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REVIEW

Exploring the Impact of the Gut Microbiota/REV-ERBα/NF-κB Axis on the Circadian Rhythmicity of Gout Flares from a Chronobiological Perspective

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Introduction: Gout is an inflammatory arthritis caused by the deposition of monosodium urate crystals in joints, severely affecting patients' health. However, the management of gout remains suboptimal. Current clinical treatments primarily focus on anti-inflammatory and urate-lowering medications, which are associated with potential toxicities and other limitations. Chronotherapy, based on chronobiology, has gradually demonstrated unique advantages in the treatment of various inflammatory diseases and holds promise as a safer and more effective new strategy for treating gout.

Objective: This article aims to explore the biological mechanisms underlying the circadian rhythmicity of gout flares and the potential role of chronobiology-based therapeutic approaches in the treatment of gout.

Methods: The referenced research articles were sourced from major scientific databases, including Google Scholar, PubMed, and Web of Science. The search strategy employed keywords such as "Gout", "Circadian rhythm", and "Chronobiology".

Results: As the core inflammatory signaling pathway in gout, the NF-κB signaling pathway exhibits strong circadian rhythmicity under the regulation of circadian clock genes such as REV-ERBα. The gut microbiota may induce circadian oscillations in serum uric acid(UA) levels and trigger the rhythmic occurrence of gout flares by influencing the expression of REV-ERBα, rhythmically activating the NF-κB inflammatory signaling pathway, and altering the abundance. Therefore, the gut microbiota/REV-ERBα/NF-κB axis may be the potential biological mechanism underlying the circadian rhythmicity of gout flares.

Conclusion: From the perspective of chronobiology, a chronobiology-based therapeutic approach targeting the gut microbiota/REV-ERBα/NF-κB axis—such as adjusting medication timing, dietary interventions to modulate the gut microbiota, and targeted pharmacological agents—holds promise as a novel clinical strategy for treating gout and has potential clinical value. However, the conclusions drawn in this paper lack scientific experimental and clinical validation. Therefore, exploring this therapeutic approach represent a key and promising direction for treating gout.

Keywords: gout flare, circadian rhythm, chronobiology, gut microbiota, REV-ERBα, NF-κB

Gout

Gout is a metabolic disorder characterized by recurrent inflammatory flares, primarily stemming from disturbances in purine metabolism that lead to the accumulation of monosodium urate (MSU) crystals in and around joints.[1] This condition results in a spectrum of clinical manifestations, including acute and chronic arthritis, the formation of soft tissue tophi (gout stones), kidney stones, and urate nephropathy.[2,3] While the specific pathogenesis of gout is not yet fully elucidated, elevated serum urate concentration, known as hyperuricemia, is recognized as a significant risk factor for the development of the disease.[4] MSU crystals are widely acknowledged as potent endogenous danger signals that activate the innate immune system, thereby triggering an inflammatory response in gout.[5] The affected joints of gout patients are marked by the presence of a variety of pro-inflammatory cytokines and chemokines, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and IL-18. Among these, IL-1β is considered a pivotal mediator in the inflammatory cascade induced by MSU crystals.[6] The global prevalence of gout has significantly increased over the past few decades,

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closely associated with obesity, metabolic syndrome, an aging population, and changes in dietary patterns (such as increased consumption of high-fructose beverages and red meat). From 1990 to 2019, the number of gout patients worldwide increased from 22 million (95% UI 17.52–27.37) to 53 million (95% UI 43.38–66.34), with an incidence growth rate of 63.44% (95% UI 57.33–68.78%).[7] In addition to its impact on health, gout also imposes significant economic burdens, including increased healthcare costs.[8] Moreover, gout is significantly associated with multiple comorbidities, such as kidney disease[9] and cardiovascular disease,[10] which place a heavy burden on the population. Frequent flares of gout can also lead to decreased quality of life and even productivity loss. In 2020, the global age-standardized incidence rate of years lived with disability due to gout was 20.5 (14.4–28.2) per 100,000 individuals.[11] Despite advances in medical treatment, the global burden of gout continues to increase. Therefore, it is urgent to develop targeted interventions to address this growing health concern.

Circadian Rhythm

In mammals, the circadian clock functions as a complex network of transcription factors that drive the rhythmic expression of clock genes through a precisely regulated transcription-translation feedback loop operating over a 24-hour cycle. Specifically, the transcriptional activators CLOCK and BMAL1 regulate the expression of repressor proteins, including the period (PER1, PER2, PER3) and cryptochrome (CRY1 and CRY2) families, thereby modulating CLOCK/BMAL1-dependent gene transcription.[12] Retinoid-related orphan receptors (RORs) and REV-ERBs are both regulated by CLOCK/BMAL1 but can also exert feedback control over CLOCK/BMAL1 expression.[13] Specifically, REV-ERBα and RORα alternately regulate the expression of genes containing RORE elements, including BMAL1 and NFIL3.[14] The biological clock is present in nearly all tissues and is synchronized with the ambient photoperiod through neuronal and hormonal signals from the brain's central clock.[15]

Furthermore, Pan et al[16] have explored the regulation of circadian clocks in phospholipid metabolism and metabolic disorders. Similar to many other physiological processes, the immune response is also governed by circadian clock networks. Both innate and adaptive immunity components within the immune system exhibit discernible circadian oscillations.[17] Key immune cells, such as macrophages and natural killer cells, display circadian rhythms driven by cellular autonomy mediated by the circadian clock.[18] In summary, the transcriptional oscillation of circadian clock genes generates a crucial circadian rhythm that plays an integral role in regulating human metabolism and immune response, thereby being essential for maintaining environmental homeostasis in the human body.

The Circadian Rhythm of Gout Attacks

Recent studies[19] have established a clear link between circadian rhythms and the onset of gout, demonstrating a 3-fold higher likelihood of acute gout flares occurring nocturnally or matutinally (during transitions from rest to activity) compared to diurnal episodes.[20] Furthermore, Oh et al[21] showed that individuals engaged in shift work experience disruptions in their endogenous circadian oscillations, resulting in elevated serum urate levels and increased susceptibility to gout flares. Choi et al[20] proposed that localized dehydration around the joints, caused by the supine position during sleep, may elevate the risk of gout attacks during nighttime and early morning. Another intriguing hypothesis suggests that sleep apnea may trigger gout flares by enhancing nucleotide turnover due to hypoxia, leading to increased production of purines that are metabolized into UA. Additionally, evidence indicates a positive correlation between symptoms of obstructive sleep apnea and the incidence of gout.[22] The circadian rhythmicity of gout attacks also suggests the potential value of chronotherapy for the treatment of gout. Additionally, it has been reported that methotrexate chronotherapy is associated with significant improvements in RA activity scores.[23] Similar effects have also been observed in polymyalgia rheumatica and gout,[24] although the existing literature remains limited. Interestingly, in a multicenter, randomized, double-blind trial involving 288 patients with active rheumatoid arthritis over a 12-week period,[25] it was found that the use of extended-release prednisone at night was more effective in alleviating morning stiffness than the use of conventional immediate-release prednisone in the morning. Our study results may have similar implications for the optimal timing of various anti-gout therapeutic measures. These findings suggest several potential biological mechanisms that may underlie the circadian pattern of gout attacks.

The Significance of NLRP3 Inflammatories as the Core of the Body's Inflammatory Response in Inducing the Onset of Gout

The NLRP3 inflammasome is widely recognized as a pivotal factor in the pathogenesis of gout[26] and is expressed in a diverse array of immune cells, including T lymphocytes, B lymphocytes, granulocytes, macrophages, and antigen-presenting cells. The NLRP3 inflammasome is a multiprotein complex composed of the sensor protein NLRP3, the apoptosis-associated speck-like protein (ASC), and the effector protein caspase-1.[27] The activation of the NLRP3 inflammasome is widely recognized to require two distinct signal transduction processes: priming and activation.[26] During the priming phase, nuclear factor kappa-B (NF-κB) is activated through engagement of pattern recognition receptors, such as Toll-like receptors (TLRs), by pathogen-associated molecular patterns (PAMPs) like lipopolysaccharides. This interaction leads to the transcriptional activation of the NLRP3 inflammasome gene via the TLR4/NF-κB signaling pathway. During the activation phase, the assembly and activation of the NLRP3 inflammasome are completed through processes such as K^+ efflux,[28] Ca^{2+} mobilization,[29] release of reactive oxygen species (ROS),[30] and lysosomal rupture.[31] These processes lead to the secretion of various inflammatory factors, such as IL-1β and IL-6.

Gout is an autoinflammatory disease characterized by the NLRP3 inflammasome-mediated production of pro-inflammatory cytokines in response to the deposition of MSU crystals in the joints and surrounding tissues. MSU crystals function as DAMPs, activating TLR4 and the NLRP3 inflammasome in a manner similar to PAMPs.[26] This activation results in the release of cytokines such as IL-1β, IL-18, and IL-6. IL-1β, in particular, binds to its receptor on endothelial cells and macrophages within the joint, initiating downstream signaling and gene activation, thereby perpetuating NF-κB activation and exacerbating the inflammatory response. Moreover, dysregulation of the NLRP3 signaling cascade has been implicated in a variety of inflammatory, autoimmune, and metabolic conditions, including gout, inflammatory bowel disease, Sjögren's syndrome, diabetes, and atherosclerosis.[32–35]

NF-κB

NF-κB Underlies the Interregulation of the Circadian Clock and Inflammation

NF-κB, as a transcriptional activator of NLRP3, is implicated in the development of numerous inflammatory diseases and mediates immune responses, such as in rheumatoid arthritis and inflammatory bowel disease. In recent years, studies have shown that various pro-inflammatory factors can affect the function of the biological clock. For instance, inflammation induced by TNF-α and endotoxin[36] or lipopolysaccharide(LPS)[37] leads to abnormal expression of circadian clock genes. Conversely, inflammatory responses mediated by circadian clock genes can exhibit diurnal oscillations, as observed in hepatitis B,[38] periodontitis,[39] and gouty arthritis.[40] Notably, Shen et al found that NF-κB perturbations alter circadian oscillations in cells, tissues, and mice, suggesting that NF-κB plays an essential role in directly regulating the circadian clock and highlighting the interregulation between circadian rhythms and inflammatory pathways.[41] Further studies revealed that the inflammatory signaling transcription factor NF-κB antagonizes the transcription of CLOCK/BMAL1 target genes by directly binding to the promoters of the core clock repressors PER and CRY, resulting in highly specific transcriptional inhibition of core clock genes.[42] This NF-κB-mediated transcriptional inhibition of clock feedback loops is emphasized as the cause of circadian rhythm disturbances in response to inflammation. Importantly, the NLRP3 inflammasome pathway exhibits a circadian rhythm due to the oscillatory nature of NLRP3 transcription and expression. In summary, the basal level of NF-κB expression is critical for the regulation of circadian homeostasis and inflammation.

REV-ERBα Regulates the Circadian Rhythm Expression of NLRP3 Inflammasome by Inhibiting NF-κB Signaling and NLRP3 Gene Transcription

REV-ERBα, encoded by the gene NR1D1 (nuclear receptor subfamily 1, group D, member 1), is a core component of the circadian clock and functions as a transcription factor that negatively regulates NLRP3 in macrophages. This regulatory activity suppresses the expression of genes involved in diverse physiological processes, including circadian rhythm, inflammation, and metabolism, thereby emerging as a central regulator linking metabolic homeostasis, immune response, and circadian rhythmicity. Zhao et al demonstrated that activation of REV-ERBα mitigates the LPS-induced

inflammatory response in human endometrial stromal cells by inhibiting TLR4-regulated NF-κB.[43] Similarly, Wang et al showed through in vivo and in vitro experiments in mice that REV-ERBα attenuates colitis by inhibiting NF-κB and Nlrp3 transcription via inactivation of the NLRP3 inflammasome.[44]

Furthermore, additional studies have explored the molecular mechanisms underlying the inhibition of the NF-κB signaling pathway by REV-ERBα. Specifically, it has been shown that REV-ERBα reduces LPS-induced neuroinflammation in mouse microglia by inhibiting the phosphorylation and degradation of the NF-κB inhibitor IκBα and by blocking the nuclear translocation of the NF-κB subunit p65.[45] Subsequent investigations by Pourcet et al revealed that the mRNA expression of NLRP3 inflammasome components oscillates daily in peritoneal mouse macrophages under the control of REV-ERBα, with peak expression occurring during the active phase, which corresponds to the lowest expression level of REV-ERBα mRNA.[46]

Platr4 Regulates the Circadian Rhythm of the NLRP3 Inflammasome by Inhibiting the NF-κB Signaling Pathway

In recent years, Lin et al[47] experimentally identified a novel molecular mechanism underlying the regulation of inflammation through the biological clock, mediated by the long non-coding RNA (lncRNA) Platr4. Platr4 is an oscillating lncRNA regulated by the circadian clock component REV-ERBα. In their study, Platr4-deficient mice exhibited significantly reduced Nlrp3 inflammasome activity and disrupted circadian rhythms in the liver, rendering them more susceptible to experimental steatohepatitis. As a repressor of NF-κB, Platr4 inhibits the activation of the NLRP3 inflammasome in macrophages by suppressing NF-κB-dependent transcription of inflammasome components, including NLRP3 and ASC. Thus, Platr4 is crucial for driving the diurnal oscillations of Nlrp3 inflammasome expression and activity. Based on these findings, Platr4 appears to function as an integrator of the circadian clock and inflammation through the NF-κB/NLRP3 inflammasome axis. However, there is currently no evidence indicating a direct impact of Platr4 on the circadian rhythm of gout attacks, and further investigation into this potential mechanism is warranted.

The Potential Role of Gut Microbiota Imbalance in the Circadian Rhythm of Gout Attacks

Gut Microbiota

The gut microbiota is a complex and diverse community of viruses, fungi, and bacteria that inhabit the gastrointestinal tract, playing essential roles in food digestion and maintaining host homeostasis. Often referred to as gut bacteria, the gut microbiota primarily consists of up to 1000 bacterial species.[48] The gut microbiota is predominantly composed of four phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, with the former two being the most abundant. Moreover, the byproducts (such as LPS) and metabolites (such as short-chain fatty acids [SCFAs], tryptophan [Trp], and bile acid metabolites) of the gut microbiota play crucial roles in modulating immune cell function and inflammatory responses. Recent studies have provided compelling evidence highlighting the key roles of the gut microbiota in human metabolism, immune regulation, and defense against pathogenic microorganisms. Consequently, disturbances in the gut microbiota have been implicated in a range of metabolic and immune disorders, including obesity,[49] type 2 diabetes,[50] inflammatory bowel disease,[51] gout,[52] and others.

Gut Microbiota and Gout are Closely Related in Metabolic Relationship

Gout is directly linked to elevated levels of UA, which can result from disrupted purine metabolism, reduced UA excretion, or increased UA production. UA is the end product of purine metabolism. Purine nucleotides are hydrolyzed to form adenine and guanine, which are then deaminated to produce xanthine. Xanthine is subsequently oxidized by xanthine oxidase (XOD) to generate UA. In healthy individuals, UA is excreted through two primary pathways: approximately 25% via the gastrointestinal tract and 75% via the kidneys. This gastrointestinal excretion pathway may lead to alterations in the composition of the gut microbiota due to exposure to UA. Previous studies have identified that patients with gout indeed experience an imbalance in the gut microbiota,[53] and Lin et al[54] developed a classification model based on bacterial genera that are significantly enriched in healthy individuals compared to those with gout. The

results showed that, through receiver operating characteristic (ROC) analysis, the average area under the curve (AUC) was as high as 0.973. Given the significant correlation between the gut microbiota and the development of gout, a gout-specific gut microbiota profile may serve as a diagnostic marker. Therefore, the imbalance in the gut microbiota characteristic of gout could potentially become a non-invasive diagnostic tool for gout. This suggests that it offers a promising avenue for future clinical interventions.

The gut microbiota can modulate UA levels and inflammatory signaling pathways through its bacteria, derivatives, metabolites, and other metabolic activities, thereby impacting the onset of gout. Specifically, the gut microbiota may regulate UA levels by influencing purine metabolism. For instance, certain strains of gut bacteria, such as Lactobacillus casei PA-3, have been shown to absorb and utilize purines, thereby reducing the intestinal absorption of dietary purines and lowering serum UA levels.[55] Secondly, LPS, a byproduct of the gut microbiota, is a key component of the cell wall of Gram-negative bacteria. Dysbiosis of the gut microbiota can increase intestinal permeability, facilitating the translocation of LPS into the human circulatory system. This process can induce metabolic endotoxemia and trigger inflammatory pathways. Ramos et al[56] observed that chronic inflammation resulting from elevated serum LPS levels is frequently associated with increased XOD activity. A recent study reported that Phascolarctobacterium and Bacteroides are enriched in patients with gout, and identified a "core microbiota" of three Bacteroides species in the gout group.[57] Lactobacillus gasseri has been shown to reduce purine levels in the gut, with its fermentation products exhibiting urate-lowering effects.[58] Additionally, Lactobacillus reuteri TSR332 and Lactobacillus fermentum TSF331 can control the level of UA by degrading purine.[59]

In addition to modulating UA levels, the gut microbiota can also regulate the activation of the NLRP3 inflammasome, thereby impacting the onset of gout. For example, Bacteroides fragilis exerts a negative regulatory effect on the NLRP3-mediated inflammatory signaling pathway, inhibiting macrophage activation and the secretion of pro-inflammatory mediators such as IL-18 and IL-1β, thereby reducing intestinal inflammation.[60] Lactic acid bacteria mitigate the generation of ROS by restoring aberrant mitochondrial membrane potential, thereby suppressing NLRP3 activation.[61] Conversely, SCFAs produced through gut microbiota metabolism exert a dual impact on the initiation and progression of inflammation. Vieira et al[62] found that SCFAs are essential for inflammasome assembly and IL-1β production. Among these, acetate plays a pivotal role in inflammasome assembly in response to MSU crystals. The production of ROS induced by acetate in immune cells may represent a potential mechanism for regulating the NLRP3 inflammasome, suggesting that acetate contributes to the pathogenesis of gout. However, certain SCFAs may exert protective effects against inflammation. For example, butyrate[63] is associated with increased expression of IκBα, which inhibits the phosphorylation and nuclear translocation of NF-κB p65, as well as the expression of downstream inflammatory cytokines such as MCP-1 and IL-1β. Interestingly, there is also a close relationship between tryptophan metabolism and gout. Mahbub et al[64] observed significant alterations in the plasma amino acid profile of gout patients by analyzing free amino acids in their plasma. Specifically, elevated levels of alanine, isoleucine, leucine, phenylalanine, tryptophan, and valine were found to be significantly positively correlated with gout ($P < 0.005–0.05$), while glycine and serine showed significant negative correlations with gout.

Effects of Gut Microbiota on the Circadian Rhythm of Gout Attacks

Nuclear factor interleukin 3 (NFIL3) is an immunomodulatory transcription factor predominantly expressed in natural killer cells, B lymphocytes, T lymphocytes, monocytes, and other immune cells. It plays a pivotal role in the pathogenesis of autoimmune diseases.[65] Wang et al[66] demonstrated that the gut microbiota modulates host body composition by influencing the circadian transcription factor NFIL3. Nfil3 transcription exhibits diurnal oscillations in intestinal epithelial cells, and the amplitude of these circadian fluctuations is regulated by the microbiota through Group 3 innate lymphoid cells, STAT3, and the epithelial circadian clock. Consequently, NFIL3 is considered a crucial molecular bridge connecting the microbiome, the circadian clock, and host metabolism. The expression of NFIL3 is directly regulated by the core clock transcriptional repressor REV-ERBα. In T cells[67] and hepatocytes,[68] REV-ERBα binds to conserved sequences in the NFIL3 gene loci, suppressing transcription and resulting in rhythmic diurnal patterns of NFIL3 expression. This implies that REV-ERBα governs the circadian rhythm of NFIL3 expression, and that the microbiome may induce NFIL3 expression by inhibiting REV-ERBα. Moreover, empirical evidence has shown that NFIL3 can

potentiate NF-κB signaling by inhibiting IκBα.[69] As a transcriptional activator of NLRP3, NF-κB triggers aberrant activation of the NLRP3 inflammasome, initiating an inflammatory cascade that may contribute to the pathogenesis of gout. Therefore, when the gut microbiota is dysfunctional, the circadian clock gene REV-ERBα suppresses the diurnal oscillation of NFIL3 expression. This leads to aberrant activation of the NF-κB signaling pathway and upregulation of transcription for various inflammatory factors, such as IL-1β, IL-6, and TNF-α, thereby exacerbating the inflammatory response in gout patients. This mechanism may underlie the circadian pattern of gout attacks.

Based on current research, it is hypothesized that the gut microbiota may influence the rhythmic expression of XOD by modulating bile acid metabolism, thereby causing circadian variations in UA levels and potentially triggering gout flares. The gut microbiota is involved in bile acid biotransformation through processes such as deconjugation, dehydroxylation, and reconjugation of bile acids.[70] Additionally, bile acid synthesis exhibits a robust circadian rhythm,[71] which is crucial for maintaining metabolic homeostasis. Conversely, XOD, a rate-limiting enzyme in the terminal phase of purine nucleotide degradation, plays a key role in UA metabolism. The diurnal regulation of XOD activity can contribute to rhythmic fluctuations in serum UA levels. Kanemitsu et al[72] demonstrated that periodic modulation of bile acids can regulate the circadian fluctuations of UA by modulating XOD via the orphan nuclear receptor PPAR-α. This mechanism may represent an endogenous pathway by which the gut microbiota influences circadian gout attacks through metabolic regulation.

Exploring Chronobiological Therapeutic Approaches Based on the Gut Microbiota/REV-ERBα/NF-κB Axis

The gut microbiota and the circadian clock coordinate to establish homeostasis, which generates diurnal rhythms in gut innate immunity.[73] Based on the aforementioned theories, restoring the homeostasis of the gut microbiota and circadian rhythms to lower UA levels may emerge as a potential therapeutic strategy for gout, such as probiotics combined with prebiotic diets and fecal microbiota transplantation. Dietary fibers, prebiotics, and probiotics that can be metabolized by gastrointestinal microbiota are generally considered dietary strategies for modulating the microbiota.[74] Zhao et al[75] investigated the role of the gut microbiota in gout management following probiotic supplementation and found that Lactobacillus fermentum GR-3 significantly reduced UA levels and inflammation in individuals at high risk for gout. Feng et al[76] discovered that prebiotic diets, such as β-carotene and green tea powder, lowered serum UA and pro-inflammatory cytokine levels, improved the gut microbiota profile, and reduced the metabolism of purines and pyrimidines, thereby alleviating joint swelling and pain in gout mice and mitigating acute gout flares. Numerous studies have demonstrated that the gut microbiota of gout patients significantly differs in abundance from that of healthy individuals.[52,53] Washed Microbiota Transplantation (WMT) leverages this principle by transplanting the fecal microbiota from healthy individuals, after purification and separation, into the gastrointestinal tract of patients.[77] Its mechanism of action is strongly associated with the restoration of gut microbiota homeostasis,[78] and it has been effectively applied in the treatment of many diseases.[79] Xie et al[80] found that WMT can effectively reduce serum UA levels and improve gout symptoms in patients with gout, and also helps to restore impaired intestinal barrier function. Since the homeostasis of the gut microbiota is intrinsically linked to the balance of circadian rhythms, restoring the homeostasis of the gut microbiota and circadian rhythms may represent an emerging therapeutic strategy for gout, deserving further in-depth investigation.

Considering that the diurnal variation in the severity of inflammatory diseases may be related to the circadian regulator REV-ERBα, an increasing body of evidence supports the targeting and activation of REV-ERBα as a promising approach for managing inflammation.[44,46,81] Once activated, REV-ERBα may exert anti-inflammatory effects by inhibiting the NF-κB signaling pathway,[45] downregulating Nlrp3 inflammasome activity,[44] and directly modulating immune-related genes (eg, IL-1β, TLR4, IL-6).[82,83] Although the pharmacological effects of a series of REV-ERBα agonists (such as heme, GSK4112, SR9009, etc). have been demonstrated in animal studies (preclinical research), progress in translating these findings into clinical trials has been limited.[84] Therefore, REV-ERBα agonists hold potential as a new targeted therapeutic strategy for gout in future clinical applications.

Regarding the mechanism underlying the peak incidence of gout flares at night, some researchers have speculated[85] that the lower body temperature from night to early morning may increase the risk of urate crystal formation, thereby triggering gout attacks. This study suggests that elevated UA levels are associated with nocturnal acute gout attacks, and the diurnal variation in UA levels may directly influence the circadian differences in acute gout flares. Therefore, based on the circadian rhythmicity of gout flares, administering sustained-release urate-lowering and anti-inflammatory medications at night or before bedtime may offer a novel chronotherapy approach for the clinical treatment of gout. However, robust clinical research evidence is currently lacking.

Conclusion

Based on our observations and summary of the literature, we propose that REV-ERBα serves as a key link between the gut microbiota and the NF-κB pathway. The NF-κB signaling pathway, as the core inflammatory pathway in gout, exhibits strong circadian rhythmicity under the regulation of circadian clock genes such as REV-ERBα. The gut microbiota can also rhythmically activate the NF-κB inflammatory signaling pathway by influencing the expression of REV-ERBα and can alter its own population abundance, diversity, metabolic pathways, and metabolites,[63] thereby inducing circadian oscillations in UA levels and triggering the rhythmic occurrence of gout flares. In summary, the Gut microbiota/REV-ERBα/NF-κB axis (Figure 1) may represent a potential biological mechanism underlying the circadian

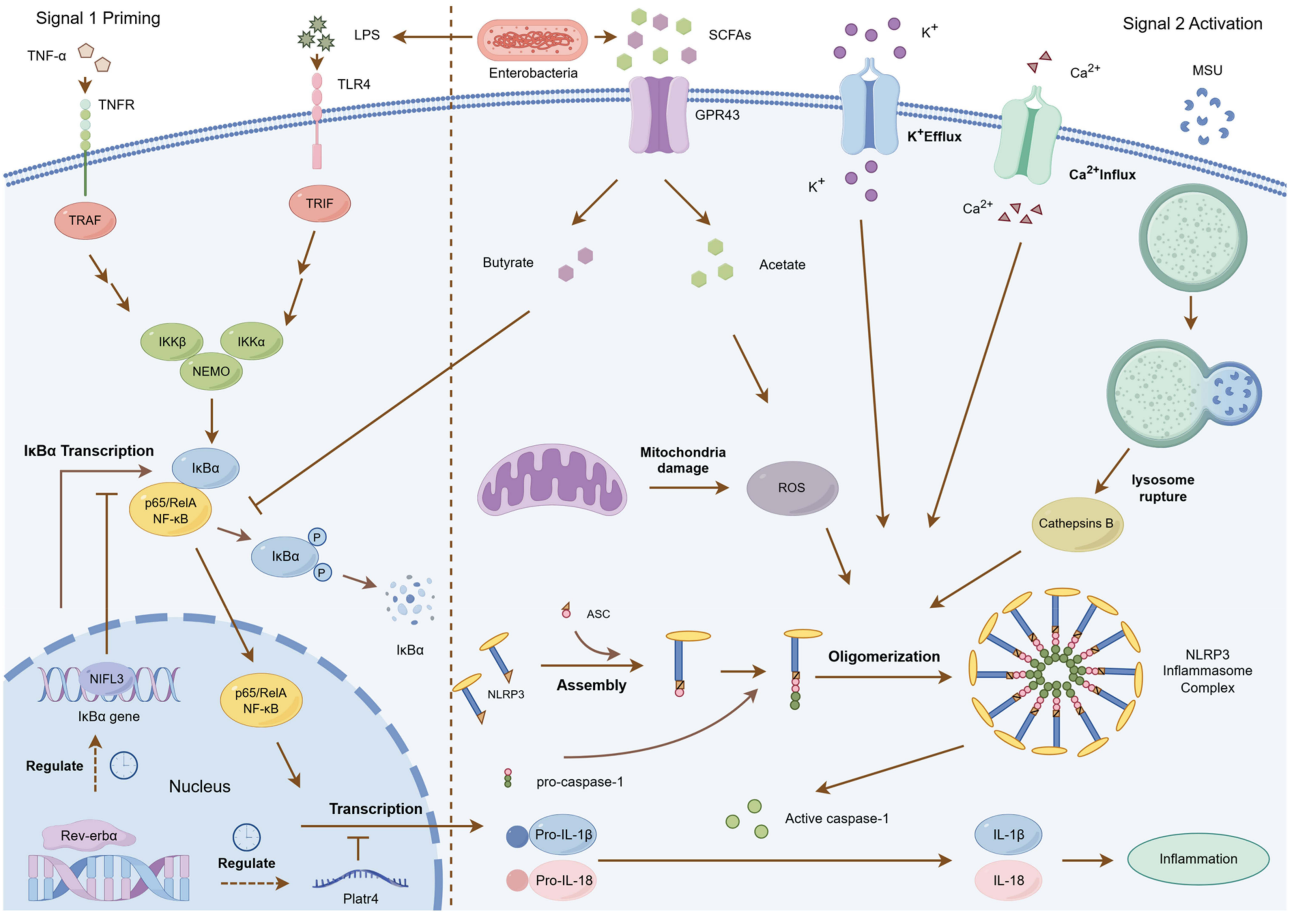

Figure 1 Gut microbiota/REV-ERBα/NF-κB axis. Derivatives (such as LPS) and metabolites (such as SCFAs) of the gut microbiota influence the NF-κB signaling pathway by modulating the priming and activation steps of the NLRP3 inflammasome. On one hand, after LPS is recognized and bound by TLR4, IKKα, IKKβ, and NEMO are activated within the cell under the induction of TRIF. This leads to the phosphorylation and subsequent degradation of IκBα. NF-κB itself and its p65/RelA subunit then translocate to the nucleus, where they participate in the synthesis of the NLRP3 inflammasome and various inflammatory factors. On the other hand, SCFAs enter cells via GPR43. Butyrate inhibits the phosphorylation and nuclear translocation of NF-κB p65, thereby blocking the NF-κB signaling pathway. In contrast, acetate induces the production of ROS, which promotes the activation of the NLRP3 inflammasome. The transcription and expression of Platr4 and NFIL3 oscillate diurnally under the regulation of REV-ERBα, thereby influencing the NF-κB signaling pathway. The former inhibits the transcription of NLRP3 inflammasome components to prevent the release of inflammatory factors, while the latter enhances the activity of the NF-κB signaling pathway by inhibiting the transcription of IκBα.

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pattern of gout attacks. Additionally, Platr4 and NFIL3 could emerge as therapeutic targets within this pathway, suggesting a promising future direction for gout treatment. Therefore, a chronobiology-based therapeutic approach (such as adjusting medication timing, dietary interventions to modulate the gut microbiota, and targeted pharmacological agents) targeting the gut microbiota/REV-ERBα/NF-κB axis holds promise as a safer and more effective new avenue for the treatment of gout. Similarly, a chronotherapy-based treatment paradigm may also be applicable to other inflammatory diseases, with potentially significant clinical implications. However, the conclusions drawn in this paper lack compelling experimental and clinical validation. Future research should focus on designing high-quality randomized controlled trials with double-blinding to verify these findings, thereby more effectively guiding clinical practice and medication use.

Abbreviations

MSU, monosodium urate; IL-1β, interleukin-1β; RORs, Retinoid-related orphan receptors; TLRs, Toll-like receptors; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; UA, uric acid; ROC, receiver operating characteristic; AUC, area under the curve; XOD, xanthine oxidase; TNF-α, Tumor necrosis factor alpha; TNFR, tumor necrosis factor receptor; LPS, Lipopolysaccharide; TLR4, Toll-like receptor 4; TRAF, tumour necrosis factor receptor-associated factor; TRIF, Toll/IL-1 receptor domain-containing adaptor-inducing IFN-beta; IKKβ, IkappaB kinase-beta; IKKα, IkappaB kinase-alpha; IκBα, NFκB inhibitor alpha; NF-κB, Nuclear factor kappa B; P, phosphoric acid; NEMO, The nuclear factor (NF)-κB essential modulator; SCFAs, Short-Chain Fatty Acids; ASC, Apoptosis-associated speck-like protein; GPR43, G protein–coupled receptors 43; Platr4, Pluripotency-associated transcript 4; NFIL3, Nuclear factor interleukin 3.

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Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Dalbeth N, Gosling AL, Gaffo A, et al. Gout. *Lancet*. 2021;397(10287):1843–1855.
2. Ni Z, Xiao Q, Xia Z, Kuang K, Yin B, Peng D. Electroacupuncture for acute gouty arthritis: a systematic review and meta-analysis of randomized controlled trials. *Front Immunol*. 2024;14:1295154. doi:10.3389/fimmu.2023.1295154
3. Wang M, Lin X, Yang X, et al. Research progress on related mechanisms of uric acid activating NLRP3 inflammasome in chronic kidney disease. *Ren Fail*. 2022;44(1):615–624. doi:10.1080/0886022X.2022.2036620
4. Wu X, You C. The biomarkers discovery of hyperuricemia and gout: proteomics and metabolomics. *PeerJ*. 2023;11:e14554. doi:10.7717/peerj.14554
5. Renaudin F, Orliaguet L, Castelli F, et al. Gout and pseudo-gout-related crystals promote GLUT1-mediated glycolysis that governs NLRP3 and interleukin-1β activation on macrophages. *Ann Rheum Dis*. 2020;79(11):1506–1514. doi:10.1136/annrheumdis-2020-217342
6. Kluck V, Liu R, Joosten LAB. The role of interleukin-1 family members in hyperuricemia and gout. *Joint Bone Spine*. 2021;88(2):105092. doi:10.1016/j.jbspin.2020.105092
7. He Q, Mok TN, Sin TH, et al. Global, regional, and national prevalence of gout from 1990 to 2019: age-period-cohort analysis with future burden prediction. *JMIR Public Health Surveill*. 2023;9:e45943. doi:10.2196/45943
8. Asghari KM, Zahmatyar M, Seyedi F, et al. Gout: global epidemiology, risk factors, comorbidities and complications: a narrative review. *BMC Musculoskelet Disord*. 2024;25(1):1047. doi:10.1186/s12891-024-08180-9
9. Johnson RJ, Mandell BF, Schlesinger N, et al. Controversies and practical management of patients with gout and chronic kidney disease. *Kidney Int*. 2024;106(4):573–582. doi:10.1016/j.kint.2024.05.033
10. Cipolletta E, Tata LJ, Nakafero G, et al. Association between gout flare and subsequent cardiovascular events among patients with gout. *JAMA*. 2022;328(5):440–450. doi:10.1001/jama.2022.11390
11. Cross M, Ong KL, Culbreth GT, GBD 2021 Gout Collaborators. Global, regional, and national burden of gout, 1990-2020, and projections to 2050: a systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol*. 2024;6(8):e507–e517. doi:10.1016/S2665-9913(24)00117-6
12. Gekakis N, Staknis D, Nguyen HB, et al. Role of the CLOCK protein in the mammalian circadian mechanism. *Science*. 1998;280:1564–1569. doi:10.1126/science.280.5369.1564
13. Crumbley C, Burris TP. Direct regulation of CLOCK expression by REV-ERB. *PLoS One*. 2011;6:e17290. doi:10.1371/journal.pone.0017290
14. Waggoner SN. Circadian Rhythms in Immunity. *Curr Allergy Asthma Rep*. 2020;20(1):2. doi:10.1007/s11882-020-0896-9

15. Izumo M, Pejchal M, Schook AC, et al. Differential effects of light and feeding on circadian organization of peripheral clocks in a forebrain Bmal1 mutant. *Elife*. 2014;3:e04617.
16. Pan X, Mota S, Zhang B. Circadian clock regulation on lipid metabolism and metabolic diseases. *Adv Exp Med Biol*. 2020;1276:53–66.
17. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. *Nat Rev Immunol*. 2013;13:190–198.
18. Timmons GA, O'Siorain JR, Kennedy OD, et al. Innate rhythms: clocks at the center of monocyte and macrophage function. *Front Immunol*. 2020;11:1743.
19. Schlesinger N, Brunetti L, Androulakis IP. Does seasonality of the microbiota contribute to the seasonality of acute gout flare? *Clin Exp Rheumatol*. 2022;40(9):1793–1800. doi:10.55563/clinexprheumatol/hdtge7
20. Choi HK, Niu J, Neogi T, et al. Nocturnal risk of gout attacks. *Arthritis Rheumatol*. 2015;67(2):555–562.
21. Oh JS, Choi WJ, Lee MK, et al. The association between shift work and hyperuricemia in steelmaking male workers. *Ann Occup Environ Med*. 2014;26(1):42. doi:10.1186/s40557-014-0042-z
22. Gu X, Tang D, Xuan Y, et al. Association between obstructive sleep apnea symptoms and gout in US population, a cross-sectional study. *Sci Rep*. 2023;13(1):10192. doi:10.1038/s41598-023-36755-4
23. Wang X, Wang X, Wang F, et al. Role of methotrexate chronotherapy in collagen-induced rheumatoid arthritis in rats. *Z Rheumatol*. 2018;77(3):249–255. doi:10.1007/s00393-016-0236-6
24. Ursini F, De Giorgi A, D'Onghia M, et al. Chronobiology and chronotherapy in inflammatory joint diseases. *Pharmaceutics*. 2021;13(11):1832.
25. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet*. 2008;371(9608):205–214. doi:10.1016/S0140-6736(08)60132-4
26. Kim SK. The mechanism of the NLRP3 inflammasome activation and pathogenic implication in the pathogenesis of gout. *J Rheum Dis*. 2022;29(3):140–153. doi:10.4078/jrd.2022.29.3.140
27. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol*. 2023;41(1):301–316. [Sharp stones are under 1-316]. doi:10.1146/annurev-immunol-081022-021207
28. Koumangoye R. The role of Cl and K efflux in NLRP3 inflammasome and innate immune response activation. *Am J Physiol Cell Physiol*. 2022;322(4):C645–C652. doi:10.1152/ajpcell.00421.2021
29. Liu J, Qiu R, Liu R, et al. Autophagy mediates Escherichia coli-induced cellular inflammatory injury by regulating calcium mobilization, mitochondrial dysfunction, and endoplasmic reticulum stress. *Int J Mol Sci*. 2022;23(22):14174. doi:10.3390/ijms232214174
30. Liu X, Li M, Chen Z, et al. Mitochondrial calpain-1 activates NLRP3 inflammasome by cleaving ATP5A1 and inducing mitochondrial ROS in CVB3-induced myocarditis. *Basic Res Cardiol*. 2022;117(1):40.
31. Biasizzo M, Kopitar-Jerala N. Interplay between NLRP3 inflammasome and autophagy. *Front Immunol*. 2020;11(59):1803. doi:10.3389/fimmu.2020.591803
32. Zhen Y, Zhang H. NLRP3 inflammasome and inflammatory bowel disease. *Front Immunol*. 2019;10. Length to 6. doi:10.3389/fimmu.2019.00276
33. Xia X, Long Q, Zha J, et al. IL-27 regulates NLRP3 inflammasome activation of MDSCs in experimental Sjogren's syndrome. *Int Immunol*. 2023;35(11):531–542. doi:10.1093/intimm/dxad037
34. Zheng X, Wan J, Tan G. The mechanisms of NLRP3 inflammasome/pyroptosis activation and their role in diabetic retinopathy. *Front Immunol*. 2023;14:1151185. When 51185.
35. Tall AR, Bornfeldt KE. Inflammasomes and Atherosclerosis: a Mixed Picture. *Circ Res*. 2023;132(11):1505–1520. doi:10.1161/CIRCRESAHA.123.321637
36. Ertosun MG, Kocak G, Ozes ON. The regulation of circadian clock by tumor necrosis factor alpha. *Cytokine Growth Factor Rev*. 2019;46:10–16. [Striving to 16]. doi:10.1016/j.cytogfr.2019.04.001
37. Li H, Song S, Wang Y, et al. Low-grade inflammation aggravates rotenone neurotoxicity and disrupts circadian clock gene expression in rats. *Neurotox Res*. 2019;35(2):421–431. doi:10.1007/s12640-018-9968-1
38. Zhuang X, Forde D, Tsukuda S, et al. Circadian control of hepatitis B virus replication. *Nat Commun*. 2021;12(1):1658. doi:10.1038/s41467-021-21821-0
39. Liu X, Cao N, Liu X, et al. Circadian rhythm disorders aggravate periodontitis by modulating BMAL1. *Int J Mol Sci*. 2022;24(1):374. doi:10.3390/ijms24010374
40. Liu YR, Wang JQ, Li J. Role of NLRP3 in the pathogenesis and treatment of gout arthritis. *Front Immunol*. 2023;14. When 37822. doi:10.3389/fimmu.2023.1137822
41. Shen Y, Endale M, Wang W, et al. NF-κB modifies the mammalian circadian clock through interaction with the core clock protein BMAL1. *PLoS Genet*. 2021;17(11):e1009933. doi:10.1371/journal.pgen.1009933
42. Hong HK, Maury E, Ramsey KM, et al. Requirement for NF-κB in maintenance of molecular and behavioral circadian rhythms in mice. *Genes Dev*. 2018;32(21, 22):1367–1379. doi:10.1101/gad.319228.118
43. Zhao W, Cui L, Huang X, et al. Activation of Rev-erbα attenuates lipopolysaccharide-induced inflammatory reactions in human endometrial stroma cells via suppressing TLR4-regulated NF-κB activation. *Acta Biochim Biophys Sin*. 2019;51(9):908–914. doi:10.1093/abbs/gmz078
44. Wang S, Lin Y, Yuan X, et al. REV-ERBα integrates colon clock with experimental colitis through regulation of NF-κB/NLRP3 axis. *Nat Commun*. 2018;9(1):4246. doi:10.1038/s41467-018-06568-5
45. Guo DK, Zhu Y, Sun HY, et al. Pharmacological activation of REV-ERBα represses LPS-induced microglial activation through the NF-κB pathway. *Acta Pharmacol Sin*. 2019;40(1):26–34. doi:10.1038/s41401-018-0064-0
46. Pourcet B, Zecchin M, Ferri L, et al. Nuclear receptor subfamily 1 group D member 1 regulates circadian activity of NLRP3 inflammasome to reduce the severity of fulminant hepatitis in mice. *Gastroenterology*. 2018;154(5):1449–1464.e20. doi:10.1053/j.gastro.2017.12.019
47. Lin Y, Wang S, Gao L, et al. Oscillating lncRNA Platr4 regulates NLRP3 inflammasome to ameliorate nonalcoholic steatohepatitis in mice. *Theranostics*. 2021;11(1):426–444. doi:10.7150/thno.50281
48. Wang J, Zhu N, Su X, et al. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. *Cells*. 2023;12(5):793. doi:10.3390/cells12050793
49. Liu BN, Liu XT, Liang ZH, et al. Gut microbiota in obesity. *World J Gastroenterol*. 2021;27(25):3837–3850. doi:10.3748/wjg.v27.i25.3837

50. Zhou Z, Sun B, Yu D, Zhu C. Gut microbiota: an important player in type 2 diabetes mellitus. *Front Cell Infect Microbiol*. 2022;12:834485. doi:10.3389/fcimb.2022.834485
51. Qiu P, Ishimoto T, Fu L, et al. The gut microbiota in inflammatory bowel disease. *Front Cell Infect Microbiol*. 2022;12:733992. doi:10.3389/fcimb.2022.733992
52. Shirvani-Rad S, Khatibzade-Nasari N, Ejtahed HS, Larijani B. Exploring the role of gut microbiota dysbiosis in gout pathogenesis: a systematic review. *Front Med*. 2023;10:1163778. doi:10.3389/fmed.2023.1163778
53. Chu Y, Sun S, Huang Y, et al. Metagenomic analysis revealed the potential role of gut microbiome in gout. *NPJ Biofilms Microbiomes*. 2021;7(1):66. doi:10.1038/s41522-021-00235-2
54. Lin S, Zhang T, Zhu L, et al. Characteristic dysbiosis in gout and the impact of a uric acid-lowering treatment, febuxostat on the gut microbiota. *J Genet Genomics*. 2021;48(9):781–791. doi:10.1016/j.jgg.2021.06.009
55. Yamada N, Iwamoto C, Kano H, et al. Evaluation of purine utilization by Lactobacillus gasseri strains with potential to decrease the absorption of food-derived purines in the human intestine. *Nucleosides Nucleotides Nucleic Acids*. 2016;35(10–12):670–676. doi:10.1080/15257770.2015.1125000
56. Ramos MFP, Monteiro de Barros ADCM, Razvickas CV, et al. Xanthine oxidase inhibitors and sepsis. *Int J Immunopathol Pharmacol*. 2018. 32. Moreover,58738418772210. doi:10.1177/2058738418772210
57. Méndez-Salazar EO, Vázquez-Mellado J, Casimiro-Soriguer CS, et al. Taxonomic variations in the gut microbiome of gout patients with and without tophi might have a functional impact on urate metabolism. *Mol Med*. 2021;27(1):50. doi:10.1186/s10020-021-00311-5
58. Li M, Yang D, Mei L, et al. Screening and characterization of purine nucleoside degrading lactic acid bacteria isolated from Chinese sauerkraut and evaluation of the serum uric acid lowering effect in hyperuricemic rats. *PLoS One*. 2014;9(9):e105577. doi:10.1371/journal.pone.0105577
59. Kuo YW, Hsieh SH, Chen JF, et al. Lactobacillus reuteri TSR332 and Lactobacillus fermentum TSF331 stabilize serum uric acid levels and prevent hyperuricemia in rats. *PeerJ*. 2021;9:e11209. doi:10.7717/peerj.11209
60. Shao X, Sun S, Zhou Y, et al. Bacteroides fragilis restricts colitis-associated cancer via negative regulation of the NLRP3 axis. *Cancer Lett*. 2021;523:170–181. doi:10.1016/j.canlet.2021.10.002
61. Saber S, Abd El-Fattah EE, Yahya G, et al. A novel combination therapy using rosuvastatin and lactobacillus combats dextran sodium sulfate-induced colitis in high-fat diet-fed rats by targeting the TXNIP/NLRP3 interaction and influencing gut microbiome composition. *Pharmaceuticals*. 2021;14(4):341. doi:10.3390/ph14040341
62. Vieira AT, Macia L, Galvão I, et al. A role for gut microbiota and the metabolite-sensing receptor GPR43 in a murine model of gout. *Arthritis Rheumatol*. 2015;67(6):1646–1656. doi:10.1002/art.39107
63. Tong S, Zhang P, Cheng Q, et al. The role of gut microbiota in gout: is gut microbiota a potential target for gout treatment. *Front Cell Infect Microbiol*. 2022;12:1051682. doi:10.3389/fcimb.2022.1051682
64. Mahbub MH, Yamaguchi N, Takahashi H, et al. Alteration in plasma free amino acid levels and its association with gout. *Environ Health Prev Med*. 2017;22(1):7. doi:10.1186/s12199-017-0609-8
65. Du J, Zheng L, Chen S, et al. NFIL3 and its immunoregulatory role in rheumatoid arthritis patients. *Front Immunol*. 2022;13:950144. doi:10.3389/fimmu.2022.950144
66. Wang Y, Kuang Z, Yu X, et al. The intestinal microbiota regulates body composition through NFIL3 and the circadian clock. *Science*. 2017;357(6354):912–916. doi:10.1126/science.aan0677
67. Yu X, Rollins D, Ruhn KA, et al. TH17 cell differentiation is regulated by the circadian clock. *Science*. 2013;342(6159):727–730. doi:10.1126/science.1243884
68. Valcin JA, Udoh US, Swain TM, et al. Alcohol and liver clock disruption increase small droplet macrosteatosis, alter lipid metabolism and clock gene mRNA rhythms, and remodel the triglyceride lipidome in mouse liver. *Front Physiol*. 2020;11:1048. doi:10.3389/fphys.2020.01048
69. Yang W, Li J, Zhang M, et al. Elevated expression of the rhythm gene NFIL3 promotes the progression of TNBC by activating NF-κB signaling through suppression of NFKBIA transcription. *J Exp Clin Cancer Res*. 2022;41(1):67. doi:10.1186/s13046-022-02260-1
70. Ridlon JM, Kang DJ, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*. 2006;47(2):241–259. doi:10.1194/jlr.R500013-JLR200
71. Yang Y, Zhang J. Bile acid metabolism and circadian rhythms. *Am J Physiol Gastrointest Liver Physiol*. 2020;319(5):G549–G563. doi:10.1152/ajpgi.00152.2020
72. Kanemitsu T, Tsurudome Y, Kusunose N, et al. Periodic variation in bile acids controls circadian changes in uric acid via regulation of xanthine oxidase by the orphan nuclear receptor pparα. *J Biol Chem*. 2017;292(52):21397–21406. doi:10.1074/jbc.M117.791285
73. Brooks JF 2nd, Behrendt CL, Ruhn KA, et al. The microbiota coordinates diurnal rhythms in innate immunity with the circadian clock. *Cell*. 2021;184(16):4154–4167.e12. doi:10.1016/j.cell.2021.07.001
74. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes*. 2017;8(2):172–184. doi:10.1080/19490976.2017.1290756
75. Zhao S, Feng P, Hu X, et al. Probiotic Limosilactobacillus fermentum GR-3 ameliorates human hyperuricemia via degrading and promoting excretion of uric acid. *iScience*. 2022;25(10):105198. doi:10.1016/j.isci.2022.105198
76. Feng Y, Yu Y, Chen Z, et al. Effects of β-carotin and green tea powder diets on alleviating the symptoms of gouty arthritis and improving gut microbiota in C57BL/6 mice. *Front Microbiol*. 2022;13:837182. doi:10.3389/fmicb.2022.837182
77. Nezhadi J, Fadaee M, Ahmadi S, et al. Microbiota transplantation. *Heliyon*. 2024;10(20):e39047. doi:10.1016/j.heliyon.2024.e39047
78. Czepiel J, Dróżdż M, Pituch H, et al. Clostridium difficile infection: review. *Eur J Clin Microbiol Infect Dis*. 2019;38(7):1211–1221. doi:10.1007/s10096-019-03539-6
79. Wang Y, Zhang S, Borody TJ, et al. Encyclopedia of fecal microbiota transplantation: a review of effectiveness in the treatment of 85 diseases. *Chin Med J*. 2022;135(16):1927–1939. doi:10.1097/CM9.0000000000002339
80. Xie WR, Yang XY, Deng ZH, et al. Effects of washed microbiota transplantation on serum uric acid levels, symptoms, and intestinal barrier function in patients with acute and recurrent gout: a pilot study. *Dig Dis*. 2022;40(5):684–690. doi:10.1159/000521273
81. Pariollaud M, Gibbs JE, Hopwood TW, et al. Circadian clock component REV-ERBα controls homeostatic regulation of pulmonary inflammation. *J Clin Invest*. 2018;128(6):2281–2296. doi:10.1172/JCI93910

82. Gibbs JE, Blaikley J, Beesley S, et al. The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A*. 2012;109(2):582–587. doi:10.1073/pnas.1106750109
83. Sato S, Sakurai T, Ogasawara J, et al. Direct and indirect suppression of interleukin-6 gene expression in murine macrophages by nuclear orphan receptor REV-ERBα. *ScientificWorldJournal*. 2014;2014:685854. doi:10.1155/2014/685854
84. Wang S, Li F, Lin Y, et al. Targeting REV-ERBα for therapeutic purposes: promises and challenges. *Theranostics*. 2020;10(9):4168–4182. doi:10.7150/thno.43834
85. Dong H, Wang LM, Wang ZQ, et al. [Diurnal differences in acute gout attacks: a clinical study of male gout patients]. *Beijing Da Xue Xue Bao Yi Xue Ban*. 2023;55(5):915–922. Dutch. doi:10.19723/j.issn.1671-167X.2023.05.021