxicity of ricin, saporin or a saporin immunotoxin: Xanthine oxidase activity in rat liver and blood serum, Virchows Arch. 427 (1996) 529–535, https://doi.org/10.1007/BF00199514.
[31] K. Sato, A. Naganuma, T. Nagashima, Y. Arai, Y. Mikami, Y. Nakajima, Y. Kanayama, T. Murakami, S. Uehara, D. Uehara, Y. Yamazaki, T. Murase, T. Nakamura, T. Uraoka, A newly developed method-based xanthine oxidoreductase activities in various human liver diseases, Biomedicines 11 (2023) 1445, https://doi.org/10.3390/biomedicines11051445.
[32] L.R. Aldaba-Muruato, M.G. Moreno, E. Hernández-Mercado, M. Shibayama, P. Muriel, Secondary biliary cirrhosis in the rat is prevented by decreasing NF-kappaB nuclear translocation and TGF-beta expression using allopurinol, an inhibitor of xanthine oxidase, Can. J. Physiol. Pharmacol. 90 (2012) 1469–1478, https://doi.org/10.1139/y2012-125.
[33] L.R. Aldaba-Muruato, M.G. Moreno, M. Shibayama, V. Tsutsumi, P. Muriel, Allopurinol reverses liver damage induced by chronic carbon tetrachloride treatment by decreasing oxidative stress, TGF-beta production and NF-kappaB nuclear translocation, Pharmacology 92 (2013) 138–149, https://doi.org/10.1159/000339078.
[34] M. Matboli, M. Saad, M.F. Ahmed, A. Helmy Hasanin, G.M. Ellithy, M. S. Abdelwahab, E.H.B. Eltantawy, G.G. Hamam, A.E. Hamoud, M.M. El-Shafei, N. Samir, Febuxostat alleviate metabolic dysfunction-associated steatohepatitis in rat model via targeting inflammation, cell death, and intestinal barrier dysfunction, Biomed. Pharmacother. 187 (2025) 118086, https://doi.org/10.1016/j.biopha.2025.118086.
[35] N. Gupta, K.J. Singh, Exploring the role of xanthine oxidase and aldehyde oxidase in metabolic dysfunction-associated steatotic liver disease (MASLD), Mol. Histol. 56 (2025) 237, https://doi.org/10.1007/s10735-025-10507-2.
[36] G. Weber, Enzymes of purine metabolism in cancer, Clin. Biochem. 16 (1983) 57–63, https://doi.org/10.1016/s0009-9120(83)94432-6.
[37] A. Yamanoi, N. Nagasue, H. Kohno, T. Kimoto, T. Nakamura, Clinical and enzymatic investigation of induction of oxygen free radicals by ischemia and reperfusion in human hepatocellular carcinoma and adjacent liver, HPB Surg. 8 (1995) 193–199, https://doi.org/10.1155/1995/16191.
[38] M.G. Battelli, L. Polito, M. Bortolotti, A. Bolognesi, Xanthine oxidoreductase in cancer: more than a differentiation marker, Cancer Med. 5 (2016) 546–557, https://doi.org/10.1002/cam4.601.
[39] P. Xu, P.A. LaVallee, J.J. Lin, J.R. Hoidal, Characterization of proteins binding to E-box/Ku86 sites and function of Ku86 in transcriptional regulation of the human xanthine oxidoreductase gene, J. Biol. Chem. 279 (2004) 16057–16063, https://doi.org/10.1074/jbc.M305856200.
[40] M. Saksela, R. Lapatto, K.O. Raivio, Xanthine oxidoreductase gene expression and enzyme activity in developing human tissues, Biol. Neonate 74 (1998) 274–280, https://doi.org/10.1159/000014034.
[41] N. Linder, J. Rapola, K.O. Raivio, Cellular expression of xanthine oxidoreductase protein in normal human tissues, Lab. Invest. 79 (1999) 967–974.
[42] A. Krishnan, S.A. Nair, M.R. Pillai, Biology of PPAR gamma in cancer: a critical review on existing lacunae, Curr. Mol. Med. 7 (2007) 532–540, https://doi.org/10.2174/156652407781695765.
[43] M.G. Chapa, R.D. King, Z.W. Dean, A. Maskey, R.M. Park, M. Velayutham, E. N. Pugacheva, O.M. Woodward, B.A. Webb, D.R. Spitz, E.E. Kelley, Xanthine oxidoreductase expression is diminished in breast cancer as a response to uric acid mediated chelation of redox active iron, Free Radic. Biol. Med. 238 (2025) 329–343, https://doi.org/10.1016/j.freeradbiomed.2025.06.019.
[44] N. Linder, C. Haglund, M. Lundin, S. Nordling, A. Ristimäki, A. Kokkola, J. Mrena, J.P. Wiksten, J. Lundin, Decreased xanthine oxidoreductase is a predictor of poor prognosis in early-stage gastric cancer, J. Clin. Pathol. 59 (2006) 965–971, https://doi.org/10.1136/jcp.2005.032524.
[45] M. Akhter, A.H. Parry, A.W. Dar, I.R. Gadda, Molybdenum deficiency among esophageal cancer patients, Asian Pac. J. Cancer Prev. 26 (2025) 3599–3602, https://doi.org/10.31557/APJCP.2025.26.10.3599.
[46] L. Liu, Y. Zhang, X. Wang, H. Meng, Y. He, X. Xu, H. Xu, C. Wei, X. Yan, X. Tao, K. Dang, P. Ma, X. Guo, S. Yang, J. Wang, Y. Li, Xanthine oxidase promotes hepatic lipid accumulation through high fat absorption by the small intestine, JHEP Rep. 6 (2024) 101060, https://doi.org/10.1016/j.jhepr.2024.101060.
[47] Y. Nakatsu, Y. Seno, A. Kushiyama, H. Sakoda, M. Fujishiro, A. Katasako, K. Mori, Y. Matsunaga, T. Fukushima, R. Kanaoka, T. Yamamotoya, H. Kamata, T. Asano, The xanthine oxidase inhibitor febuxostat suppresses development of nonalcoholic steatohepatitis in a rodent model, Am. J. Physiol. Gastrointest. Liver Physiol. 309 (2015) G42–G51, https://doi.org/10.1152/ajpgi.00443.2014.
[48] N. Prajda, H.P. Morris, G. Weber, Imbalance of purine metabolism in hepatomas of different growth rates as expressed in behavior of xanthine oxidase (EC 1.2.3.2), Cancer Res. 36 (1976) 4639–4646.
[49] T. Ikegami, Y. Natsumeda, G. Weber, Decreased concentration of xanthine dehydrogenase (EC 1.1.1.204) in rat hepatomas, Cancer Res. 46 (1986) 3838–3841.
[50] P. Archontakis-Barakakis, T. Mavridis, A. Chalkias, Oxygen-mediated molecular mechanisms involved in intestinal ischemia and reperfusion injury, Int. J. Mol. Sci. 26 (2025) 8398, https://doi.org/10.3390/ijms26178398.
[51] M. Zakkar, G. Guida, M.S. Suleiman, G.D. Angelini, Cardiopulmonary bypass and oxidative stress, Oxid. Med. Cell. Longev. 2015 (2015) 189863, https://doi.org/10.1155/2015/189863.
[52] R. Feinman, E.A. Deitch, A.C. Watkins, B. Abungu, I. Colorado, K.B. Kannan, S. U. Sheth, F.J. Caputo, Q. Lu, M. Ramanathan, S. Attan, C.D. Badami, D. Doucet, D. Barlos, M. Bosch-Marce, G.L. Semenza, D.Z. Xu, HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia-reperfusion injury, Am. J. Physiol. Gastrointest. Liver Physiol. 299 (2010) G833–G843, https://doi.org/10.1152/ajpgi.00065.2010.
[53] D.A. Parks, D.N. Granger, Contributions of ischemia and reperfusion to mucosal lesion formation, Am. J. Physiol. 250 (1986) G749–G753, https://doi.org/10.1152/ajpgi.1986.250.6.G749.
[54] D.N. Granger, J.M. McCord, D.A. Parks, M.E. Hollwarth, Xanthine oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine, Gastroenterology 90 (1986) 80–84, https://doi.org/10.1016/0016-5085(86)90078-8.
[55] D.N. Granger, P.R. Kvietys, Reperfusion injury and reactive oxygen species: the evolution of a concept, Redox Biol. 6 (2015) 524–551, https://doi.org/10.1016/j.redox.2015.08.020.
[56] W. Zhang, C. Jin, S. Zhang, L. Wu, B. Li, M. Shi, Gut lymph purification alleviates acute lung injury induced by intestinal ischemia-reperfusion in rats by removing danger-associated molecular patterns from gut lymph, Heliyon 10 (2024) e25711, https://doi.org/10.1016/j.heliyon.2024.e25711.
[57] Z. Ren, Z. Zheng, X. Feng, Role of gut microbes in acute lung injury/acute respiratory distress syndrome, Gut Microbes 16 (2024) 2440125, https://doi.org/10.1080/19490976.2024.2440125.
[58] B.I. Ucar, A. Erikci, K. Kosemehmetoglu, C. Ozkul, A.B. Iskit, G. Ucar, S. Zeren, Effects of endothelin receptor blockade and COX inhibition on intestinal I/R injury in a rat model: experimental research, Int. J. Surg. 83 (2020) 89–97, https://doi.org/10.1016/j.ijsu.2020.08.061.
[59] R.E. Akhigbe, B.O. Adedamola Aminat, T.M. Akhigbe, M.A. Hamed, Glutamine alleviates I/R-induced intestinal injury and dysmotility via the downregulation of xanthine oxidase/uric acid signaling and lactate generation in Wistar rats, J. Surg. Res. 295 (2024) 431–441, https://doi.org/10.1016/j.jss.2023.11.041.
[60] L.S. Terada, J.J. Dormish, P.F. Shanley, J.A. Leff, B.O. Anderson, J.E. Repine, Circulating xanthine oxidase mediates lung neutrophil sequestration after intestinal ischemia-reperfusion, Am. J. Physiol. 263 (1992) L394–L401, https://doi.org/10.1152/ajplung.1992.263.3.L394.
[61] R.S. Poggetti, F.A. Moore, E.E. Moore, K. Koeike, A. Banerjee, Simultaneous liver and lung injury following gut ischemia is mediated by xanthine oxidase, J. Trauma 32 (1992) 723–728, https://doi.org/10.1097/00005373-199206000-00008.
[62] K. Koike, F.A. Moore, E.E. Moore, R.A. Read, V.S. Carl, A. Banerjee, Gut ischemia mediates lung injury by a xanthine oxidase-dependent neutrophil mechanism, J. Surg. Res. 54 (1993) 469–473, https://doi.org/10.1006/jsre.1993.1072.
[63] S. Tan, S. Gelman, J.K. Wheat, D.A. Parks, Circulating xanthine oxidase in human ischemia reperfusion, South. Med. J. 88 (1995) 479–482, https://doi.org/10.1097/00007611-199504000-00021.

[64] J. Chen, Y. Wang, Y. Shi, Y. Liu, C. Wu, Y. Luo, Association of gut microbiota with intestinal ischemia/reperfusion injury, Front. Cell. Infect. Microbiol. 12 (2022) 962782, https://doi.org/10.3389/fcimb.2022.962782.
[65] J. Hu, F. Deng, B. Zhao, Z. Lin, Q. Sun, X. Yang, M. Wu, S. Qiu, Y. Chen, Z. Yan, S. Luo, J. Zhao, W. Liu, C. Li, K.X. Liu, Lactobacillus murinus alleviate intestinal ischemia/reperfusion injury through promoting the release of interleukin-10 from M2 macrophages via toll-like receptor 2 signaling, Microbiome 10 (2022) 38, https://doi.org/10.1186/s40168-022-01227-w.
[66] M. Rasti Ardakani, A. Al-Dam, A. Rashad, A. Shayesteh Moghadam, Effect of systemic antioxidant allopurinol therapy on skin flap survival, World J. Plast. Surg. 6 (2017) 54–61.
[67] M. Fakhoury, R. Negrulj, A. Mooranian, H. Al-Salami, Inflammatory bowel disease: clinical aspects and treatments, J. Inflamm. Res. 7 (2014) 113–120, https://doi.org/10.2147/JIR.S65979.
[68] L.J. Derijks, D.R. Wong, Pharmacogenetics of thiopurines in inflammatory bowel disease, Curr. Pharm. Des. 16 (2010) 145–154, https://doi.org/10.2174/138161210790112773.
[69] R.L. Roberts, R.B. Gearry, M.L. Barclay, Allopurinol-thiopurine combination therapy in inflammatory bowel disease: are there genetic clues to this puzzle? Pharmacogenomics 11 (2010) 1505–1508, https://doi.org/10.2217/pgs.10.143.
[70] K. Amirshahrokhi, Febuxostat attenuates ulcerative colitis by the inhibition of NF-κB, proinflammatory cytokines, and oxidative stress in mice, Int. Immunopharmacol. 76 (2019) 105884, https://doi.org/10.1016/j.intimp.2019.105884.
[71] Y. He, D. Aikepa, M. Liang, W. Chen, M. Du, Y. Zhu, D. Yang, X. Chen, Q. Yang, Y. Sun, Limosilactobacillus fermentum M5e attenuates hyperuricemia and renal injury via dual modulation of gut microbiota and purine metabolic pathways, ACS Pharmacol. Transl. Sci. 8 (2025) 2117–2131, https://doi.org/10.1021/acsptsci.5c00197.
[72] S. He, Q. Xiong, C. Tian, L. Li, J. Zhao, X. Lin, X. Guo, Y. He, W. Liang, X. Zuo, C. Ying, Inulin-type prebiotics reduce serum uric acid levels via gut microbiota modulation: a randomized, controlled crossover trial in peritoneal dialysis patients, Eur. J. Nutr. 61 (2022) 665–677, https://doi.org/10.1007/s00394-021-02669-y.
[73] Y. Liu, J.B. Jarman, Y.S. Low, H.E. Augustijn, S. Huang, H. Chen, M.E. DeFeo, K. Sekiba, B.H. Hou, X. Meng, A.M. Weakley, A.V. Cabrera, Z. Zhou, G. van Wezel, M.H. Medema, C. Ganesan, A.C. Pao, S. Gombar, D. Dodd, A widely distributed gene cluster compensates for uricase loss in hominids, Cell 186 (2023) 3400–3413.e20, https://doi.org/10.1016/j.cell.2023.06.010.
[74] X. Qi, Y. Ma, K. Guan, L. Zhao, Y. Ma, R. Wang, Whey protein peptide pro-glu-trp ameliorates hyperuricemia by enhancing intestinal uric acid excretion, modulating the gut microbiota, and protecting the intestinal barrier in rats, J. Agric. Food Chem. 72 (2024) 2573–2584, https://doi.org/10.1021/acs.jafc.3c00984.
[75] Q. Wang, J. Liang, Q. Zou, W. Wang, G. Yan, R. Guo, T. Yuan, Y. Wang, X. Liu, Z. Liu, Tryptophan metabolism-regulating probiotics alleviate hyperuricemia by protecting the gut barrier integrity and enhancing colonic uric acid excretion, J. Agric. Food Chem. 72 (2024) 26746–26761, https://doi.org/10.1021/acs.jafc.4c07716.
[76] H. Wang, Y. Xi, F. Gu, L. Peng, J. Li, Protective effects of a polyherbal mixture on intestinal injury via the NF-κB signaling pathway and gut microbiota modulation in hyperuricemic mice, Foods 14 (2025) 1118, https://doi.org/10.3390/foods14071118.
[77] K. Sato, K. Yamazaki, T. Kato, Y. Nakanishi, T. Tsuzuno, M. Yokoji-Takeuchi, M. Yamada-Hara, N. Miura, S. Okuda, H. Ohno, K. Yamazaki, Obesity-related gut microbiota aggravates alveolar bone destruction in experimental periodontitis through elevation of uric acid, mBio 12 (2021) e0077121, https://doi.org/10.1128/mBio.00771-21.
[78] T. Zhang, S. Liu, S. Liu, P. Zhao, C. Zhang, X. Wang, Y. Meng, Y. Lu, Oleanolic acid alleviates hyperuricemia via gut microbiota control the integrity of gut barrier and the expressions of urate transporter in mice, J. Agric. Food Chem. 73 (2025) 5899–5914, https://doi.org/10.1021/acs.jafc.4c09270.
[79] Q. Lv, D. Xu, X. Zhang, X. Yang, P. Zhao, X. Cui, X. Liu, W. Yang, G. Yang, S. Xing, Association of hyperuricemia with immune disorders and intestinal barrier dysfunction, Front. Physiol. 11 (2020) 524236, https://doi.org/10.3389/fphys.2020.524236.
[80] L. Rizzetto, F. Fava, K.M. Tuohy, C. Selmi, Connecting the immune system, systemic chronic inflammation and the gut microbiome: the role of sex, J. Autoimmun. 92 (2018) 12–34, https://doi.org/10.1016/j.jaut.2018.05.008.
[81] M.A.F. Caetano, P. Castelucci, Role of short chain fatty acids in gut health and possible therapeutic approaches in inflammatory bowel diseases, World J. Clin. Cases 10 (2022) 9985–10003, https://doi.org/10.12998/wjcc.v10.i28.9985.
[82] J. Cai, L. Sun, F.J. Gonzalez, Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis, Cell Host Microbe 30 (2022) 289–300, https://doi.org/10.1016/j.chom.2022.02.004.
[83] M. Schirmer, M. Stražar, J. Avila-Pacheco, D.F. Rojas-Tapias, E.M. Brown, E. Temple, A. Deik, K. Bullock, S. Jeanfavre, K. Pierce, S. Jin, R. Invernizzi, M. M. Pust, Z. Costliow, D.R. Mack, A.M. Griffiths, T. Walters, B.M. Boyle, S. Kugathasan, H. Vlamakis, J. Hyams, L. Denson, C.B. Clish, R.J. Xavier, Linking microbial genes to plasma and stool metabolites uncovers host-microbial interactions underlying ulcerative colitis disease course, Cell Host Microbe 32 (2024) 209–226.e7, https://doi.org/10.1016/j.chom.2023.12.013.
[84] V.A. Ionescu, G. Gheorghe, N. Bacalbasa, A.L. Chiotoroiu, C. Diaconu, Colorectal cancer: from risk factors to oncogenesis, Medicina (Kaunas) 59 (2023) 1646, https://doi.org/10.3390/medicina59091646.
[85] R. Qu, Y. Zhang, Y. Ma, X. Zhou, L. Sun, C. Jiang, Z. Zhang, W. Fu, Role of the gut microbiota and its metabolites in tumorigenesis or development of colorectal cancer, Adv. Sci. (Weinh). 10 (2023) e2205563, https://doi.org/10.1002/advs.202205563.
[86] H. Li, C. Zhang, H. Zhang, H. Li, Xanthine oxidoreductase promotes the progression of colitis-associated colorectal cancer by causing DNA damage and mediating macrophage M1 polarization, Eur. J. Pharmacol. 906 (2021) 174270, https://doi.org/10.1016/j.ejphar.2021.174270.
[87] H. Li, X. Li, Y. Wang, W. Han, H. Li, Q. Zhang, Hypoxia-mediated upregulation of xanthine oxidoreductase causes DNA damage of colonic epithelial cells in colitis, Inflammation 47 (2024) 1142–1155, https://doi.org/10.1007/s10753-024-01966-y.
[88] N. Linder, E. Martelin, M. Lundin, J. Louhimo, S. Nordling, C. Haglund, J. Lundin, Xanthine oxidoreductase - clinical significance in colorectal cancer and in vitro expression of the protein in human colon cancer cells, Eur. J. Cancer 45 (2009) 648–655, https://doi.org/10.1016/j.ejca.2008.10.036.