

Review

Gut microbiota circadian rhythms: a key regulator of immunometabolic homeostasis

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Abstract

Emerging studies have revealed that disruptions in circadian crosstalk between the gut microbiota and the host play an essential role in the pathogenesis of metabolic disorders. Under physiological conditions, host circadian clocks regulate microbial diurnal oscillations through rhythmic behaviors, including feeding patterns and sleep-wake cycles. This temporal regulation manifests as robust 24-hour oscillations in microbial community composition, spatial organization, and metabolic activity. These rhythmic microbial signals and their metabolic outputs are subsequently translated into host immune modulation, establishing a bidirectional temporal dialogue between the host and microbiota. Modern lifestyle disruptions, including erratic eating patterns and shift work, desynchronize this temporal dialogue, leading to the loss of microbial rhythms, impaired intestinal barrier function, maladaptive immune responses, chronic inflammation, and systemic metabolic dysregulation. This review delineates the mechanisms through which host-microbiota circadian crosstalk governs immunometabolic homeostasis, provides a mechanistic framework for understanding immunometabolic diseases, and highlights therapeutic strategies that target microbial rhythms to reset host immunity and metabolism.

Key words circadian rhythm, gut microbiota, immunometabolism, host-microbiota crosstalk

Introduction

The Earth's rotation over 24 hours establishes a daily cycle of light and darkness, acting as a universal clock that has driven the development of circadian rhythms in almost all living organisms [1]. These molecular oscillators, which are centered on transcriptional-translational feedback loops that involve “*Bmal1/Clock*” and “*Per/Cry*” genes, enable organisms to anticipate and adapt to daily environmental fluctuations, optimizing physiological processes such as metabolism, immune function, and behavior [2,3]. Circadian rhythms are characterized by three fundamental properties: (1) sustained oscillations with extreme precision under constant environmental conditions; (2) temperature compensation, as evidenced by period stability despite environmental temperature variations; (3) synchronization of the endogenous pacemaker to the environmental light-dark cycle [4]. Remarkably, these properties are conserved even in isolated mammalian cells, underscoring their evolutionary optimization under natural selection [4–6]. In humans, circadian regulation extends beyond sleep-wake cycles to

orchestrate systemic metabolism, immune function, and neurobehavioral processes. Accumulating evidence implicates that the gut microbiota, a complex ecosystem comprising approximately 100 trillion microbes encoding 150-fold more genetic material than the human genome, serves as a critical mediator of host circadian physiology [7,8]. The microbiota, referred to as the “forgotten organ”, demonstrates circadian fluctuations in its composition, the production of metabolites and spatial organization, synchronizing with host rhythms to regulate energy harvest, immune homeostasis, and metabolic gene expression [9]. For instance, microbial-derived butyrate and propionate oscillate rhythmically under normal conditions, directly modulating hepatic gluconeogenesis and adipose tissue lipolysis while synchronizing circadian oscillators in the liver and adipocytes, thereby linking microbial rhythms to host metabolic outputs.

For the gut microbial diurnal rhythm, a recent investigation demonstrated circadian transcriptional oscillations of molecular clock genes in *Escherichia coli*, namely, *radA*, a *kaiC* homologue

[10], indicating that the gut microbiota may have endogenous rhythms. However, the prevailing consensus among current studies suggests that the gut microbial diurnal rhythm might be modulated by particular environmental stimuli within the gut, including dietary patterns, behaviors, and the expression of host clock genes [11]. This bidirectional temporal dialogue between the host and microbiota results in crosstalk, wherein host clocks regulate microbial oscillation through host rhythmic behaviors such as feeding rhythms, whereas microbial oscillations reciprocally entrain and modulate the host immune system. Modern lifestyle challenges, including pervasive shift work, chronic jet lag, and Western-style dietary patterns, disrupt this delicate temporal dialogue and lead to the development of immunometabolic diseases. A comprehensive understanding of the mechanisms underlying circadian host-microbiota crosstalk in immunometabolism remains to be elucidated. This review therefore aims to synthesize current evidence on the specific mechanisms underlying the circadian crosstalk between the host and microbiota, and how this dialogue regulates host immunometabolism. We further discuss the emerging therapeutic strategies targeting the microbiota to restore metabolic health.

Circadian Rhythms in Gut Microbiota under Physiological Conditions

To fully understand how host-microbiota circadian crosstalk regulates host immunometabolism, we must first establish whether the gut microbiota itself exhibits rhythmic behavior. For decades, the prevailing view held that structurally simple prokaryotes lacked the evolutionary capacity to develop circadian clocks. This notion persisted until pioneering studies on the *cyanobacterium Synechococcus* RF-1 revealed a self-sustained 24-hour rhythm of nitrogen fixation under constant conditions following light-dark entrainment [12,13]. Subsequent studies demonstrated that the clock orchestrates global rhythms of gene transcription and chromosomal topology, all of which in turn control metabolic processes (e.g., nitrogen/carbon metabolism) and cell division through interconnected post-translational and transcriptional feedback loops [14–18]. These findings not only overturned assumptions about prokaryotic “simplicity” but also provided a framework for exploring timekeeping mechanisms in other bacteria, including the gut microbiota.

Recently, an increasing number of studies have revealed the existence of rhythms in the gut microbiota, refuting the long-held assumption of its inherent stability over time. *K. aerogenes* was found to exhibit temperature-compensated circadian rhythms that govern swarming motility, which synchronizes with thermal cycles that mimic body temperature variations. Melatonin, a hormone known for its role in circadian regulation, impacts the transcriptional profile of *K. aerogenes* and affects genes governing biofilm formation and environmental adaptation [19,20]. Additionally, the intestinal microbiota undergoes rapid alterations following dietary modifications [21,22]. In 2014, Thaïss *et al.* [23] first documented diurnal rhythmic fluctuations in the gut microbiota of mice and humans, which are synchronized to feeding rhythms and lead to temporally distinct compositional configurations and functional states over the course of a day. During the same period, Amir Zarrinpar *et al.* [24] also reported that the mammalian gut microbiota displays diurnal oscillations across diverse dietary and feeding patterns. Collectively, these findings indicate that environ-

mental cues drive circadian oscillations in the gut microbiota, facilitating temporal adaptation that synchronizes with host physiology and contributes to metabolic homeostasis. The gut microbiota exhibits diurnal oscillations in microbial composition, metabolite production, and spatial localization within the intestine (Figure 1).

Diurnal oscillation mode of gut microbiota—composition

Analysis of the fecal microbiota of mice fed ad libitum under 12-hour light/dark (LD) cycles reveals significant fluctuations in the diurnal abundance of more than 15% of operational taxonomic units (OTUs) [23]. These rhythmic OTUs, primarily from the *Clostridia* and *Lactobacillales* classes, constituted approximately 60% of the microbial composition, creating temporally distinct taxonomic configurations. In addition, human studies similarly demonstrate that approximately 10% of bacterial OTUs exhibit diurnal oscillations with characteristic daily peak-trough phase variations, and the gut microbiota in jet-lagged humans display compositional changes induced by time, including elevated *Firmicutes* proportions, which are associated with obesity and metabolic disorders according to epidemiological studies.

Diurnal oscillation mode of gut microbiota—metabolites

Short chain fat acids (SCFAs)

SCFAs, primarily acetate, propionate, and butyrate, are generated by the gut microbiota via the fermentation of indigestible dietary fibers [25]. These metabolites function as both energy substrates for host cells (e.g., colonocytes and adipocytes) [26] and signaling molecules that regulate host metabolism [27]. Under physiological conditions, a significant proportion of rhythmically oscillating OTUs are taxonomically classified within the *Lachnospiraceae* family, a group recognized for its butyrate-synthesizing capacity. Accordingly, butyrate levels in both the cecal and fecal contents exhibited robust circadian rhythmicity, whereas propionate levels demonstrated similar, although less pronounced, diurnal fluctuations. Furthermore, the key butyrate-producing enzyme acetyl-CoA transferase also shows circadian regulation in cecal contents [28].

Bile acids (BAs)

Primary BAs, which are biosynthesized hepatically from cholesterol and subsequently stored in the gallbladder, are secreted into the intestinal lumen, where they undergo gut microbiota-mediated biotransformation into secondary bile acids, promoting the uptake of dietary lipids and fat-soluble vitamins [29]. The gut microbiota regulates BA metabolism through hepatic enzyme modulation [30] and BA transformation via bile salt hydrolase activity in *Firmicutes* [31]. Both BA synthesis enzymes [32,33] and serum BA levels exhibit circadian rhythms in mice, with primary BAs peaking near the conclusion of the dark phase and secondary BAs peaking during the light phase [34,35]. These temporal variations suggest a dynamic coordination between microbial regulation of BA metabolism and the host circadian rhythm [36].

Other metabolites

Hydrogen sulfide (H₂S), which is produced primarily in the distal colon by dissimilatory sulfite reductase (DsrAB), is predominantly found in *Deltaproteobacteria* [37] and serves as a powerful inhibitor of microbial functions, including butyrate production [38]. Experimental evidence has demonstrated its capacity to induce a temporal

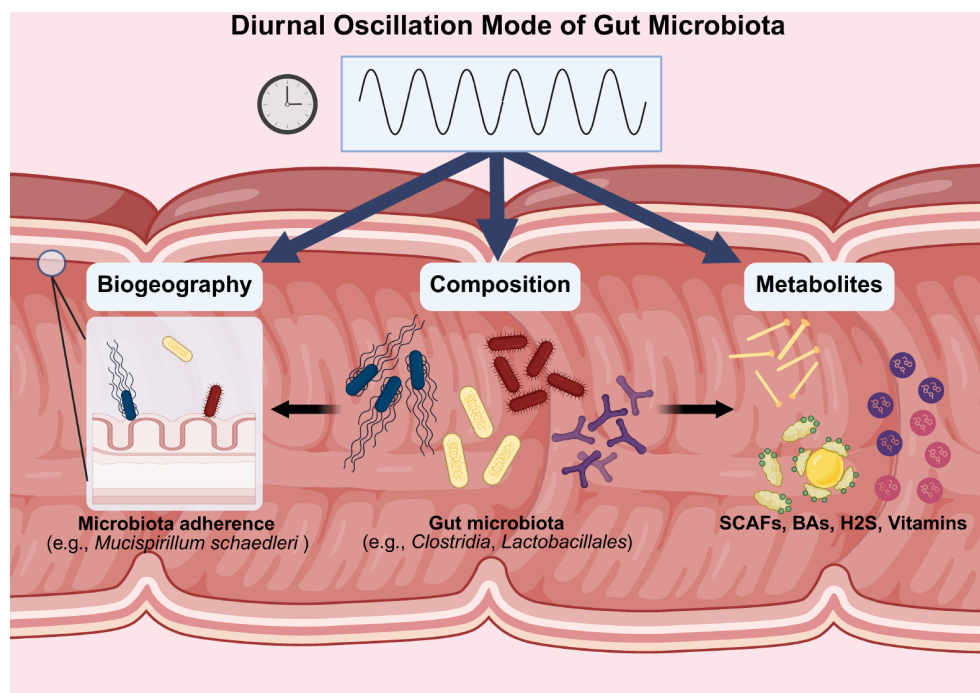


Figure 1. Diurnal oscillation mode of the gut microbiota under physiological conditions The gut microbiota exhibits robust circadian rhythms characterized by fluctuations in three major dimensions: composition, metabolite production, and biogeography. The microbial composition varies throughout the day, with rhythmic shifts in key bacterial taxa (e.g., *Clostridia*, *Lactobacillales*). The production of metabolites, including SCFAs, BAs, H_2S , and vitamins, follows a diurnal pattern that is tightly coupled to host feeding rhythms. Microbial biogeography is also rhythmic, characterized by time-dependent fluctuations in mucosal adherence within the intestinal tract (e.g., *Mucispirillum schaedleri*). These rhythmic patterns suggest that gut microbial activity is temporally structured under physiological conditions.

shift in the peak expression of *Bmal1* in murine hepatic tissues [28]. Diurnal oscillations in the cecal H_2S concentration and *dsrAB* gene abundance occurred specifically in high-fat diet (HF)-fed mice but not in regular chow (RC)-fed controls. Conversely, fecal H_2S measurements demonstrated robust circadian rhythmicity in RC-fed mice but a loss of periodicity in HF-fed animals [28].

Vitamins are essential micronutrients that function as enzyme precursors in vital biochemical reactions [39]. Although predominantly diet-derived, approximately 40–65% of gut microbial taxa are capable of producing each of the eight B-group vitamins [40]. Oscillating genera such as *Bifidobacterium* and *Lactobacillus* are likely major contributors to this function [41,42]. Certain B vitamins demonstrate direct and indirect regulatory relationships with circadian clock mechanisms [43]. For example, vitamin B_2 derivatives serve as essential light-sensing cofactors in non-visual photoreceptors that synchronize circadian rhythms to environmental light [43]. Owing to diurnal oscillations in the gut microbial composition and activity, it is plausible that microbiota-synthesized vitamin concentrations also exhibit circadian rhythmicity. However, direct evidence demonstrating rhythmic fluctuations in microbiota-derived vitamin levels is currently lacking and remains an important area for future research.

Diurnal oscillation mode of gut microbiota—biogeography

In 2016, Thaïss *et al.* [44] demonstrated diurnal oscillations in gut microbiota biogeography, which significantly influences host physiology. Commensal bacteria that significantly impact host

physiology are located mainly near the intestinal mucosal surface. Compared with those in the light phase, mice housed under LD cycling conditions and fed ad libitum demonstrate significant diurnal oscillations in epithelial colonization density, exhibiting approximately 10-fold greater bacterial adherence during the dark phase. Similarly, the mucosal niche bacterial composition displayed temporal oscillations, with approximately 24% (148/633) of the OTUs showing rhythmic epithelial adherence patterns, including *Mucispirillum schaedleri* and *Lactobacillus reuteri*. These findings reveal diurnal fluctuations in bacterial exposure at the host mucosal interface. Additionally, given that *Reg3γ*-deficient mice exhibit increased bacterial colonization adjacent to the intestinal epithelium, and that the disrupted adherence rhythms in clock-deficient (*Per1/2^{-/-}*) mice could be rescued by temporally restricted feeding (RF), the host contributes significantly to the oscillations in the biogeography of the gut microbiota. However, assessment of rhythmic changes in the abundance of bacterial Kyoto Encyclopedia of Genes and Genomes (KEGG) genes in epithelial proximity suggests that pathways involved in mucus degradation and bacterial motility are among the microbial functions featuring the most significant oscillations in relative abundance, as exemplified by bacterial chemotaxis and flagellar assembly. Consequently, the concerted interaction of host and microbial factors rhythmically regulates mucus layer thickness, modulates microbial penetration depth, and determines spatial segregation between the intestinal epithelium and commensal bacteria. These parameters exhibit diurnal oscillations, with maximal microbial proximity to the mucosal interface occurring during the dark phases.

Circadian Rhythms in Gut Microbiota under Pathological Conditions

Various pathological conditions significantly disrupt the intrinsic circadian rhythms of the gut microbiota. This disruption manifests as altered circadian fluctuations in microbial composition and abnormal temporal patterns of metabolic activity. This rhythmic dysregulation not only compromises gut microbiome homeostasis but also exacerbates pathological processes through mechanisms such as impaired gut barrier function, dysregulated immune responses, and disrupted metabolic signaling [45]. Characteristic alterations in gut microbiota rhythms are observed in diseases, including type 2 diabetes (T2D), inflammatory bowel disease (IBD), and obstructive sleep apnea hypopnoea syndrome (OSA).

Type 2 diabetes (T2D)

T2D can induce circadian dysregulation of the gut microbiota through dysfunction of host circadian clock genes and metabolic imbalance. In T2D mouse models, microbial genera, including *Akkermansia*, *Bifidobacterium*, and *Allobaculum*, lose circadian oscillations, whereas *Prevotella* and *Proteobacteria* exhibit phase shifts, accompanied by rhythmic disruptions in metabolites linked to oxidative phosphorylation, amino acid metabolism, and fatty acid cycling [46]. Human studies mirror these findings: individuals with T2D or obesity (BMI ≥ 30) display abolished diurnal fluctuations in *Bacteroidetes/Firmicutes* ratios and alpha diversity, alongside a subset (3.5%) of operational taxonomic units (OTUs) adopting novel compensatory rhythms, suggesting microbial plasticity in response to metabolic dysfunction [47]. For the mechanisms underlying altered rhythm of the gut microbiota in the state of T2D, a previous transcriptomic study, showed a notable

upregulation of *Bmal1* mRNA in the colonic tissue of diabetic mice under physiological constraints, along with a significant enhancement of the expression of *Per2* during the night [46]. This dysregulated expression of clock genes perturbs the diurnal rhythmicity of the gut microbiota in murine models [23]. Moreover, imbalances in glucose homeostasis and insulin resistance may disrupt cyclic fluctuations in the gut microbiota by altering intestinal osmolarity, bile acid composition, or the inflammatory microenvironment (Figure 2). For example, hyperglycemia may suppress diurnal abundance changes in protective strains such as *Akkermansia muciniphila* [47]. Notably, in the pathological context of T2D, pharmacological interventions can also modulate the composition of the gut microbiota. For example, the beneficial bacteria *Blautia* and *Faecalibacterium* are increased after treatment with metformin, and the abundance of *Bacteroidetes* was elevated following treatment with DPP-4 inhibitors [48]. These factors may affect the diurnal rhythmic fluctuations of the gut microbiota in patients with T2D.

Obstructive sleep apnea (OSA)

OSA primarily disrupts the circadian rhythms of the gut microbiota via intermittent hypoxia and hypercapnia [49]. This dysregulation manifests as reduced microbial diversity and richness, alongside altered relative abundances of specific microbial communities. Crucially, the characteristic circadian fluctuations of bacterial families such as *Ruminococcaceae* and *Lachnospiraceae*, which are associated with atherosclerosis, are abolished [49]. The underlying mechanisms involve both direct and indirect pathways: Directly, IHC alters oxygen and carbon dioxide levels within the gut lumen, impacting the microbial habitat (Figure 2). Indirectly, it

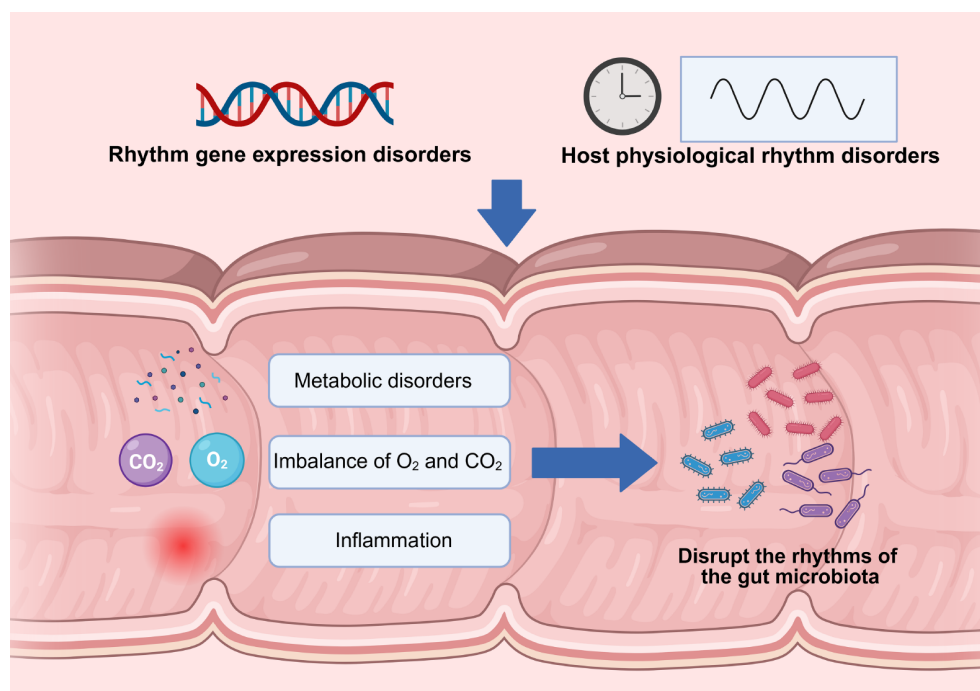


Figure 2. Diurnal oscillation mode of the gut microbiota under pathological conditions The core triggering factors include disorders of the host circadian rhythm genes and the host physiological rhythm, which lead to a series of microenvironmental imbalances. These imbalances include abnormal oxygen and carbon dioxide regulation, metabolic disorders and inflammation, which collectively disrupt the rhythms of the gut microbiota.

disrupts the host's core physiological rhythms (e.g., sleep-wake cycles and feeding patterns) and activates the immune system. These combined effects alter the gut microenvironment, ultimately leading to circadian dysregulation of both the microbiota and its metabolites.

Inflammatory bowel disease

In IBD patients, the altered intestinal microenvironment disrupts the circadian rhythmicity of the gut microbiota. Some beneficial bacteria (such as *Faecalibacterium prausnitzii*) normally reach their peak levels at night, but in IBD patients, the rhythmicity of these bacteria is weakened or absent [50]. Microbial metabolites are consequently altered. Specifically, the rhythmic synthesis of beneficial metabolites (e.g., butyrate) is reduced, and the rhythmic release of pro-inflammatory metabolites (e.g., endotoxins, branched-chain amino acids) is dysregulated. Concurrently, gut microbiota rhythms no longer fluctuate with feeding times, instead overlapping with abnormal rhythms of inflammatory cytokines (e.g., TNF- α , IL-6) [51]. Inflammatory cytokines suppress the rhythmic expression of tight junction proteins (such as OCCLUDIN and CLAUDIN-1) and core circadian genes in intestinal epithelial cells by activating downstream signaling pathways (e.g., NF- κ B and MAPK), thereby further influencing the rhythmicity of the gut microbiota (Figure 2) [52–54]. This phenomenon is closely associated with reduced rhythmic gene expression in patients, abnormal feeding or light exposure patterns, and alterations in the intestinal microenvironment [51].

Shift work (irregular sleep)

Disturbances in environmental circadian rhythms (e.g., irregular light exposure) impair central clock function and feeding rhythms and regulate gut microbial rhythms (Figure 2). Frequent disruptions in external light conditions (e.g., shift work, irregular sleep) impair hypothalamic central clock function and the adaptability of host molecular clocks. In mice, jet lag or simulated shift work models disrupted feeding rhythms and gut microbial rhythms (e.g., loss of rhythmicity in 50% of zOTUs, including *Lactobacillus* and *Odoribacter*), resembling genetic circadian disruption [23,55]. Human studies have shown that night-shift workers have decreased *Bacteroidetes* and increased *Actinobacteria/Firmicutes*, with increased *Dorea* species [56]. These shifts likely arise from misaligned central or GI clocks altering feeding rhythms, indirectly destabilize microbial communities [55].

While conditions such as Alzheimer's disease and heart failure are also associated with alterations in the composition of the gut microbiota [57,58], their circadian rhythm dynamics remain unexplored. Critically, observed microbial dysrhythmia may arise bidirectionally: disease-associated factors (e.g., chronic inflammation, metabolic dysregulation) likely perturb microbial rhythms, which in turn exacerbate pathological processes. Resolving this interplay demands longitudinal human cohorts, gnotobiotic animal models, and multi-omics approaches to disentangle causality and identify therapeutic targets for circadian-based interventions (Figure 2).

Host Drives Microbial Circadian Oscillation

The circadian rhythms of the gut microbiota are pivotal for maintaining host health, with their stability and dynamic fluctuations primarily regulated by multidimensional host-associated

factors [59]. These encompass both intrinsic host rhythmic genes and the spatio-temporal characteristics of the gut, alongside extrinsic elements such as dietary patterns, gender, and age. The core network constituting the rhythmic interactions between host and microbiota provides a foundation for subsequent elucidation of regulatory mechanisms and development of intervention strategies.

Host biological clock genes

Host rhythm genes dynamically shape gut microbiota rhythms in space and time by regulating central-peripheral biological clock coordination, feeding rhythms and cyclic secretion of host metabolites (Figure 3). Studies have shown that disrupting host circadian clock genes (e.g., *Per1* and *Per2* or the central clock gene *Bmal1* in mice) leads to the loss of gut microbial rhythmicity [23, 55]. *Bmal1^{SCNfl/-}* mice present disrupted 24-hour rhythms in gut microbiota diversity, major phyla (*Firmicutes*, *Bacteroidetes*), and functional bacterial families (*Lactobacillaceae*, *Clostridiaceae*). Key genera linked to SCFA and bile acid metabolism (e.g., *Faecalibaculum* and *Agathobaculum*) also lose rhythmicity. These changes, associated with altered gastrointestinal clock gene expression and feeding patterns, suggest that host circadian rhythms regulate gut microbial dynamics, potentially influencing metabolic health.

Effects of diet

Diet composition and feeding timing modulate gut microbial rhythmicity through nutrient-dependent modulation and feeding-fasting cycles (Figure 3). The composition of an individual's diet is a

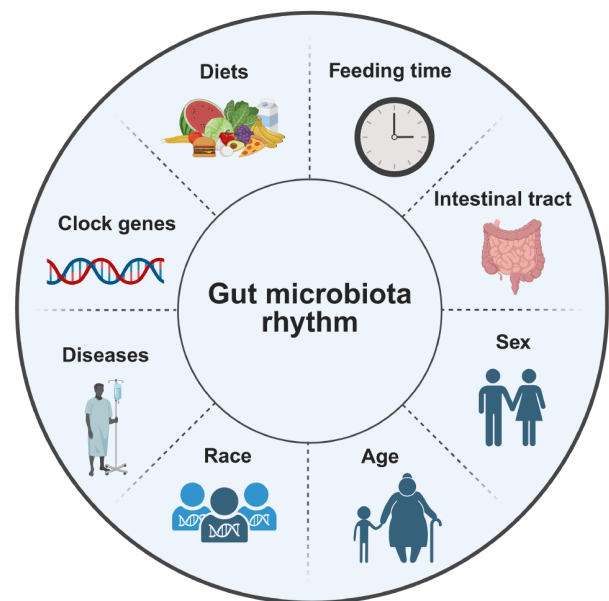


Figure 3. Factors influencing the rhythms of gut microbiota This diagram illustrates various factors involved in the host-driven regulation of the diurnal oscillation mode of the gut microbiota. Host clock genes, dietary composition, and feeding time directly synchronize microbial oscillations. Regional gut niches further shape spatial rhythmic diversity, whereas population variables (gender, age, and ethnicity) modulate rhythmicity between individuals. Patients with different diseases also exhibit distinct gut microbiota rhythmicity characteristics.

critical factor shaping the structure and rhythmicity of the gut microbiota. Seasonal food availability, urban versus rural dietary practices, and variations in nutrient intake (e.g., fiber, fats) directly influence the diversity of microbial consortia and the enriched levels of particular bacterial groups [60]. For example, a high-fat diet (HFD) disrupts microbial circadian rhythms in mice, significantly reducing the number and proportion of rhythmically fluctuating operational taxonomic units (OTUs) [24,61]. This disruption is linked to suppressed expression of REG3 γ , an antimicrobial peptide secreted by intestinal epithelial cells that maintains microbial homeostasis and rhythmicity [61]. Notably, while a HFD does not reduce the overall abundance of *Lactobacillus* in mice, it causes a phase shift in their rhythmic activity, suggesting that microbial timing rather than quantity may play a dominant role in metabolic outcomes [62]. These findings highlight how dietary quality can destabilize microbial rhythms, exacerbating metabolic dysfunction. The timing and frequency of food intake are equally pivotal in regulating gut microbial rhythms. In mice, feeding during the light phase (in contrast to their natural nocturnal eating pattern) induces phase shifts in bacterial OTUs, whereas timed feeding restored microbial oscillations even in circadian clock-deficient mice [23]. This underscores the dominance of feeding rhythms over intrinsic host clocks in driving microbial dynamics. Human-relevant studies suggest that structured eating patterns, such as limiting meals to 2–3 per day with regular fasting intervals, can enhance circadian alignment and microbial stability [63]. Fasting periods may synchronize the host's internal clock with microbial metabolic cycles, improving gut barrier function and reducing inflammation. For example, intermittent fasting has been shown to increase microbial diversity and reinforce rhythmic fluctuations in beneficial taxa, potentially buffering against metabolic disorders [63]. Together, these findings emphasize that when and how often we eat are as crucial as what we eat in maintaining gut microbial harmony and metabolic health.

Influence of intestinal factors

Circadian nutrient dynamics and intestinal niches shape gut microbial rhythms and metabolic diversity (Figure 3). The gut microbiota is regulated by two distinct nutrient supply modes: luminal-side nutrients (derived from the diet and microbial metabolites) and plasma-side nutrients (from the host systemic metabolism) [64]. Luminal-side nutrients enhance lipid and bile acid metabolism, promoting lipid absorption, epithelial barrier integrity, and hormone secretion, while enriching bacteria are linked to these processes. In contrast, plasma nutrients support anabolic pathways such as fatty acid and amino acid synthesis, favoring bacteria such as *Parabacteroides*, which thrive in biosynthetic environments [64]. These nutrient modes dynamically interact with circadian rhythms, with luminal-side dominance during feeding phases and plasma-side activity during fasting. This rhythmic nutrient shift may synchronize microbial metabolic cycles with host physiology, influencing both microbial abundance and temporal activity patterns. Microbial composition and rhythms vary significantly across intestinal regions due to environmental and functional gradients. The small intestine, characterized by high motility, high levels of bile acids, and digestive enzymes, limits microbial colonization and prioritizes nutrient absorption. In contrast, the low-oxygen, neutral-pH environment of the large intestine supports dense microbial communities (e.g., *Bacteroidota*)

that specialize in fermenting complex carbohydrates [65]. These spatial differences create distinct microbial niches, and the stable conditions of the colon allow robust microbial rhythms tied to dietary and host metabolic cycles. These factors collectively drive compartment-specific microbial dynamics and contribute to gut-wide rhythmic diversity.

Influence of population factors

The influence of population factors (gender, age and ethnicity) on circadian rhythms of the gut microbiota is still not fully understood, with key questions unresolved (Figure 3). In wild-type mice, a study [66] revealed that female individuals exhibited more pronounced circadian oscillations in the abundance of *Bacteroidetes* than males did. Research revealed sex-associated variations in the composition of the gut microbiota [67], with evidence indicating that oscillations in estrogen levels modulate microbial communities [68]. However, the role of sex as a determinant of circadian rhythmicity in the human gut microbiota remains underexplored. Significant disparities in the composition of the gut microbiota are observed across human populations and ethnicities [67], which are likely attributed to variations in climate, environmental factors, and dietary patterns. Additionally, age-related shifts in microbial diversity and abundance have been reported [69]. The extent to which these demographic and lifestyle variables influence the circadian rhythms of the gut microbiota warrants further investigation (Figure 3).

Microbiota Regulates Host Circadian Immunometabolism

Recent studies revealed complex bidirectional crosstalk between immune and metabolic homeostasis, and this imbalance in cross-system crosstalk is a central mechanism driving the pathogenesis of metabolic disorders, autoimmune disorders, and even malignancies [70,71]. For example, proinflammatory cytokines from activated immune cells impair insulin signaling, promoting tissue insulin resistance and T2D progression [70]. Notably, circadian regulation of the gut microbiota is emerging as a new method for resolving immunometabolism interactions (Figure 4). Emerging evidence has revealed two major pathways by which the microbiota modulates host circadian immunometabolism homeostasis [72](Figure 4). First, the gut microbiota facilitates HDAC3-NCoR complex assembly, and the core clock repressor REV-ERB α orchestrates the rhythmic recruitment of this complex to specific target genes. Consequently, this process gives rise to diurnal oscillations in histone deacetylation within intestinal epithelial cells (IECs), along with corresponding rhythmic patterns in the expression of intestinal metabolic genes, nutrient absorption, and lipid metabolism [73]. Notably, this mechanism requires MyD88-dependent immune signaling [72]. Second, gram-negative gut microbiota-derived flagellin/LPS modulates NFIL3 expression oscillations through a sequential ILC3-STAT3-epithelial clock pathway. Microbial activation of TLR-MyD88 signaling in dendritic cells induces IL-23-dependent ILC3 stimulation, leading to IL-22 secretion, which triggers STAT3 phosphorylation in epithelial cells, and phosphorylated STAT3 then binds to and represses the REV-ERB α promoter, thereby relieving REV-ERB α -mediated transcriptional repression at the NFIL3 locus and ultimately regulating lipid storage and body composition [74]. These two pathways are key mechanisms by which the microbiota rhythmically regulates host immunometabo-

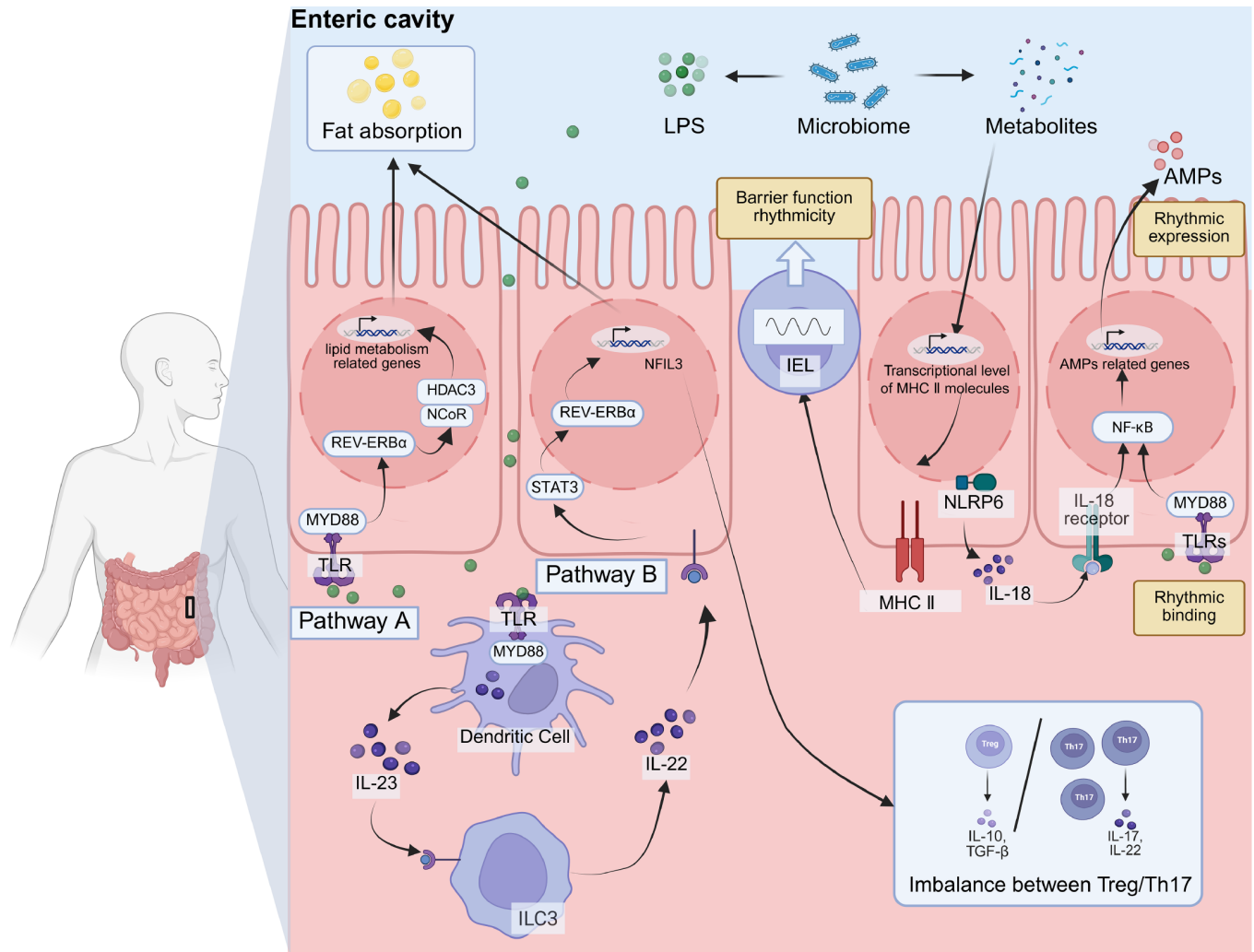


Figure 4. Microbiota-regulated circadian immunometabolic mechanisms in the gut This schematic illustrates the key pathways through which the gut microbiota influences host immunometabolic processes in a circadian manner. The intestinal epithelial layer serves as a central interface, integrating microbial signals into rhythmic host responses. Pathway A: microbial LPS signals through the TLRs-MYD88 pathway to activate the circadian regulator REV-ERB α in the nucleus, REV-ERB α then recruits HDAC3-NCoR complex to periodically silence genes involved in lipid metabolism. Pathway B: microbial stimulation through the TLRs-MYD88 pathway to induces IL-22 production via the DC-ILC3 axis, activating epithelial STAT3, which suppresses REV-ERB α and promotes NFIL3 expression, further coordinating the rhythm of lipid metabolism and immune cell. Immune barrier: bacteria and their products rhythmically bind to epithelial TLRs, driving the rhythmic expression of antimicrobial peptides (AMPs). The microbiota can induce circadian rhythmic expression of MHC class II molecules in small intestinal epithelial cells (SIECs), driving periodic proliferation of intestinal epithelial lymphocytes (IELs). Immune cell regulation: NFIL3 modulates Th17/Treg differentiation. Disruption of these rhythms contributes to inflammation, obesity, and insulin resistance. Inflammasome activity: microbial metabolites activate the NLRP6 inflammasome, promoting IL-18 secretion and AMPs expression under circadian control of REV-ERB α .

lism. Therefore, we discuss the multilevel mechanisms by which host-microbiota circadian crosstalk modulates immunometabolic regulation, including immune barrier maintenance, immune cell programming, and molecular immune networks, to establish systemic metabolic coordination.

Immune barrier

Positioned at the host-microbe interface, the gut microbiota orchestrates diurnal rhythms in intestinal barrier immunity, thereby governing immunometabolic homeostasis. Through the integration of temporal dietary inputs (feeding rhythms and dietary composition), the microbiota entrains diurnal MHC class II expression in small intestinal epithelial cells (SIECs), which drives the cyclical

expansion of intraepithelial lymphocytes (IELs). This microbially programmed interplay between SIEC MHC class II and IEL-derived IL-10 establishes circadian variations in barrier integrity. Disruption of microbial oscillations (e.g., by HF diets or antibiotics) ablates this regulatory axis, impairing rhythmic barrier integrity [75]. Additionally, the integrity of the intestinal epithelial cells (IECs)' circadian clock is required for microbiota-IECs crosstalk. Within IECs, CLOCK protein and TLRs collaborate to transform non-rhythmic bacterial signals into circadian gene expression. Many of these rhythmically expressed genes play critical homeostatic roles in gut innate immunity (e.g., in IECs) or indirectly influence adaptive immunity (e.g., in the lamina propria) [76]. The core clock components *Clock/Bmal1* directly modulate tight junction proteins (OCCLUDIN/

CLAUDIN-1) through E-box-mediated transcriptional control, creating diurnal oscillations in gut permeability that peak during active phases [77].

By synthesizing rhythmically fluctuating metabolites, the microbiota directly gate immune-metabolic crosstalk. The engagement of bacterial products (e.g., LPS) with host pattern recognition receptors, particularly TLR family members, is pivotal for maintaining intestinal epithelial integrity and contributing to gut mucosal homeostasis [78]. Microbial products engage epithelial TLRs in a clock-dependent manner, driving circadian expression of antimicrobial proteins and lamina propria immune activation [72]. Rhythmic barrier weakening permits transient LPS translocation, through TLR4 activation, induces pro-inflammatory cytokines capable of impairing insulin signaling and β -cell function—a key mechanism linking chronodisruption to T2D [79]. Concurrently, microbial metabolites such as butyrate exhibit circadian production [80,81], nourishing enterocytes and stimulating antimicrobial peptide secretion to reinforce barrier integrity [82]. When the rhythm of SCFAs production is disrupted, the integrity and permeability of the intestinal barrier may be affected.

Via spatiotemporally constrained biogeography, the microbiota orchestrates localized immune circuits. Daily rhythmic epithelial attachment of segmented filamentous bacteria (SFB) initiates an immune signaling cascade involving group 3 innate lymphoid cells and induces rhythmic fluctuations in epithelial STAT3 expression and activation, which generate rhythmic antimicrobial peptide production [72]. In addition, John *et al.* [83] demonstrated that segmented filamentous bacteria (SFB) exhibit feeding-time-dependent adherence rhythms, activating ILC3-STAT3 signaling to induce rhythmic STAT3 phosphorylation. This suppresses the clock regulator REV-ERB α , relieving its inhibition of NFIL3 and thereby synchronizing intestinal lipid metabolism genes with the microbial cycle [74]. STAT3-REV-ERB α crosstalk thus governs antimicrobial defense and lipid homeostasis, with dysregulation predisposing individuals to obesity and insulin resistance via disrupted metabolic rhythms [74].

Immune cells

Circadian regulation of immune cell trafficking and function is mediated by the host clock. The intrinsic circadian clock synchronizes host immunity with diurnal cycles by orchestrating immune cell migration and development, thereby coordinating complex multicellular immune responses. *Bmal1* directs the rhythmic trafficking of monocytes and lymphocytes across tissues. Concurrently, circadian oscillators regulate T lymphocyte passage through developmental checkpoints governing immune cell differentiation. However, although the role of the circadian clock in innate lymphoid cell (ILC) development requires further investigation, clock-mediated regulation of intestinal ILC3 function is well established [72]. Additionally, the functions of peritoneal macrophages, including phagocytosis and cytokine expression, display intrinsic circadian rhythms governed by *Bmal1* [84].

Host-microbiota crosstalk coordinates the Th17/Treg rhythmic balance in metabolic regulation (Figure 4). Th17 cells, a subset of CD4 T helper cells, secrete proinflammatory cytokines such as IL-17 and IL-22 to protect mucosal surfaces against bacterial and fungal pathogens. The intestinal accumulation of Th17 cells requires the commensal microbiota [85], with specific members, such as segmented filamentous bacteria (SFB), capable of inducing the

accumulation of CD4 T cells [86]. The rhythmically expressed transcription factor NFIL3 connects circadian clock outputs via REV-ERB α to regulate Th17 differentiation. Circadian disruption elevates intestinal Th17 frequencies, causing an imbalance between proinflammatory Th17 cells and anti-inflammatory regulatory T cells (Tregs), and this dysregulation contributes to insulin resistance, metabolic syndrome, and diabetes [87–89].

Disrupted monocyte rhythms exacerbate metabolic inflammation. Disrupted diurnal rhythms in Ly6C^{hi} monocytes promote chronic inflammatory diseases, including obesity and insulin resistance. Mice with a disrupted diurnal rhythm of monocytes develop Ly6C^{hi} monocytosis and elevated Ly6C^{hi} macrophage infiltration in epididymal white (eWAT) and brown adipose tissue (BAT) under HFD conditions, and these adipose macrophages overexpress monocyte-attracting chemokines, exacerbating obesity-related inflammation. These mice exhibit increased susceptibility to insulin resistance with impaired glucose clearance, abnormal triglyceride accumulation, and leukocyte infiltration. Collectively, disrupted diurnal variation in monocytes increases diet-induced obesity and insulin resistance susceptibility through Ly6C^{hi} monocytosis and subsequent adipose tissue recruitment [90].

Inflammasome

Inflammasomes guard host-microbiota metabolic homeostasis. The NLRP6 inflammasome serves as a critical molecular interface between microbial metabolites and host immunity. Microbiota metabolites such as histamine and taurine activate NLRP6 inflammasome signaling to stimulate IL-18 production. This cytokine subsequently induces downstream colonic antimicrobial peptide (AMP) expression, shaping host-microbiota interactions. Inflammasome deficiency disrupts the balanced AMP landscape, promoting the growth of a dysbiotic microbiota that gains the ability to suppress inflammasomes by altering its metabolite profile [91]. Importantly, the NLRP6 and the NLRP3 inflammasome negatively regulate multiple aspects of metabolic syndrome through microbiota modulation, establishing their central role in immunometabolic regulation [92].

Circadian control regulates inflammasome activities in metabolic inflammation. NLRP3 expression and inflammasome activation exhibit REV-ERB α -controlled circadian oscillations in macrophages, peaking during the active phase and coinciding with the lowest expression levels of REV-ERB α mRNA. Comparable rhythmic patterns are also observed in primary macrophages derived from mouse bone marrow and human monocytes. REV-ERB α knockdown disrupts NLRP3 expression patterns, consequently triggering alternations in IL-1 β and IL-18 secretion [93,94]. Pathologically, intestinal dysbiosis (*Candida* overgrowth) activates the JAK-STAT1 pathway via the pattern recognition receptor Dectin-3, which drives STAT1-dependent transcription of the *NLRP3*, *Caspase-1* genes and IL-1 β genes. Moreover, Dectin-3 enhances glycogen metabolism in MDSCs, supports glycolysis (manifested as lactate production and elevated ECAR), provides energy for NLRP3 inflammasome activation, and creates an inflammatory amplification loop [95], which affects the progression of T2D or obesity by interfering with insulin signaling and the normal metabolic function of adipose tissue [96]. Notably, the NLRP3 inflammasome can sense obesity-associated danger signals and contribute to obesity-induced inflammation and insulin resistance, linking metabolic stress to chronic inflammation [97].

Despite these advances, the tripartite relationships among microbiota rhythms, inflammasome dynamics, and metabolic health remain poorly understood and require systematic investigation.

Therapy

The underlying mechanism of host-microbiota circadian crosstalk provide a foundation for therapeutic intervention. By targeting these rhythms, it's possible to develop strategies to reset the disrupted crosstalk and restore immunometabolic health (Table 1).

Timing-based microbial rhythm restoration therapies

Nocturnal restricted feeding (RF) synchronizes with endogenous clocks and ameliorates inflammatory responses, and these effects are achieved by restoring the rhythmic expression of clock genes (e.g., *Per1/2*) in intestinal epithelial cells and reestablishing the metabolic rhythmicity of the microbiota (e.g., *Lachnospiraceae* and *Oscillospiraceae*) [98]. Moreover, this intervention promotes synchronization between bacterial metabolite rhythms and host nutrient uptake cycles. It increases the transcriptional activity of NFIL3 through the DC-ILC3-STAT3 immune pathway, thereby regulating the rhythmic expression of antimicrobial proteins [83]. These effects further stabilize the biological clock gene oscillations and ameliorate lipid metabolism disorders [99]. Differences in the improvement of disease by interventions at different time points of day have also been highlighted in studies of exogenous melatonin supplementation [100] and nocturnal RF [98]. Notably, microbiota transplanted during the donor feeding phase (but not the fasting phase) significantly improved nonalcoholic steatohepatitis (NASH) and restored the circadian rhythmicity of the gut microbiota [101]. These findings underscore the importance of intervention at different time points of day (e.g., night-time feeding, drugs, etc.) to manage metabolic disease by remodeling microbial rhythms.

Feeding-based microbial rhythm restoring therapies

Emerging therapies have the capacity to rescue dysregulated microbial circadian rhythms, thereby improving metabolic health. Oral administration of miRNA-10a-5p significantly prevents diet-induced obesity and improves insulin sensitivity by reinstating the rhythm of clock gene (e.g., *Clock*, *Per2*, *Cry1*) expression and microbial genera fluctuations (e.g., *Oscillospira*, *Lachnospiraceae*),

[102]. Moreover, taurine normalizes downregulated *Per1* expression in pancreatic β -cells, improves glucose-insulin homeostasis, and stabilizes 24-hour plasma insulin and leptin rhythms, demonstrating therapeutic potential for circadian realignment in individuals with obesity and diabetes [103]. Similarly, exogenous melatonin ameliorates HFD-induced intestinal dysbiosis and partially rescued the circadian rhythmicity of biological clock genes (e.g., *Clock*) and lipid indices (e.g., triglycerides) by restoring the abundance and diurnal fluctuations of specific genera of bacteria (e.g., *Lactobacillus* and *Bacteroides*) in the study of Yin *et al.* [100]. In addition, dietary fiber can induce the proliferation of beneficial bacteria, such as *Lactobacillus*, increase the circadian expression of antimicrobial peptides (e.g., REG3 γ) through a MyD88-dependent pathway, affecting the rhythmicity of bacterial adhesion to the colonic mucosal surface and thus modulating the immune barrier and metabolic gene rhythms in the intestinal epithelium [104]. Moreover, short-chain fatty acids (SCFAs) enhance barrier integrity, inhibit histone deacetylase (HDAC) and activate free fatty acid receptors (FFARs). Through these actions, they regulate enteroendocrine hormone secretion, and affect the metabolic state of the body by suppressing appetite and improving insulin metabolism [104].

Microbial stability and diagnostic potential

Approximately 70% of core strains in an individual's gut microbiota remain after one year, and extrapolated modeling suggests that the microbiota can maintain stability for decades. Moreover, the gut microbiota show dynamic stability across time scales, and changes in composition are more strongly associated with physiological status (e.g., changes in body weight) than with time intervals alone [105]. The potential of dynamic changes in the gut microbiota as sensitive markers of host metabolism and tools for long-term health monitoring has been confirmed. In patients with rheumatoid arthritis [106], *P. distasonis* and its metabolite GLY show circadian rhythmic fluctuations (increased concentrations during the daytime or active periods and decreased concentrations during the nighttime or resting periods) and are significantly negatively correlated with serum inflammatory factors and RA disease activity. This rhythmic profile could be used as a novel biomarker for the dynamic monitoring of disease activity. These findings suggest a role for gut microbiota rhythms in future disease typing, precise subtype

Table 1. Therapeutic strategies targeting microbial circadian rhythms

Therapy	Strategy	Mechanism	Reported effects
Timing-based microbial rhythm restoring therapies	Nocturnal restricted feeding	Restores host clock and microbial rhythms via feeding pattern	Reduces intestinal inflammation, restores rhythmic gene expression
	Time-restricted microbiota transplantation	Aligns microbiota transfer with donor feeding phase	Improves NASH, restores microbial rhythms
Feeding-based microbial rhythm restoring therapies	miR-10a-5p	Restores oscillations of clock genes and microbial genera	Improves insulin sensitivity, prevents diet-induced obesity
	Taurine	Normalizes PER1 expression in β -cells, restores insulin rhythmicity	Enhances glucose tolerance, reduces metabolic disorder
	Melatonin	Modulates microbial abundance and rhythmicity	Ameliorated HFD-induced intestinal dysbiosis, restores circadian rhythms
	Dietary fiber	Increases beneficial bacteria, promotes rhythmic AMP expression via MyD88	Strengthens barriers, modulates immunometabolic gene rhythms
Diagnostic potential	Rhythmic microbial metabolites	Circadian fluctuation correlates with disease severity	May guide disease staging and chronotherapy

diagnosis and disease severity assessment. This combination of stability and metabolic sensitivity positions microbial rhythms as valuable tools for precision diagnostics and chronotherapy development.

Discussion

The intricate interplay between host circadian rhythms and the gut microbiota underscores a fundamental biological synchrony critical for systemic immunometabolic homeostasis. Our review synthesizes evidence that host clocks hierarchically coordinate microbial oscillations through feeding patterns and immune surveillance, whereas microbial metabolites and temporal adherence patterns reciprocally regulate immunometabolic responses. Disruption of this bidirectional crosstalk through genetic clock ablation, jet lag, or HFDs reprograms oscillation in the microbiota. These perturbations culminate in systemic metabolic disturbances, exemplified by obesity, insulin resistance, and diabetes.

Notably, the implications of circadian host-microbiota interactions extend beyond local gastrointestinal effects to encompass systemic physiological regulation via axes such as the gut-brain and gut-lung pathways. Metabolites produced by the gut microbiota, such as SCFAs, exhibit rhythmic secretion patterns. Functioning as signaling molecules, SCFAs exert effects on distant organs via the bloodstream while simultaneously transmitting temporal signals through pathways including the gut-brain axis, thereby regulating organ function. Among SCFAs, acetate activates chromaffin cells in the gut to release serotonin, which in turn activates 5-HT₃ receptors on vagal afferent fibers. This signal travels via the vagus nerve to brain regions including the dorsal raphe nucleus (DRN) and locus coeruleus (LC), thereby influencing mood regulation and stress responses [107,108]. Additionally, propionic acid regulates appetite by stimulating L cells in the colon to release the appetite-suppressing hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1). These hormones act via the bloodstream on the brain's appetite regulation center, thereby reducing food intake and improving energy balance and metabolic health [109]. Aside from gut-brain pathway, the gut-lung axis mediates remote immune regulation concurrently. The gut microbiota confers broad protection against respiratory infection by priming systemic immune responsiveness through microbial stimulation of gut TLRs and NOD-like receptors [110–113]. Additionally, segmented filamentous bacteria (SFB) reprogram alveolar macrophage function and enhance antiviral immunity by reducing influenza virus-induced pro-inflammatory gene expression [114]. Interestingly, it was found that time-restricted feeding (TRF) reinforces microbial diurnal rhythms and delays lung tumor growth in mice via immunometabolic reprogramming [115], while circadian disruption induces gut dysbiosis and facilitates lung metastasis of colorectal cancer via accumulation of myeloid-derived suppressor cells (MDSCs) and impairment of CD8 T cell function [116].

These findings collectively highlight the central role of temporally structured host-microbiota crosstalk in maintaining health and triggering disease across multiple organ systems. However, key questions remain regarding the precise mechanisms through which specific microbial taxa interface with clock components to regulate immunometabolic pathways. The transmissibility of metabolic phenotypes via microbiota transplantation further underscores the therapeutic potential of targeting microbial rhythms. Future research should prioritize clarifying how microbiota-derived tem-

poral signals coordinate inter-organ communication. Clinically, optimizing time-restricted feeding windows and developing microbiota-directed chronotherapies could restore ecological balance. Ultimately, understanding host-microbiota circadian crosstalk not only refines our understanding of metabolic disease etiology but also offers new perspectives for precision therapies.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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