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COMMENTARY

Commentary: Gut microbiota reduce the risk of hyperuricemia and gout in the human body

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Gout, a prevalent and painful metabolic disease often associated with obesity and aging, is caused by the deposition of urate crystals in joints, bones, or soft tissues[1]. Urate is an intermediate metabolite within the purine degradation pathway, predominantly derived from uric acid under physiological pH levels. Hyperuricemia occurs due to excessive uric acid production or insufficient excretion[2], which is associated with various chronic diseases, including type 2 diabetes, chronic kidney disease, cardiovascular disorders, and metabolic syndrome[3,4]. Therapeutic interventions for gout through medications include inhibition of uric acid production using xanthine oxidase inhibitors (such as febuxostat), and stimulation of uric acid excretion (such as benzbromarone)[4]. Nevertheless, the clinical application of these uric acid-lowering drugs is often limited by their side effects. There is a growing demand for the development of safe and effective pharmacological therapies for gout. The human body eliminates uric acid through two primary routes: two-thirds of uric acid is excreted by the kidneys[1], while the remaining one-third is excreted into the intestine for clearance[1,5], where gut microbiota converts uric acid into nucleotides supporting bacterial DNA synthesis[6]. In the context of cancer, uric acid-derived nucleotides in the intestine have been reported to promote colon cancer growth to increase drug resistance or irradiation resistance of the tumor[7]. Thus, the gut microbiome may be a novel therapeutic target in the management of hyperuricemia or gout.

The gut microbiome encompasses an array of microorganisms residing within the gastrointestinal tract, including bacteria, archaea, fungi, and viruses. Current research emphasizes the important role of intestinal flora in the regulation of immune function and host metabolism[4]. Of particular importance is the capacity of intestinal flora to generate various small molecules, such as short-chain fatty acids (SCFAs), bacteria-derived bile acids[8], amino acids[9], dipeptidyl peptidase 4 (DPP4)[10], and lipopolysaccharide. Existing evidence has demonstrated differences in the composition of gut microbiota between gout patients and healthy controls[11]. The impact of gut microbiota on gout or hyperuricemia may involve three mechanisms: (a) Participation in purine metabolism: For example, *Lactobacillus gasseri PA*-3 has potential in the prevention of hyperuricemia by metabolizing

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inosine and hypoxanthine, thus reducing the intestinal absorption of purines[12]. Additionally, *L. brevis DM9*218 has been found to lower hyperuricemia in rats by inhibiting the activity of xanthine oxidase (XOD)[13], an important enzyme responsible for uric acid synthesis. (b) Facilitation of uric acid excretion: Certain bacteria such as *Akkermansia muciniphila* can affect uric acid excretion by regulating the expression of uric acid transporters in the intestine (ABCG2) and kidneys (ABCG2, URAT1, and GLUT9)[14]. On the other hand, bacterial metabolites, like butyrate, can repair the intestinal epithelium and stabilize the intestinal immune mucosal barrier, stimulating intestinal epithelial cells to express more uric acid transporters (ABCG2)[15], thus enhancing uric acid excretion. Furthermore, acetate from bacteria can provide energy to intestinal epithelial cells in the promotion of uric acid transportation[4]. (c) Contribution to the immune-inflammatory responses in gout: Butyrate derived from bacteria has been reported to inhibit acute gouty arthritis by suppressing histone deacetylase and reducing monosodium urate (MSU)-induced production of IL-1β, IL-6, and IL-8[16]. In the mouse models of gout, acetate has been reported to promote the resolution of MSU-induced inflammatory responses by inhibiting inflammasome activation and inducing caspase-dependent apoptosis of neutrophils *via* GPR43[17]. While these studies suggest an association between uric acid metabolism and gut microbiota, the commensal gut bacterial strains responsible for uric acid clearance remain unidentified. A recent study published in the journal *Cell* has made significant progress in this topic by identifying a broad cluster of genes in gut bacteria that encode essential enzymes for uric acid degradation[18].

To elucidate the specific bacterial strains engaged in uric acid metabolism, Liu et al.[18] conducted a screening within a repository of the human intestinal bacterial library in the new study. Employing a technology of stable isotope tracing, the authors identified 46 species of uric acid-degrading bacteria spanning four phyla, namely Actinobacteria, Firmicutes, Fusobacteria, and Proteobacteria. These uric acid-consuming bacteria possess the capability to metabolize uric acid into either xanthine or SCFAs, such as acetate and butyrate. To further analyze the genes responsible for metabolizing uric acid into SCFAs, they performed transcriptomics and found a highly prevalent but conserved bacterial gene cluster (comprising *ygeX*, *ygeY*, *ygeW*, *ygfK*, and *ssnA*), which encodes enzymes in the uric acid degradation pathway. Furthermore, they tested the role of uric acid-degrading bacteria in the control of hyperuricemia, using two genetically engineered mouse models of uricase deficiency, which develop hyperuricemia and form uric acid crystals within the kidneys, culminating in premature mortality. Depletion of the gut microbiota can exacerbate hyperuricemia, while colonization with uric acid-degrading bacteria can reduce uric acid levels. Finally, retrospective cohort analyses unveiled that the administration of broad-spectrum antibiotics, exemplified by clindamycin, could disrupt anaerobic intestinal bacteria, thereby increasing the risk of gout in humans[18].

In a recent independent study in *Cell Host & Microbe*, Kasahara et al.[19] reported findings in agreement with those of Liu et al.[18]. The study was conducted in the context of atherosclerosis, a pathological condition characterized by the deposition of atherosclerotic plaques along blood vessel walls, leading to arterial constriction[19]. It is known that uric acid may promote atherosclerosis through the inflammatory response mediated by the AMPK pathway[20]. The authors investigated the mechanism by which gut microbiome affects the progression of atherosclerosis, with a focus on uric acid metabolism[19]. They identified similar profiles of intestinal bacteria involved in the degradation of uric acid and arrived at conclusions similar to those by Liu et al.[18].

The findings of two studies convey a pivotal message: the anaerobic intestinal microbiota assumes a vital role in the body's compensation for the uricase loss, thereby maintaining uric acid in the normal range. This observation provides insight into the basis of the rising incidence of hyperuricemia and gout in association with industrialization, including shifts in dietary patterns and the excessive use of antibiotics, for inducing disorders of gut microbiota. Consequently, in clinical practice, caution is advised when administering anaerobic antibiotics to patients with hyperuricemia or gout, as they may disrupt the functions of the intestinal microbiota[18]. Furthermore, biotherapeutic agents composed of uric acid-degrading bacteria hold promise for the treatment of hyperuricemia and gout in the future. Evidence from animal studies and clinical data has increasingly demonstrated the effectiveness of probiotic bacterial strains, including *L. plantarum GKM3*[21], *L. brevis DM9218*[13], *L. gasseri PA-3*[12] and *Ligilactobacillus salivarius CECT 30632*[22], in reducing serum uric acid levels and renal damage. Additionally, prebiotics such as anserine[23] and chicory[24] have been found to ameliorate hyperuricemia through modulating gut microbiota. Compared with existing gout medicines, microbial interventions are potentially more convenient for administration as food or dietary supplements. Therefore, targeting the intestinal excretion route may mitigate adverse effects of uric acid, such as renal damage and urinary tract stone formation.

In light of the differences between humans and experimental animals in uric acid metabolism, more research is required to characterize the uric acid-consuming bacteria in uricase-deficient individuals. Additionally, clinical trials are needed to test the gut microbiota in patients with hyperuricemia and gout.

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Author contributions

Lin Wang made the draft and revision of this manuscript. Jianping Ye provided the idea and revised the manuscript in both original and revised submission.

Conflicts of interest

The authors declare no conflict of interest.

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