Inosine: A bioactive metabolite with multimodal actions in human diseases

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The nucleoside inosine is an essential metabolite for purine biosynthesis and degradation; it also acts as a bioactive molecule that regulates RNA editing, metabolic enzyme activity, and signaling pathways. As a result, inosine is emerging as a highly versatile bioactive compound and second messenger of signal transduction in cells with diverse functional abilities in different pathological states. Gut microbiota remodeling is closely associated with human disease pathogenesis and responses to dietary and medical supplementation. Recent studies have revealed a critical link between inosine and gut microbiota impacting anti-tumor, anti-inflammatory, and antimicrobial responses in a context-dependent manner. In this review, we summarize the latest progress in our understanding of the mechanistic function of inosine, to unravel its immunomodulatory actions in pathological settings such as cancer, infection, inflammation, and cardiovascular and neurological diseases. We also highlight the role of gut microbiota in connection with inosine metabolism in different pathophysiological conditions. A more thorough understanding of the mechanistic roles of inosine and how it regulates disease pathologies will pave the way for future development of therapeutic and preventive modalities for various human diseases.

KEYWORDS
inosine, cancer, inflammation, infection, cardiovascular disease, neuroprotection

Introduction

Inosine, an inert purine nucleoside, is formed by breakdown (deamination) of adenosine both intracellularly and extracellularly; it also generated by the action of 5′-nucleotidase on inosine monophosphate (IMP) (Conway and Cooke, 1939; Itoh et al., 1967; Chen et al., 1996). Recent studies have revealed that inosine is also produced by several species found in the gut microbiome and modulates host immune and inflammatory functions (Wang et al., 2020; Brown et al., 2021). Inosine can be metabolized into hypoxanthine, xanthine, and uric acid (Sorensen, 1970; Zoref-Shani et al., 1988; Doyle et al., 2018; García-Gil et al., 2021). Cell membrane transport of inosine is mediated by equilibrative and concentrative nucleoside transporters (Körber et al., 1975; Belt et al., 1993; Cass et al., 1999; Miller et al., 2021). Inosine functions are mediated...
| Disease                      | Subject                                                                 | Intervention       | Effect                                           | Mechanism                                                                 | References                  |
|------------------------------|-------------------------------------------------------------------------|--------------------|-------------------------------------------------|---------------------------------------------------------------------------|----------------------------|
| **Cancers**                  |                                                                         |                    |                                                 |                                                                          |                            |
| Cervical cancer              | HPV-positive patients after cervical conization                         | Inosine pranobex   | Reduce relapse of HSIL and high-risk HPV infection | Clear cervical HPV infection                                               | Kovachev, (2020)            |
| Colon cancer, bladder cancer, and melanoma | Mice with xenograph or chemical-induced tumor                         | Inosine            | Augment immune checkpoint inhibitor efficacy     | Promote Th1 immunity through activating adenosine 2A receptor             | Mager et al. (2020)         |
| Liver cancer                 | HepG2 cells                                                             | Inosine pranobex   | Cytotoxic effect                                | Mitochondrial damage                                                      | Tobolska et al. (2018)      |
| Melanoma                     | Mice with xenograph tumor                                               | Inosine            | Enhance immunotherapy efficacy                  | Support proliferation and function of effector T cells                    | Wang et al. (2020)          |
| **Cardiovascular diseases**  |                                                                         |                    |                                                 |                                                                          |                            |
| Atherosclerosis              | Rats with hypercholesterolemic diet                                      | Inosine pranobex   | Alleviate atherogenic index and platelet aggregation | Activate eNOS and inhibit the NF-κB pathway                                | Lima et al. (2020)          |
| Mitochondrial disease        | Mt-cardiomyopathy and mt-diabetes patients                              | Inosine plus febuxostat | Decrease BNP and increase insulinogenic index | Enhance cellular ATP levels                                               | Kamatani et al. (2019)      |
| **Infectious diseases**      |                                                                         |                    |                                                 |                                                                          |                            |
| Acute respiratory viral      | Laboratory-conﬁrmed viral infection patients with ILI                  | Inosine pranobex   | Reduce time to symptom resolution                | Control viral infection                                                   | Beran et al. (2016)         |
| COVID-19                     | SARS-CoV-2-positive patients                                           | Inosine pranobex   | Reduce case-fatality rate                        | Control viral infection                                                   | Beran et al. (2020)         |
| Inﬂuenza                    | Inﬂuenza A (H1N2)-infected mice                                       | Inosine pranobex   | Extend survival time with oseltamivir and ellagic acid | Protect from damaging superoxide radicals                                 | Pavlova et al. (2018)       |
| NTM pulmonary disease        | NTM-infected mice                                                       | Inosine            | Decrease bacterial loads in lungs                | Enhance IFN-γ-related responses                                           | Kim et al. (2022)           |
| **Inflammatory disease**     |                                                                         |                    |                                                 |                                                                          |                            |
| Acute hepatic injury         | LPS-injected mice                                                       | Inosine            | Suppress inﬂammatory cytokines and conserve liver function | Alter the microﬂora composition and attenuate the TLR4 pathway             | Guo et al. (2021)           |
| Alcoholic liver disease      | Mice with alcohol-induced liver injury                                  | Inosine plus LGG   | Improve the liver structure and function         | Suppress oxidative stress and attenuate inﬂammatory cytokine expression | Zhu et al. (2022)           |
| IPEX syndrome                | Scurfy mouse                                                            | Inosine            | Prolong lifespan and reduce multiorgan inﬂammation | Inhibit Th1 and Th2 cell differentiation through adenosine A2 receptor | He et al. (2017)            |
| NSAID-induced enteropathy    | Mice with indomethacin-induced enteropathy                             | Inosinic acid plus pottassium oxonate | Conserve intestinal function                     | Remove ROS through serum uric acid accumulation                           | Yatsukite et al. (2017)     |
| Sepsis                       | LPS-injected mice                                                       | Inosine monophosphate | Decrease TNF-α and increase IL-10 | Augment inosine produced by ecto-5′-nucleotidase Increase phosphorylated S6 and decrease phosphorylated IRF3 | Lovási et al. (2021)       |
| Systemic lupus erythematosus | LPS-treated human monocytes                                              | Inosine            | Inhibit autophagy and IFN-β release              | Activate adenosine A2 receptor/PPAR-γ axis                                | Wu et al. (2022)            |
| Ulcerative colitis           | Mice with DSS-induced colitis                                           | Inosine            | Protect intestinal function                      |                                                                          | Li et al. (2021b)           |
| **Neuropsychological disease**|                                                                         |                    |                                                 |                                                                          |                            |
| Alzheimer’s disease          | Rats with streptozotocin-induced Alzheimer’s disease                    | Inosine            | Prevent memory deﬁcits and weight loss          | Increase BDNF and anti-inﬂammatory cytokines                              | Teixeira et al. (2022a)     |
| Alzheimer’s disease          | Rats with streptozotocin-induced Alzheimer’s disease                    | Inosine            | Attenuate memory loss                           | Modulate the ion pump activities and clear the oxidative stress           | Teixeira et al. (2020)      |
| Alzheimer’s disease          | Rats with scopolamine-induced cognitive impairment                      | Inosine            | Protect from memory consolidation impairment     | Modulate the ion pump and AchE activities and reduce the oxidative stress | Teixeira et al. (2022b)     |
| Bipolar disorder             | Rats with ketamine-induce mania                                         | Inosine            | Prevent hyperlocomotion behavior                |                                                                          | Camerini et al. (2020)      |

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in receptor-dependent or–independent manners. The receptor-mediated function of inosine is thought to be related to adenosine receptor family members including A₁, A₂A, A₂B, and A₃ G-protein coupled receptors (Kypson and Hait, 1976; Fredholm et al., 2001; Fredholm et al., 2011; Welihinda et al., 2018). Compared with the known role of adenosine as a signaling molecule, the function of inosine in the context of physiological and pathological responses in human health and diseases remain poorly understood.

Earlier studies suggested that the inert purine nucleoside inosine has neuroprotective, cardioprotective, and immunomodulatory effects in different experimental models (Aviado, 1983; Haskó et al., 2004; Guinzing et al., 2006). The beneficial function of inosine has been thought to be mediated through modulation of oxidative stress and inflammatory responses (Haskó et al., 2004). More recent studies have revealed therapeutic effects of inosine in motor function improvement during neurologic injury or stroke (Benowitz et al., 1999; Kuricova et al., 2014), learning and memory (Ruhal and Dhingra, 2018), and Parkinson’s disease (Schwarzschild et al., 2014). Inosine treatment also results in decrease in uric acid and dimethylaminoisopropanol, for treatment of neurological disorders and acute respiratory viral infections (Beran et al., 2016; Sliva et al., 2019; Teixeira et al., 2020; Mager et al., 2020). Importantly, the beneficial effects of inosine have been demonstrated with the preclinical and clinical use of Isoprininosine (inosine prinobex), formed by inosine with the immunostimulatory dimepranol acedoben (acetamidobenzoic acid and dimethylaminoisopropanol), for treatment of neurological disorders and acute respiratory viral infections (Beran et al., 2016; Silva et al., 2019; Teixeira et al., 2020; Kovachev, 2020; Mager et al., 2020). In this Review, we discuss recent updates on the regulation of pathological responses by inosine and its association with gut microbiota remodeling in different contexts. Furthermore, we discuss the functions of exogenous

| Disease                     | Subject                              | Intervention                | Effect                                                                 | Mechanism                                                                 | References                                                                 |
|-----------------------------|--------------------------------------|----------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| CNS injury                  | Rat with unilateral CST transection  | Contralateral inosine      | Stimulate axon collateral growths, Improve recovery of motor and urinary function | Induce axon sprouting and crossing, Increase axonal ramification           | Benowitz et al. (1999)                                                    |
| CNS injury                  | Rat with spinal cord compression     | Inosine                    | Improve recovery of motor and urinary function                         | Increase axonal ramification                                              | Kypson et al. (2014)                                                      |
| Cognitive dysfunction       | Aged female rats                     | Inosine                    | Elevate learning and memory function                                  | Conserve hippocampal CA1 region with anti-inflammatory and antioxidant effect | Ruhal and Dhingra, (2018)                                                 |
| Diabetic peripheral neuropathy | Rats with streptozotocin and nicotinamide induced diabetes | Inosine                    | Improve recovery of motor and urinary function                         | Increase axonal ramification                                              | Abdelkader et al. (2022)                                                  |
| Huntington’s disease        | Rats with 3-NP-induced neurotoxicity | Inosine                    | Mitigate the disease symptoms                                           | Activate adenosine A2 receptor/BDNF/ERK axis                              | El-Shamarka et al. (2022)                                                 |
| Methamphetamine withdrawal syndrome | Methamphetamine-treated mice | Inosine                    | Restore the anxiety and depression-like behavior                         | Potential neuroprotective function                                        | Yang et al. (2022)                                                        |
| Multiple system atrophy     | Multiple system atrophy patients     | Inosine monophosphate       | Improve cognitive function                                              | Increase serum uric acid                                                  | Jung Lee et al. (2021)                                                    |
| Parkinson’s disease         | Early Parkinson’s disease patients   | Inosine                    | Mitigate the disease progression                                        | Increase cerebrospinal fluid urate                                        | Schwarzschild et al. (2014)                                               |
| Parkinson’s disease         | Parkinson’s disease patients          | Inosine plus febuxostat     | Improve disease symptoms                                                | Increase blood hypoxanthine and xanthine but decrease uric acid           | Watanabe et al. (2020)                                                    |
| Parkinson’s disease         | Early Parkinson’s disease patients   | Inosine                    | No significant difference in the disease progression                    | --                                                                        | Schwarzschild et al. (2021)                                               |
| PNS injury                  | Mice with sciatic nerve crush        | Inosine                    | Ascelerate axonal regeneration and functional recovery                  | Reduce the number of macrophages and myelin ovoids                       | Soares Dos Santos et al. (2019)                                            |

**Abbreviation**: 3-NP, 3-nitropropionic acid; AChE, acetylcholinesterase; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; BNP, brain natriuretic peptide; CNS, central nervous system; CST, corticospinal tract; DSS, dextran sulfate sodium; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; HHL, high-grade squamous intraepithelial lesion; HPV, human papilloma virus; IFN, interferon; IL, interleukin; IIL, influenza-like illnesses; IPEX syndrome, immune dysregulation, polyendocrinopathy, and enteropathy, with X-linked inheritance; IRF3, interferon regulatory factor 3; LGG, Lactobacillus rhamnosus GG; LPS, lipopolysaccharide; Mt, mitochondria; NF-κB, nuclear factor-κB; NSAID, nonsteroidal anti-inflammatory drug; NTM, nontuberculous mycobacteria; PNS, peripheral nervous system; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; TLR4, toll-like receptor 4; TNF, tumor necrosis factor.
Overview of inosine biology

Inosine, an intermediate in purine metabolism, consists of hypoxanthine and ribose. Three enzymatic reactions can form inosine endogenously (Figure 1). First, adenosine deaminase (ADA) irreversibly removes the amine group of adenine ring intracellularly and extracellularly (Akedo et al., 1972; Van Heukelom et al., 1976; Van der Weyden and Kelley, 1977; Akeson et al., 1988). In particular, double-stranded RNA (dsRNA)-specific adenosine deaminases (ADARs) mediate adenosine-to-inosine editing (Liddicoat et al., 2015; George et al., 2016; Eisenberg and Levanon, 2018; Nakahama and Kawahara, 2020; Pfaller et al., 2021). ADAR1 and ADAR2 maintain balanced immune activation and self-tolerance through inhibiting dRNA-binding proteins, such as RIG-I-like receptors, protein kinase R, and oligoadenylate synthases-RNase L (Yang et al., 2014; Liddicoat et al., 2015; George et al., 2016; Jain et al., 2019; Lamers et al., 2019; Schaffer et al., 2020; Pfaller et al., 2021; Li et al., 2022). In a recent study, the severe autoinflammatory disease Aicardi–Goutières syndrome mouse model with ADAR1 mutation reveals immunopathology associated with type I interferon signaling and Z-binding protein 1 (Rice et al., 2012; de Reuver et al., 2022). Contrary to ADAR1 and ADAR2, ADAR3 suppresses A-to-I editing by binding to RNA-binding domains (Chen et al., 2000; Oakes et al., 2017; Raghava Kurup et al., 2022). Second, 5’-nucleotidase catalyzes the reversible dephosphorylation of IMP both inside and outside cells (Barsotti et al., 2005; Ipata and Balestri, 2013). Cytosolic 5’-nucleotidase (NT5C2) is correlated with chemotherapy resistance in acute lymphoblastic leukemia (Tzoneva et al., 2013). Ecto-5’-nucleotidase (NT5E, CD73) mediates immune suppression (Romio et al., 2011; Lovási et al., 2021). Third, purine nucleoside phosphorylase (PNP) converts hypoxanthine and ribose-1-phosphate (R-1-P) into inosine and thermodynamically favors this enzymatic synthesis over phosphorolysis (Kalckar, 1947; Friedman, 1950; Tozzi et al., 2006). However, the PNP reaction equilibrium is biased toward inosine degradation due to the more significant concentration of inorganic phosphate than base and R-1-P (Traut, 1994), and the linked reaction of hypoxanthine catalyzed by hypoxanthine phosphoribosyl transferase and xanthine oxidase (Pugmire and Ealick, 2002; Il’icheva et al., 2020). Xanthine oxidase catabolizes hypoxanthine into uric acid via xanthine (Heinz et al., 1980; Moriwaki et al., 1999; Doyle et al., 2018). Humans and higher primates excrete uric acid in their urine, but other mammals convert uric acid to allantoin by uricase and then excrete it in urine (Heinz et al., 1980; Kurtz et al., 1986; Moriwaki et al., 1999). Uric acid, the end product of human purine metabolism, is one of the major antioxidants (Ames et al., 1981; Whiteman et al., 2002; Muraoka and Miura, 2003) and protects against neurological and intestinal diseases (Hooper et al., 1998; Hooper et al., 2000; Toncev et al., 2002; Ascherio et al., 2009; Matsuo et al., 2015; Yasutake et al., 2017). Consequently, inosine-related metabolism should be extensively explored for its multidimensional effects on human illnesses.

In the human gut, 10^{13}–10^{14} microorganisms are found and are emerging as important players in the pathogenesis and therapeutics of a variety of human diseases (Wardman et al., 2022). Recently, a mechanistic link between microbiota and inosine has been revealed. For example, the microbiome-derived Bxa, an abundant ADP-ribosyltransferase (ADPRT) of Bacteroides, induced secretion of inosine as a carbon source, thus acting as a bacterial fitness factor (Brown et al., 2021). Gut microbiota remodeling enriched Bifidobacterium pseudolongum and supplementation with its metabolite inosine increased the anti-tumor effects of immune checkpoint blockade and functioned as a carbon source for CD8+ effector T-cell function (Wang et al., 2020). In a more recent study, inosine was found to be a microbiota-derived immunostimulatory metabolite that enhanced immunotherapeutic effects and antitumor T-cell responses (Kroemer and Zitvogel, 2020; Mager et al., 2020). Indeed, gut microbiota remodeling enriched B. pseudolongum significantly increased the anticancer immunotherapy response through the generation of inosine via A2A receptors (Mager et al., 2020).
A multifaceted role for inosine in cancer

Multiple studies have suggested that inosine functions as a crucial biomarker metabolite associated with cancer metastasis, drug resistance and/or treatment, and tumor progression (Li et al., 2021a; Lee et al., 2021; Stockard et al., 2021). A recent study showed that inosine can predict the metastatic potential of lung squamous cell carcinoma (Lee et al., 2021). Inosine has also been shown to be associated with acute myeloid leukemia with cytarabine resistance (Stockard et al., 2021). In esophageal squamous cell carcinoma, inosine has been associated with cancer progression (Li et al., 2021a). In colorectal cancer organoids, inosine was elevated following treatment with 5-fluorouracil (Neef et al., 2020), although the underlying mechanism is unclear. In head and neck squamous cell carcinoma, inosine and adenosine are abundant purine metabolites present in exosomes from the supernatant of UMSCC47 cells (Ludwig et al., 2020). Inosine is a crucial serum metabolite that can differentiate between low- and high-grade bladder cancer patients (Tan et al., 2017). Moreover, urine and serum levels of inosine as well as other metabolites can be used to characterize hepatocellular carcinoma patients (Chen et al., 2011; Ladep et al., 2014). These data suggest that inosine has a promising role in the diagnosis and grading of tumors as a signature metabolite. By contrast, inosine levels are generally decreased in pancreatic cancer patients, and elevated by a low carbohydrate ketogenic diet, compared to a general hospital diet (Kang et al., 2019). These data collectively suggest that inosine functions as a potential biomarker for prediction of cancer risk, drug response, and early detection of metastasis of various tumors.

Several recent studies have indicated the role of inosine in anti-tumor responses in various cancers. In a xenograft model of pancreatic ductal adenocarcinoma, gemcitabine-mediated chemotherapy significantly induced activation of nuclear factor (NF)-κB-mediated inflammatory responses and decreased the proportion of Firmicutes and Bacteroides. The chemotherapy also suppressed serum levels of inosine and xanthine (Panebianco et al., 2018), suggesting chemotherapy may influence gut microbiota remodeling and changes in serum metabolites. Moreover, inosine supplementation promoted immune checkpoint blockade and provided a carbon source for CD8+ effector T-cell function (Wang et al., 2020). In a more recent study, inosine was found to be a microbiota-derived immunostimulatory metabolite that enhanced immunotherapeutic effects and antitumor T-cell responses (Kroemer and Zitvogel, 2020; Mager et al., 2020). Indeed, gut microbiota remodeling enriched B. pseudolongum and significantly increased the effects of immunotherapy through the generation of inosine via A3A receptors (Mager et al., 2020).

Although inosine proanobex (isoprinosin) has been shown to exhibit significant antiviral effects (Beran et al., 2021), few studies have investigated its effects in cancer. Treatment with isoprinosin significantly increased the clearance of cervical human papillomavirus (HPV) infection during postoperative immunotherapy in women receiving surgical treatment for high-grade squamous intraepithelial cervical lesions (Kovachev, 2020). Additionally, a previous study revealed increased cytotoxicity of fibroblasts and hepatocellular carcinoma HepG2 cells following inosine proanobex treatment (Tobólska et al., 2018). Because inosine proanobex is useful in viral infections and has remarkable immunomodulating functions in both cellular and humoral immune responses (Kovachev, 2021), the therapeutic application of inosine proanobex is challenging in terms of virus-related tumors accompanied with chronic inflammation and immunosuppression. Although it would have been shown to be therapeutically beneficial in animal studies, the use of inosine proanobex in anticancer regimens should be considered following more data from clinical trials.

Inosine and antimicrobial immunity

In nonhuman primate models infected with human immunodeficiency virus type 1/simian immunodeficiency virus (HIV-1/SIV), elevated inosine levels have been related to immune activation and disease progression markers (He et al., 2015). The disease-progressive model reveals higher ADA activity and CD26 expression on intestinal T cells than the nonprogressive model, suggesting that adenosine degradation stimulates T cells (He et al., 2015). In addition, several recent studies have suggested a link between inosine and antimicrobial function during bacterial infection. Our recent study showed that inosine, as a metabolite of B. pseudolongum, contributes to antimicrobial responses in mouse models with Mycobacteroides abscessus (Mabc) infection (Kim et al., 2022). Interestingly, l-arginine administration of Mabc-infected mice led to gut microbiota remodeling toward enrichment of B. pseudolongum, which promoted effector T-cell responses with IFN-γ activation and inducible nitric oxide synthase (iNOS) expression, indicating a Th1-mediated M1 shift (Kim et al., 2022). Importantly, l-arginine administration upregulated the serum level of inosine in mice infected with Mabc, and inosine treatment exhibited a similar protective phenotype as observed in l-arginine-treated conditions in the context of NTM infections (Sun et al., 2020; Kim et al., 2022). It was previously reported suberic acid is produced by B. pseudolongum (Sun et al., 2020), however, treatment of Mabc-infected mice with suberic acid did not show any protective immune responses during Mabc infection. These data strongly suggest that inosine, produced by B. pseudolongum, plays a distinct role in the enhancement of antimicrobial responses during NTM infection.

Isoprinosine appears to be an effective treatment for various viral infections through pleiotropic immunomodulatory roles.
including T-cell activation and proinflammatory cytokine-mediated functions (Sliva et al., 2019; Beran et al., 2021). Isoprinosine combined with antiviral and antioxidant drugs has been shown to produce a protective effect, with increased survival and decreased lung pathologies, in influenza H3N2 virus-infected mice (Pavlova et al., 2018). In addition, a Phase 4 clinical study showed that isoprinosine is safe for treatment of patients with acute respiratory viral infections and is effective in the resolution of influenza-like symptoms in individuals less than 50 years of age (Beran et al., 2016). A preliminary report emphasized the effectiveness of isoprinosine pranobex in the reduction of the case-fatality rate in older COVID-19 patients in the Czech Republic (Beran et al., 2020), although larger-scale trials are warranted to clarify the therapeutic effects of isoprinosine pranobex against COVID-19. Isoprinosine acedoben dimepranol (IAD), another licensed inosine-based drug, has been shown to boost NK cell numbers in clinical trials (Rumel Ahmed et al., 2017). Future clinical studies are needed to determine whether isoprinosine or IAD can be effectively used as adjunctive drugs in antiviral therapeutics without overt complications.

**Inosine and therapeutic implications for inflammation**

A recent report showed that inosine, metabolized from IMP, suppressed tumor necrosis factor (TNF)-α in vitro and in vivo, although A3A, A2B, and A3 receptors were not involved (Lovásvi et al., 2021). In addition, inosine augmented IL-β production in response to NLRP3 inflammasome stimuli in macrophages (Lovásvi et al., 2021). These data suggest that inosine is involved in the activation or suppression of inflammatory responses, depending on the stimuli.

Several studies have shown the combined beneficial effects of inosine and probiotics in experimental inflammatory disease models. For example, *Lactobacillus rhamnosus* GG (LGG) combined with inosine has been shown to ameliorate hepatic inflammation and restore regulatory T-cell function in an alcohol-induced liver injury model (Zhu et al., 2022). Importantly, combined treatment of LGG and inosine significantly improved immune homeostasis and intestinal microecology with amelioration of gut dysbiosis during liver injury (Zhu et al., 2022). Interestingly, inosine treatment can alter gut microbiota toward an abundance of *Bifidobacterium* and *Lachnospiraceae* UCG-006 and suppress TLR4 signaling, thus negatively regulating hepatic inflammation and damage (Guo et al., 2021).

In the context of colitis, dietary barley leaf supplementation has been shown to produce anti-inflammatory effects in dextran sulfate sodium (DSS)-induced colitis and dysbiosis of the gut microbiome. Mechanistically, dietary barley leaf elicits inosine accumulation in colonic epithelial cells through the alteration of gut bacterial composition, such as an abundance of *Lactobacillus* (Li et al., 2021b). In addition, the exogenous inosine administration showed a similar protective effect on colitis through the activation of A2A receptor and peroxisome proliferator-activated receptor (PPAR)-γ signaling (Li et al., 2021b). Furthermore, indomethacin-induced enteropathy is ameliorated by inosinic acid (1,000 mg/kg, i.p.) in mice. Inosinic acid treatment leads to increased serum levels of uric acid, resulting in protection against intestinal injury via antioxidative effects (Yasutake et al., 2017).

A recent study showed that NAD + precursor nicotinamide riboside (NR) suppresses lipopolysaccharide-induced IFN-β production and autophagy activation in myeloid cells at least partly through inosine-mediated signaling (Wu et al., 2022). Importantly, NR indicated anti-inflammatory effects in monocytes from patients with the autoimmune disorder systemic lupus erythematosus (SLE), showing dysregulated type I IFN production (Wu et al., 2022). Plasma inosine increase via *Limosilactobacillus reuteri* (LR) administration exhibits a protective effect in the scurfy mouse, lacking regulatory T cells, that mimics human IPEX syndrome (immune dysregulation, polyendocrinopathy, and enteropathy, with X-linked inheritance) (He et al., 2017; Liu et al., 2021). LR reverses decreased inosine levels in plasma from scurfy mice and impacts the amelioration of disease pathologies and multiorgan inflammation through A2A receptors (He et al., 2017; Liu et al., 2021). Interestingly, the ability of LR to increase plasma inosine is unique compared to the probiotic LGG (Liu et al., 2021). These data suggest inosine may act as a bioactive molecule responsible for distinct anti-inflammatory properties in immunodeficiency and autoimmune diseases.

**Inosine and other diseases**

**Inosine and cardiovascular diseases**

Inosine is thought to be as “a coronary dilator” through relaxation of the coronary artery and inotropic action, although the mechanisms of action remain unclear (Aviado, 1983). Alternatively, the role of ADA competitive inhibition by inosine cannot be excluded. In addition, accumulating evidence suggests that adenosine has a protective role against endothelial dysfunction and vascular inflammation (Kutryb-Zajac et al., 2020). Dysregulated ADA activity leads to cardiovascular pathologies such as atherosclerosis, thrombosis, and myocardial ischemia-reperfusion injury (Kutryb-Zajac et al., 2020), suggesting that ADA may be a critical target for treatment of cardiovascular disease. Interestingly, co-administration of febuxostat and inosine exhibited a favorable response in two patients with mitochondrial diseases, cardiomyopathy and diabetes (Kamatani et al., 2019).
In a hypercholesterolemic rat model, inosine treatment improved endothelium-mediated vasodilatation and antiplatelet function (Lima et al., 2020). A recent study suggested that urinary inosine is inversely associated with coronary heart disease risk in men (Yoon et al., 2020). Several metabolites including inosine are prominent biomarkers in Kawasaki disease patients with coronary artery lesions (Qian et al., 2021). The existence of brown adipose tissue (BAT) is an independent factor for lowering cardiovascular and metabolic disease (Becher et al., 2021). Extracellular inosine enhances the energy expenditure of BAT in mice. In addition, loss of function mutation of human SLC29A1, which decreases extracellular inosine levels, is strongly correlated with lean body mass and non-obese (Niemann et al., 2022). These data underpin the protective effects of inosine on the cardiovascular system.

**Inosine in psychiatric and neurological pathologies**

Recent studies have shown neuroprotective and neuromodulatory functions of inosine in a variety of neurological and psychiatric diseases (Nascimento et al., 2021). Inosine treatment ameliorated 3-nitropropionic acid (3-NP)-induced neurotoxicity and boosted brain-derived neurotrophic factor (BDNF) levels, p-cAMP response element-binding protein (CREB) expression, and glutathione content (El-Shamarka et al., 2022). In addition, metformin-mediated amelioration of methamphetamine withdrawal syndrome is at least partly mediated through altered bacterial composition and metabolite changes such as abundance of Rikenellaceae and inosine (Yang et al., 2022). Interestingly, inosine supplementation of mice improved methamphetamine withdrawal-mediated anxiety and depression-like symptoms (Yang et al., 2022), indicating that metformin effects may depend on microbiota-derived inosine.

In rat models of Alzheimer’s disease, inosine treatment has been shown to prevent memory deficits, suppress immunoreactivity via brain A2A receptor, and enhance anti-inflammatory cytokine levels and oxidative alterations in the brain (Teixeira et al., 2020; Teixeira et al., 2022a). In addition, inosine administration had beneficial effects in a rat model of diabetic peripheral neuropathy, resulting in a hypoglycemic effect and enhanced myelination (Abdelkader et al., 2022). Inosine-induced neuroprotective function depends on Nrf2 expression, downstream HO-1, and suppression of PKC and TRPV1 (Abdelkader et al., 2022). Inosine treatment also resulted in elevated memory acquisition and consolidation in a rat model of scopolamine-induced cognitive impairment. These effects are partly mediated through modulation of brain redox status, cholinesterase function, and ion pump activity, suggesting promising approaches for neurodegenerative diseases (Teixeira et al., 2022b). In a ketamine-induced rat mania model, inosine administration may prevent hyperlocomotion and attenuation of maniac phase symptoms (Camerini et al., 2020). In an experimental model of sciatric nerve crush injury in mice, inosine treatment resulted in accelerated axonal regeneration and a recovery of motor and sensory functions (Soares Dos Santos Cardoso et al., 2019).

A clinical trial with co-administration of febuxostat and inosine showed improvement of the symptoms of Parkinson’s disease (Watanabe et al., 2020). However, another recent clinical trial showed that inosine treatment does not modify progression of early Parkinson’s disease (Schwarzschild et al., 2021). In a clinical trial for use of IMP in multiple system atrophy (MSA), IMP raised serum levels of uric acids, and was considered to be tolerable and safe during a 24-week treatment (Jung Lee et al., 2021), although a more long-term follow-up study is warranted.

**Concluding remarks**

Recent advances have contributed to our understanding of the role of inosine as a biomarker or a regulator of immunity, infection, inflammation, cancer, and other pathological conditions. In addition, accumulating reports suggest that the levels of inosine or inosine-related enzymes are dysregulated in diseases such as cancers. More studies are needed to identify how inosine levels are regulated in different tissues under various physiological and pathological conditions. The information available on the impact of inosine on immunomodulatory and protective functions has identified this metabolite as a possible therapeutic target for tumors, inflammation, infection, and cardiovascular and neurological disorders. Future studies with preclinical models and clinical research are required to bring the inosine-based therapeutic approach into the clinic.

Several microbes from the intestinal microbiota have been reported to produce inosine, exhibiting therapeutic efficacy in various disease models. Future molecular studies will be important to reveal how the link between the microbiota and inosine regulates immune and inflammatory responses in specific human diseases.

The use of isoprinosine, a synthetic agent of inosine with an immunostimulant, in several clinical trials has suggested that inosine or inosine-based drugs may be therapeutically useful in neurological and autoimmune diseases. However, most data regarding the physiological and therapeutic potential of inosine have been derived from experimental
studies. There are also concerns for the possibility of uric acid stones, which can be produced by inosine metabolism. Therefore, another strategy based on the regulation of inosine-degrading enzymes (i.e., PNP) could be also useful for potential treatment targeting inosine-based therapeutics. Future preclinical and clinical trials are needed to assess the safety and adverse effects associated with long-term use of inosine or inosine-related enzyme modulation.

To date, there is limited information on the molecular mechanisms through which inosine exerts its biological functions as a signaling mediator. Evidence suggests that inosine may function through multiple subtypes of adenosine receptors. However, it remains unclear how inosine targets adenosine receptor subtypes or whether there are alternative inosine receptors in different cell types. Understanding the pathways responsible for the dysregulation of inosine production and finding inosine-specific effectors will facilitate the development of therapeutic strategies against various disorders.

Author contributions

E-KJ and IK contributed to the conception and critically revised the manuscript. Both authors contributed to the article and approved the submitted version.

References

Abdelkader, N. F., Ibrahim, S. M., Moustafa, P. E., and Elbaset, M. A. (2022). Inosine mitigated diabetic peripheral neuropathy via modulating GLO1/AGES/RAGE/NF-κB/Nrf2 and TFG-β/PI3K/TRPV1 signaling pathways. Br. J. Pharmacol. 179(1), 58–69. doi:10.1111/bph.16454

Akedo, H., Nishihara, H., Shinaki, K., Komatsu, K., and Ishikawa, S. (1972). Multiple forms of human adenosine deaminase. I. Purification and characterization of two molecular species. Biochim. Biophys. Acta 276 (1), 257–271. doi:10.1016/0005-2744(72)90028-9

Akeson, A. L., Wiginton, D. A., Dusing, M. R., States, J. C., and Hutton, J. J. (1988). Mutant human adenosine deaminase alleles and their expression by transfection into fibroblasts. J. Biol. Chem. 263 (31), 16291–16296. doi:10.1016/s0021-9258(18)37591-4

Ames, B. N., Cathcart, R., Schwiers, E., and Hochstein, P. (1981). Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis. Proc. Natl. Acad. Sci. U. S. A. 78 (11), 6858–6862. doi:10.1073/pnas.78.11.6858

Ascherio, A., LeWitt, P. A., Xu, K., Eberly, S., Watts, A., Matson, W. R., et al. (2009). Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch. Neurol. 66 (12), 1640–1648. doi:10.1001/archneurol.2009.247

Aviado, D. M. (1983). Inosine : A naturally occurring cardiotoxic agent. J. Pharmacol. 14, 47–71.

Barsotti, C., Pesi, R., Gianneccezini, M., and Ipatu, P. L. (2005). Evidence for the involvement of cytosolic 5'-nucleotidase (cN-II) in the synthesis of guanine nucleotides from xanthosine. J. Biol. Chem. 280 (14), 13465–13469. doi:10.1074/jbc.M413437200

Becher, T., Palanisamy, S., Kramer, D. J., Eljalby, M., Marx, S. J., and Wibmer, A. G., et al. (2021). Brown adipose tissue is associated with cardiometabolic health. Adv. Enzyme Regul. 33, 235–252. doi:10.1016/j.enzymere.2020.09.002

Belt, J. A., Marina, N. M., Phelps, D. A., and Crawford, C. R. (1993). Nucleoside transport in normal and neoplastic cells. Adv. Enzyme Regul. 33, 235–252. doi:10.1016/0065-2719(93)90025-5

Benowitz, L. I., Goldberg, D. E., Madsen, J. R., Soni, D., and Irwin, N. (1999). Inosine stimulates extensive axon collateral growth in the rat corticospinal tract after injury. Proc. Natl. Acad. Sci. U. S. A. 96 (23), 13486–13490. doi:10.1073/pnas.96.23.13486

Beran, J., Salapová, E., and Spáděl, M. (2016). Inosine pranobex is safe and effective for the treatment of subjects with confirmed acute respiratory viral infections: Analysis and subgroup Analysis from a phase 4, randomised, placebo-controlled, double-blind study. BMC Infect. Dis. 16 (1), 648. doi:10.1186/s12879-016-1965-5

Beran, J., Spáděl, M., Katarzová, V., Holoušová, A., Malyš, J., Finger Rousková, J., et al. (2020). Inosine pranobex significantly decreased the case-fatality rate among PCR positive elderly with SARS-CoV-2 at three nursing homes in the Czech Republic. Pathogens 9 (12), E1055. doi:10.3390/pathogens9121055

Beran, J., Spáděl, M., and Sliva, J. (2021). Inosine pranobex deserves attention as a potential immunomodulator to achieve early alteration of the COVID-19 disease course. Viruses 13 (11), 2246. doi:10.3390/v13112246

Brown, E. M., Arellano-Santoyo, H., Temple, E. R., Costiowlou, Z. A., Pichaud, M., Hall, A. B., et al. (2021). Gut microbiome ADP-ribosyltransferases are widespread phage-encoded fitness factors. Cell Host Microbe 29 (9), 1351–1365.e11. doi:10.1016/j.chom.2021.07.011

Camerini, L., Ardais, A. P., Xavier, J., Bastos, C. R., Oliveira, S., Soares, M. S., et al. (2020). Inosine prevents hyperlactocetemia in a ketamine-induced model of mania in rats. Brain Res. 1733, 146721. doi:10.1016/j.brainres.2020.146721

Cass, C. E., Young, J. D., Baldwin, S. A., Cabrita, M. A., Graham, K. A., Griffiths, M., et al. (1999). Nucleoside transporters of mammalian cells. Pharm. Biotechnol. 12, 313–352. doi:10.1016/S0726-344X(99)00096-3

Chen, X., Xiao, D. S., Wang, Q., Lai, L., Carter, K. C., and Nishikura, K. (2000). A third member of the RNA-specific adenosine deaminase gene family, ADAR3, contains both single- and double-stranded RNA binding domains. RNA 6 (5), 755–767. doi:10.1017/S13558382000100170

Chen, T., Xie, G., Wang, X., Fan, J., Qiu, Y., Zheng, X., et al. (2011). Serum and urine metabolite profiling reveals potential biomarkers of human hepatocellular
The release of adenosine and inosine.

adenosine A2A receptors.

Resetting microbiota by Lactobacillus reuteri inhibits T reg de

69 (27), 7619

autoimmunity via adenosine A2A receptors.

The release of adenosine and inosine.

posttranscriptional mechanism and protects against endotoxin-induced shock.

neuroprotective effects of inosine.

杀菌作用のための手段としてのRNA Offices-1の役割。

immunophilic activity and protects against endotoxin-induced shock.

the activation of the A2AR/BDNF/TrKB/ERK/CREB signaling

mRNA stability via adenosine A2A receptors.

3-nitropropionic acid-induced huntington
damage and in

Nomenclature and classi

49 (6), 2293

Biochim. Biophys. Acta

http://www.sciencedirect.com/science/article/pii/S00052744679018-0006-1

ELS-Marshak, M. E., El-Sahar, A. E., Saad, M. A., Assaf, N., and Sayed, R. H. (2022). Inosine attenuates 3-nitropynomial acid-induced huntington’s disease-like symptoms in rats via the activation of the A2AR/BDNF/TrkB/ERK/CREB signaling pathway. Life Sci. 300, 120569. doi:10.1016/j.lfs.2022.120569

Friedmin, M. (1950). Desoxyribose-1-Phosphate. II. The isolation of crystalline desoxyribose-1-phosphate. J. Biol. Chem. 184 (2), 449–459.

Singh, S., and Verma, A. (2015). Inosine as an adenosine receptor agonist for treating neurodegenerative disorders. J. Mol. Cell. Cardiol. 88, 1–8. doi:10.1016/j.yjmcc.2015.04.016

Kruglikova, M. I., Markova, T. V., Lebedeva, I. O., Sozontov, A. V., and Beloluc, A. P. (2016). The role of adenosine receptor pathway in the prevention of organ injury in mice with sepsis. J. Inflamm. 13 (1), 1–7. doi:10.1186/s12950-016-0125-9

García-Gil, M., Camici, M., Allegrini, S., Pesi, R., and Tozzi, M. G. (2021). Metabolic aspects of adenosine functions in the brain. Front. Pharmacol. 12, 672182. doi:10.3389/fphar.2021.672182

George, C. X., Ramaswami, G., Li, L. B., and Samuel, C. E. (2016). Editing of cellular self-RNAs by adenosine deaminase ADAR1 suppresses innate immune stress responses. J. Biol. Chem. 291 (12), 6158–6168. doi:10.1074/jbc.M115.709014

Guinberg, R., Cortés, D., Díaz-Cruz, A., Riveros-Rosas, H., Villalobos-Molina, R., and Pita, E. (2006). Inosine released after hypoxia activates hepatic glucose production in vivo. Am. J. Physiol. Endocrinol. Metab. 290 (3), E940–E951. doi:10.1152/ajpendo.00173.2005

Guo, W., Xiang, Q., Mao, B., Tang, X., Cui, S., Li, X., et al. (2021). Protective effects of microbe-derived inosine on lipopolysaccharide-induced acute liver damage and inflammation in mice via mediating the TRAF4/NF-kB pathway. J. Agric. Food Chem. 69 (27), 7619–7628. doi:10.1021/acs.jafc.0c06781

Haskó, G., Kühler, D. G., Németh, Z. H., Mably, J. G., Stachlewitz, R. F., Virág, L., et al. (2000). Inosine inhibits inflammatory cytokine production by a posttranscriptional mechanism and protects against endotoxin-induced shock. J. Immunol. 164 (2), 1031–1049. doi:10.4049/jimmunol.164.2.1013

Haskó, G., Sitkovsky, M. V., and Szabó, C. (2004). Immunomodulatory and neuroprotective effects of inosine. Trends Pharmacol. Sci. 25 (3), 152–157. doi:10.1016/j.tips.2004.01.006

He, B., Huang, T. K., Wang, T. F., Ferris, M., Taylor, C. M., Tian, X., et al. (2017). Resisting microbiota by Lactobacillus reuteri inhibits T reg deficiency-induced autoimmunity via adenosine A2A receptors. J. Exp. Med. 214 (1), 107–123. doi:10.1084/jem.201616961

He, T., Brocca-Cofano, E., Gillespie, D. G., Xu, C., Stock, J. L., Ma, D., et al. (2015). Critical role of the adenosine pathway in controlling sirmian immunodeficiency virus-related immune activation and inflammation in gut mucosal tissues. J. Virol. 89 (18), 9616–9630. doi:10.1128/jvi.01196-15

Henz, F., Reckel, S., Piltz, R., and Kälten, J. R. (1980). A new spectrophotometric assay for enzymes of purine metabolism. IV. Determination of adenosine deaminase. Enzyme 25 (1), 50–55. doi:10.1016/0013-8299(80)90021-0

Hooper, D. C., Scott, G. S., Zborak, A., Mičkova, T., Kean, R. B., Koprowski, H., et al. (2000). Uric acid, a purinonitrile scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. Faseb J. 14 (2), 691–698. doi:10.1096/fasebj.14.2.691

Hooper, D. C., Spitsin, S., Kean, R. B., Champion, J. M., Dickson, G. M., Chaudhry, I., et al. (1998). Uric acid, a natural scavenger of purinonitrile, in experimental allergic encephalomyelitis and multiple sclerosis. Proc. Natl. Acad. Sci. U. S. A. 95 (2), 675–680. doi:10.1073/pnas.95.2.675
RNA editing underlies genetic risk of common inflammatory diseases. Nature 608 (7923), 569–577. doi:10.1038/s41586-022-05052-x

Li, X., Zhao, L., Wei, M., Li, Y., Sun, Y., Shen, X., et al. (2021). Serum metabolomics analysis for the progression of esophageal squamous cell carcinoma. J. Cancer 12 (11), 3190–3197. doi:10.7150/jca.54429

Liddicoat, B. J., Piskol, R., Chalk, A. M., Ramaaswaran, G., Higuichi, M., Hartner, J. C., et al. (2015). RNA editing by ADAR1 prevents MDA5 sensing of endogenous dsRNA and TABLE 42. 1115–1120. doi:10.1126/science.aac7049

Lima, G. F., Lopes, R. O., Mendes, B. A. R., Bracho, S. C., Autran, L. J., Motta, A. V. N. L., et al. (2020). Inosine, an endogenous purine nucleoside, improves severe asthma in a murine model. Front. Immunol. 11, 1–13. doi:10.3389/fimmu.2020.00941

Liu, Y., Huang, T. K., Taylor, C. M., Park, E. S., Freeborn, J., Luo, M., et al. (2021). Loneliness affects the immunity of mice with trefoil deficiency. Am. J. Physiol. Gastrointest. Liver Physiol. 320 (6), G969–G981. doi:10.1152/ajpgi.00722.2020

Löwén, M., Nemeth, Z. H., Gasteiger, W. C., Beesley, J., Pacher, P., and Haskó, G. (2021). Inosine monophosphate and inosine differentially regulate endotaxinemia and bacterial sepsis. Faseb. J. 35 (11), e21895. doi:10.1096/fj.20200862R

Nakashima, T., and Kawahara, Y. (2020). Adenosine-to-Inosine RNA editing in the immune system: Friend or foe? Cell. Mol. Life Sci. 77 (15), 2931–2948. doi:10.1007/s00018-020-04346-2

Nascimento, F. P., Macedo-Júnior, S. J., Lapa-Costa, F. R., Cezar-Dos-Santos, F., and Santos, A. R. S. (2021). Inosine as a tool to understand and treat central nervous system disorders: A neglected actor? Front. Neurosci. 15, 707387. doi:10.3389/fnins.2021.707387

Neef, S. K., Janssen, N., Winter, S., Wallisch, S. K., Hofmann, U., Dahlke, M. H., et al. (2020). Metabolic drug response phenotyping in colorectal cancer organoids by LC-TOF-MS. Metabolites 10 (12), E494. doi:10.3390/metabo10120494

Nießm, B., Hausf-Bruberg, S., Puetz, L., Feischt, M., Jacektein, M. Y., Hoffmann, A., et al. (2022). Apoptotic Brown adipocytes enhance energy expenditure via extracellular inosine. Nature 609 (7962), 361–368. doi:10.1038/s41586-022-05041-0

Oakes, E., Anderson, A., Cohen-Gadol, A., and Hundleby, H. A. (2017). Adenosine deaminase that acts on RNA 3 (ADAR3) binding to glutamate receptor subunit B pre-mRNA inhibits RNA editing in glioblastoma. J. Biol. Chem. 292 (10), 4326–4335. doi:10.1074/jbc.M117.779868

Paniacibio, C., Adamaberg, K., Jaagura, M., Copetti, F., Fontana, A., Adamaberg, S., et al. (2016). Influence of gemcitabine chemotherapy on the microbiota of pancreatic cancer xenografted mice. Cancer Chemother. Pharmacol. 81 (4), 773–782. doi:10.1007/s00280-018-3549-0

Pavlova, E. L., Simeonova, L. S., and Gogva, G. A. (2018). Combined efficacy of oseltamivir, isoprinosine and elagic acid in influenza A(H1N1)-infected mice. BioMed. Pharmacother. 98, 29–35. doi:10.1016/j.biopha.2017.12.014

Pfüller, C. K., George, C. X., and Samuel, C. E. (2021). Adenosine deaminases acting on RNA (ADARs) and viral infections. Annu. Rev. Virol. 8 (1), 239–264. doi:10.1146/annurev-virology-091919-065320
receptors and neurotrophic and neuroinflammatory parameters in an experimental model of Alzheimer’s disease. Mol. Neurobiol. 59 (2), 841–855. doi:10.1007/s12035-021-02627-x

Tobolska, S., Terpiłow ska, S., Jaroszewski, J., and Siwicki, A. K. (2018). Influence of inosine pranobex on cell viability in normal fibroblasts and liver cancer cells. J. Vet. Res. 62 (2), 215–220. doi:10.2478/jvetres-2018-0031

Toncev, G., Milicic, B., Toncev, S., and Sama r drac, G. (2002). Serum uric acid levels in multiple sclerosis patients correlate with activity of disease and blood-brain barrier dysfunction. Eur. J. Neurol. 9 (3), 221–226. doi:10.1046/j.1468-1331.2002.00384.x

Tozzi, M. G., Camici, M., Mascia, L., Sgarrella, F., and Ipata, P. L. (2006). Pentose phosphates in nucleoside interconversion and catabolism. Febs J. 273 (6), 1089–1101. doi:10.1111/j.1744-4658.2006.05155.x

Traft, T. W. (1994). Physiological concentrations of purines and pyrimidines. Mol. Cell. Biochem. 140 (1), 1–22. doi:10.1007/bf00928361

Tzoneva, G., Perez-Garcia, A., Carpenter, Z., Khiabanian, H., Tosello, V., Allegretta, M., et al. (2013). Activating mutations in the NT5C2 nucleotidase gene drive chemotherapy resistance in relapsed ALL. Mol. Cell. Biochem. doi:10.1007/s11010-013-1656-3

Van der Weyden, M. B., and Kelley, W. N. (1977). Adenosine deaminase: Characterization of the molecular heterogeneity of the enzyme in human tissue. Adv. Exp. Med. Biol. 76a, 235–248. doi:10.1007/978-1-4613-4223-6_29

Van Hedeloom, I. H., Boom, A., Bartstra, H. A., and Staal, G. E. (1976). Characterization of adenosine deaminase isozymes from normal human erythrocytes. Clin. Chim. Acta. 72 (3), 109–115. doi:10.1016/0009-8981(76)90041-3

Wang, T., Gnanaprakasam, J. N. R., Chen, X., Kang, S., Xu, X., Sun, H., et al. (2020). Inosine is an alternative carbon source for CD8(+) T-cell function under glucose restriction. Nat. Metab. 467, 647–657. doi:10.1038/s42255-020-0219-4

Wardman, J. F., Bains, R. K., Rahfeld, P., and Withers, S. G. (2022). Carbohydrate-active enzymes (CAZymes) in the gut microbiome. Nat. Rev. Microbiol. 20 (9), 542–556. doi:10.1038/s41579-022-00712-1

Watanabe, H., Hattori, T., Kume, A., Misu, K., Ito, T., Koike, Y., et al. (2020). Uric acid ameliorates indomethacin-induced enteropathy in mice through its antioxidant activity. J. Gastroenterol. Hepatol. 35 (2), 215–226. doi:10.1111/jgh.13785

Yoon, H. S., Jeong Yang, J., Rivera, E. S., Shu, X. O., Xiang, Y. B., Calcutt, M. W., et al. (2020). Uric acid ameliorates indomethacin-induced enteropathy in mice through its antioxidant activity. J. Gastroenterol. Hepatol. 35 (7), 1839–1845. doi:10.1111/jgh.13785

Yoon, H. S., Jeong Yang, J., Rivera, E. S., Shu, X. O., Xiang, Y. B., Calcutt, M. W., et al. (2020). Urinary metabolites and risk of coronary heart disease: A prospective investigation among urban Chinese adults. Nutr. Metab. Cardiovasc. Dis. 30 (3), 467–473. doi:10.1016/j.numecd.2019.10.011

Zeref-Shani, E., Kessler-Icekson, G., and Sperling, O. (1988). Pathways of adenine nucleotide catabolism in primary rat cardiomyocyte cultures. J. Mol. Cell. Cardiol. 20 (1), 23–33. doi:10.1016/0022-2828(88)90176-7