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New Awareness of the Interplay Between the Gut Microbiota and Circadian Rhythms

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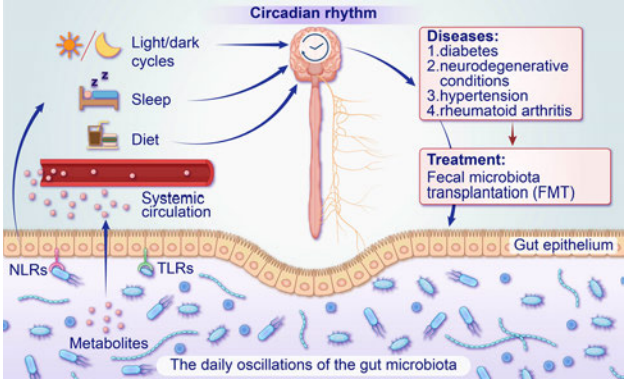
Abstract

Circadian rhythms influence various aspects of the biology and physiology of the host, such as food intake and sleep/wake cycles. In recent years, an increasing amount of genetic and epidemiological data has shown that the light/dark cycle is the main cue that regulates circadian rhythms. Other factors, including sleep/wake cycles and food intake, have necessary effects on the composition and rhythms of the gut microbiota. Interestingly, the gut microbiota can affect the circadian rhythm of hosts in turn through contact-dependent and contact-independent mechanisms. Furthermore, the gut microbiota has been shown to regulate the sleep/wake cycles through gut-brain-microbiota interaction. In addition to diabetes, the gut microbiota can also intervene in the progression of neurodegenerative diseases through the gut-brain-microbiota interaction, and also in other diseases such as hypertension and rheumatoid arthritis, where it is thought to have a spare therapeutic potential. Even though fecal microbiota transplantation has good potential for treating many diseases, the risk of spreading intestinal pathogens should not be ignored.



K e y w o r d s: circadian rhythm, the gut microbiota, metabolism, gut-brain-microbiota interaction, fecal microbiota transplantation

Introduction

Jeffrey Hall, Michael Rosbash, and Michael Young have been collectively honored with the 2017 Nobel Prize in Physiology or Medicine for their breakthrough discoveries regarding the regulation of the circadian rhythm. Michael Rosbash has put forward the theory that the internal clock plays a crucial role in influencing various aspects of our health, including the aging process, diabetes, and chronic diseases (Burki 2017). Earth's rotation results in day/dark cycles, known as the circadian rhythm. Under conditions of continuous exposure to either light or darkness, circadian rhythms can maintain consistent oscillations over 24 hours. The suprachiasmatic nucleus (SCN) at the bottom of the hypothalamus receives external daytime information (light/dark cycles) through the retina and synchronizes this information (Hastings et al. 2020). The SCN directly controls the central biological clock, as well as the peripheral clock in the surrounding tissues (such as the gastrointestinal tract and liver) (Voigt et al. 2016; Astiz et al. 2019; Blume et al. 2019). Interestingly, feeding can impact peripheral clocks independent of the SCN and influence the expression of key clock genes (Patke et al. 2020; Taleb and Karpowicz 2022).

The majority of human microbiota exists in the gastrointestinal tract, accounting for 97% of the total, with the colon being the primary site, housing a rich diversity of Firmicutes and Bacteroidetes (Sender et al. 2016; Rinninella et al. 2019). The gut microbiota (GM) mediates a wide range of physiological functions, and any disruption in its composition can lead to the

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development of diseases. Furthermore, the metabolites produced by the GM can influence the endocrine and nervous systems through the gut-brain-microbiota (GBM) interaction, which explains the close association between GM and metabolic, cardiovascular diseases, and central nervous system diseases (Rahman et al. 2022). In this review, we have summarized several factors contributing to disruptions in host circadian rhythms, such as light/dark cycles, sleep patterns, and dietary impact on GM. Conversely, the GM can also regulate host circadian rhythms, including sleep/wake cycles, through the GBM. Additionally, we have discussed the therapeutic potential of targeting GM in treating metabolic disorders, neurological diseases, hypertension, and rheumatoid arthritis. We provide the latest insights into these treatment strategies.

What is the molecular clock?

At the molecular level, circadian oscillations are generated by a complex network of genes called "clock genes". Circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator protein-1 (BMAL1, also known as ARNTL) serve as the central genes regulating the circadian rhythm in mammals. They are pivotal in orchestrating the biological processes that follow a 24-hour cycle. CLOCK and BMAL1 proteins come together to form a heterodimer, often called the "positive arm", in the cytoplasm. This heterodimer then drives the transcription of clock-controlled genes, including period circadian regulators (PERs), cryptochrome circadian regulators (CRYs), reverse erythroblastosis virus (REV-ERBs), retinoic acid receptor-related orphan receptor (RORs), nuclear factor interleukin-3-regulated protein (NFIL3), and D-box binding protein (DBP). Significantly, PER and CRY proteins can assemble into dimers, which subsequently inhibit the transcriptional activity of the CLOCK/BMAL1 complex. This exemplifies the fundamental mechanism of negative feedback regulation within the biological clock gene network (Angelousi et al. 2019; Stanton et al. 2022). The network is shown in Fig. 1.

The circadian mechanism consists of a histone acetyltransferase activator composed of CLOCK/BMAL1 and E-box motifs (CACGTG) to regulate transcription genes, such as CRYs, PERs, DBP, REV-ERBs, and other clock-controlled genes (CCGs). Among them, CLOCK/BMAL1 positively regulates the expression of other circadian regulators like PERS and CRYs. In the presence of light during the daytime, PER and CRY proteins form dimers and bind to the CLOCK /BMAL1 complex located on the E-box, ultimately inhibiting transcription. In contrast, during the nighttime, the de-dimerization of PER and CRY proteins occurs, lead-

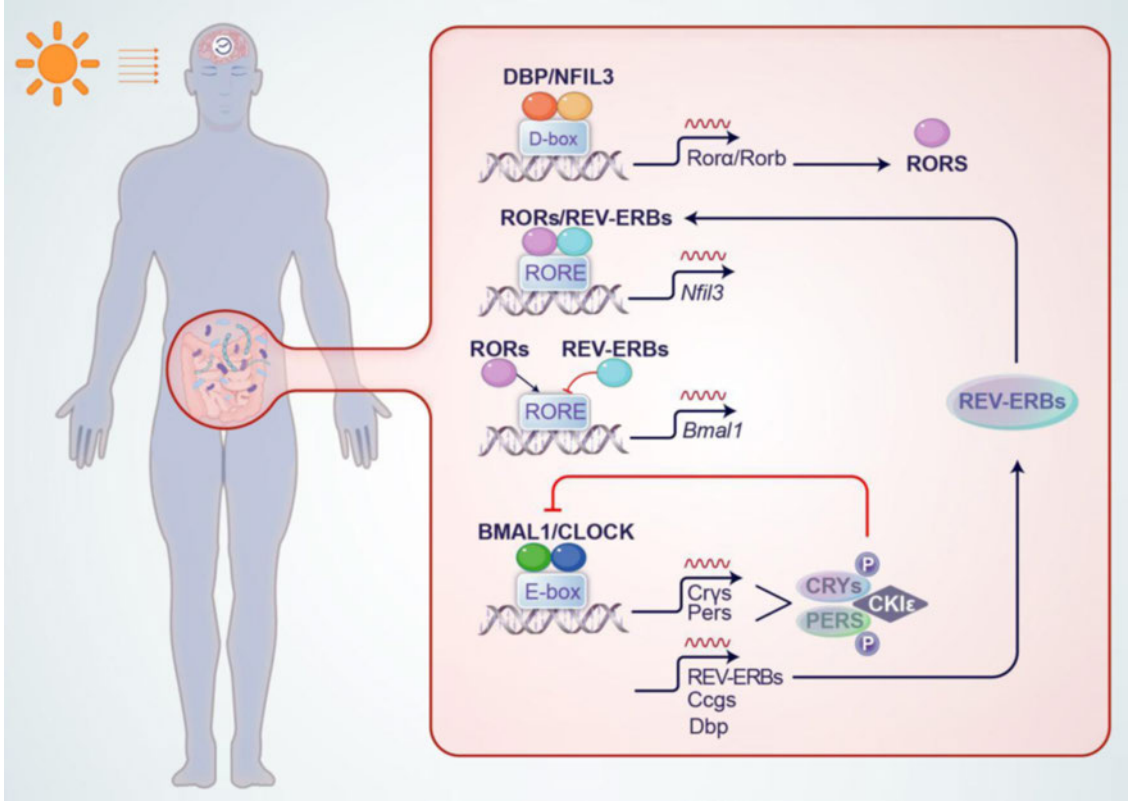

Fig. 1. The network of circadian rhythms.

Table I
Evidences for bacterial circadian rhythms relevant to human health.

Bacteria	Circadian components/time-dependent host response	References
Streptococcus pneumoniae	dependent on BMAL1 in Clara cells enhanced clearance at ZT12	Gibbs et al. 2014
Chlamydia trachomatis	enhanced clearance at ZT15	Lundy et al. 2019
Helicobacter pylori	enhanced lymphocyte migration to lymph nodes at ZT7	Druzd et al. 2017
Enterobacter aerogenes	swarming and motility rhythms	Paulose et al. 2016
Pseudomonas putida	a putative kaiC homolog was found in the genome of *Pseudomonas putida* KT2440 by bioinformatics analyses	Soriano et al. 2010
Escherichia coli	receptors for blue light	Gomelsky and Klug 2002
Legionella pneumophila	kaiB and kaiC-encoding genes	Loza-Correa et al. 2010
Salmonella Thyphimurium	enhanced clearance at ZT16	Bellet et al. 2013
Listeria monocytogenes	enhanced clearance at ZT8 dependent on BMAL1 in Ly6C^{hi} monocytes	Nguyen et al. 2013

ZT – the time (hour) for receiving light

ing to the reduction of inhibition towards the Bmal1/CLOCK factors. Casein Kinase 1 ε (CK1ε) is responsible for phosphorylating the PER and CRY proteins, which promotes their degradation. This is the first circadian transcription-translation feedback loop. RORs and REV-ERBs comprise the second circadian loop by competitively binding to the RORE element and regulating BMAL1 expression. RORs can activate BMAL1, while REV-ERB acts as a repressor of BMAL1 transcription. Additionally, DBP and NFIL3 form a heterodimer and bind to the D-box to activate the transcription of RORs.

The daily oscillations of the GM

The gut, primarily the colon, is home to the majority of the microbiome, hosting over 100 trillion bacteria from a diverse range of more than 1,000 species (Weger et al. 2019). The GM predominantly comprises Firmicutes and Bacteroidetes, followed by Proteobacteria, Actinobacteria, and Acidobacteria, which show interindividual variation (Rinninella et al. 2019). In both humans and mice, Firmicutes were predominant during the day, while Bacteroidetes were more prevalent at night (Liang et al. 2015; Reitmeier et al. 2020). Continuous exposure to light in mice leads to a reduction in the diversity of GM and alterations in the abundance of various taxa. Specifically, there is an observed increase in the abundance of *Ruminococcus torques* and a decrease in the abundance of *Lactobacillus johnsonii* (Deaver et al. 2018). However, even without exposure to the light/dark cycle, fluctuations in environmental factors such as nutrient accessibility, dietary habits, host-produced antimicrobial peptides, and autoantibodies can impact the microbiota (Wollmuth and Angert 2023)

In photosynthetic bacteria, such as cyanobacteria, a circadian clock mechanism has been specifically identified. The circadian rhythmicity is maintained by three central clock genes: kaiA, kaiB, and kaiC (Bhadra et al. 2017). Nevertheless, in non-photosynthetic bacteria, especially those significant for human health, there are only few examples describing the presence of circadian rhythm in bacteria (Table I). Fortunately, Diallo et al. (2022) made significant progress in the field of circadian rhythms in non-photosynthetic bacteria last year. They identified RadA as the homolog of KaiC in *Escherichia coli* by bioinformatics analysis. RadA expression exhibited a circadian pattern lasting at least 3 days, reaching its highest point in the morning. At the same time, the circadian oscillations of gene expression were absent in *E. coli* radA mutants (Diallo et al. 2022). The forthcoming research may unveil more GM with circadian rhythms and shed light on their underlying mechanisms. This could enable us to investigate whether the intrinsic circadian rhythms in GM hold potential as a therapeutic approach in metabolism.

Two inseparable ropes: circadian rhythms and the GM

The complex interplay between the host's GM and circadian rhythms is subject to various factors, and alterations in one component can significantly influence the other, ultimately impacting the host's sleep, metabolism, and other related processes (Pearson et al. 2020). The gut-brain axis (GBA), a two-way link between the GM and the brain, functions through neural, immune, and endocrine pathways. In the past 15 years, our understanding of the traditional GBA has evolved into a systems biology perspective of the gut-brain-microbiota

(GBM) interaction. The two main barriers to GBM are the intestinal barrier and the blood-brain barrier (BBB). Both barriers are dynamic, and factors including the GM, inflammatory signals, and stress all have the capability to modulate their permeability (Asadi et al. 2022; Mayer et al. 2022).

Impact of circadian rhythms on the GM. Here, our primary focus is exploring the impact of various internal and external factors, such as light/dark (LD) cycles, sleep patterns, and dietary habits, on GM.

Light/dark cycles. The LD cycles are the most crucial stimulus for regulating the internal clock of mammals, including humans. With the rapid pace of modern life, our lifestyles have undergone significant changes. Factors such as increased exposure to artificial light at night, disrupted eating habits, jet lag, and night shift work have become common. Unfortunately, these aspects can disrupt the natural LD cycle, impacting our circadian rhythms. Disrupted circadian rhythms have been associated with various adverse effects, such as metabolic dysregulation. (Sinturel et al. 2020; Lee et al. 2021).

In the study conducted by Zhen et al. (2023), the researchers explored the impact of different LD cycles (LD light hour/dark hour) on the interconnected rhythms of GM, hypothalamic, and hepatic clock genes, as well as immunity and metabolism. They employed multi-omics approaches to investigate four irregular LD cycles (LD0/24, LD24/0, LD8/16, LD16/8) along with a normal LD cycle (LD12/12). Their findings revealed that irregular LD cycles disrupted the rhythmicity of central clock genes while having minimal effects on the diurnal expression of peripheral clock genes in the liver, including Bmal1. Interestingly, certain GM species such as *Limosilactobacillus*, *Actinomyces*, *Veillonella*, *Prevotella* and *Campylobacter* were found to have the ability to regulate hepatic circadian rhythms even under irregular LD cycles. Furthermore, the study demonstrated that GM could influence immune and metabolic disorders caused by circadian dysregulation. These insights offer potential targets for developing probiotics specifically tailored for individuals with circadian disruption, such as shift workers (Zhen et al. 2023).

Constant darkness, an extreme alteration of the LD cycle, often brings to mind melatonin (MT), as it is primarily produced during the nighttime. MT is an "arm" of the biological clock, as it reacts to signals from the SCN. The rhythm of MT secretion provides insights into the state of the clock's phase (i.e., the internal time of the clock relative to external time) and amplitude (Arendt 2019). Increasing evidence suggests that MT can influence the typical composition and quantity of the gut bacterial population, especially in various pathological states such as inflammatory bowel diseases. Following MT administration, the ratio of Firmicutes (such as *Ruminococcaceae* and *Coprococcus*), *Bifidobacterium* and *Lactobacillus* increased, Proteobacteria and *Streptococcus* spp. decreased (Kim et al. 2020; Jing et al. 2022). Additionally, MT possesses robust antioxidative properties, effectively eliminating reactive oxygen species. Its lipophilic nature allows it to readily interact with the brain and the GM through the BBB (Liu et al. 2023).

Sleep. Sleep problems such as jet lag, delayed bedtimes, and sleep fragmentation often occur in contemporary people, and these phenomena always result in circadian disruption. Sleep fragmentation is associated with increased mean blood pressure in mice and changes in the composition of the GM. The Bacteroidetes ratio was decreased, while the Proteobacteria ratio was increased. Moreover, midsleep fragmentation was also characterized by lower alpha diversity (Maki et al. 2020), and the disturbance of the GM caused by short sleep is related to lower expression of HD5 (Shimizu et al. 2023). Recently, many studies have identified that disturbed sleep has the potential to impact the balance and stability of GM. Liu et al. (2020) conducted a study that simulated an irregular sleep/wake cycle in young adults representative of the contemporary population. They defined microbial taxa from their fecal samples by 16S rRNA gene amplicon sequencing, and they found that the functions of the microbes were enriched during the irregular sleep/wake cycle rather than the relative abundances of the microbes (Liu et al. 2020).

Diet. While the SCN serves as the central regulator of the circadian system, peripheral clocks in organs can become disconnected from SCN control due to external factors, such as food intake (Kolbe et al. 2019). The arrangement and makeup of the GM can adapt quickly to shifts in macronutrients within 24 to 48 hours, demonstrating a remarkable level of flexibility. However, these adaptations may only be temporary and last for shorter durations. On the other hand, more lasting changes to the GM composition may necessitate a more extended period of adherence to a specific dietary pattern (Romaní-Pérez et al. 2021). Animal-based diets increase the quantity of bacteria such as *Alistipes* spp. and *Bilophila* spp. because of bile tolerance. Diets with a high intake of fiber and carbohydrates increase the quantity of *Bifidobacterium* spp., Bacteroidetes and *Akkermansia muciniphila*. Diets high in fat can increase the propagation of Firmicutes and Proteobacteria (Schmalle and Lorentz 2020; Choi et al. 2021; Gutierrez Lopez et al. 2021). It was found that a high-fat diet can decrease the alpha diversity of the GM and lead to a decrease in the number of microbial species exhibiting diel oscillation patterns of relative abundance (Frazier et al. 2022). Although we hold the view that a high-fat diet is not favorable for overall health, it is worth noting that mice subjected to a high-fat diet but restricted to nighttime feeding during their active phase exhibit a noteworthy rise in the diversity of gut bacterial

species displaying diel patterns of relative abundance, in contrast to mice on an unrestricted high-fat diet. This highlights the potential significance of feeding time and frequency on the composition of GM. Moreover, it is crucial to acknowledge that mistimed eating can have detrimental effects on metabolic well-being (Challet 2019; Wollmuth and Angert 2023).

The role of the GM in the regulation of circadian rhythms. ***Mechanisms of GM regulation of circadian rhythms.*** In the small and large intestines, the absence of GM in germ-free (GF) or antibiotic-treated mice can alter the expression of circadian genes or reduce the number of genes that display rhythmic expression. Schmalle and Lorentz (2020) showed that antibiotic-treated or GF mice exhibit reduced expression of Bmal1 and Cry1 and increased expression of Per1 and Per2 in the intestinal epithelium under normal LD cycles. In contrast, the absence of GM increases the number of genes with rhythmic expression in the liver. Moreover, many serum metabolites exhibit daily rhythms, and the presence or absence of GM can influence these rhythms. Several metabolites lose their rhythmicity in the serum of GF and antibiotic-treated mice.

There are two primary mechanisms by which the GM can influence host circadian rhythms: contact-dependent and contact-independent. Contact-dependent mechanisms involve direct interactions between gut bacteria and gastrointestinal cells, leading to the activation of pattern recognition receptors like NOD-like receptors (NLRs) and Toll-like receptors (TLRs) (Bishehsari et al. 2020). TLRs can detect bacterial metabolites and incorporate them into the rhythmic processes of c-Jun N-terminal kinase (JNK) and inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ). This integration helps inhibit PPARα-mediated activation of REV-ERBα (Liang and FitzGerald 2017). This signaling rhythm then triggers the periodic corticosterone production by intestinal epithelial cells (IECs) in the ileum. However, if no microbiota is present, the constitutive expression of PPARa causes the IEC clock to malfunction, leading to excessive production of corticosterone (hypercortisolism) (Henao-Mejia et al. 2013). Contact-independent mechanisms, on the other hand, rely on small molecular metabolites produced by the GM, such as bile acids and short-chain fatty acids (SCFAs), to act as mediators (Bishehsari et al. 2020). The metabolites of the GM influence the host's circadian rhythm, such as lactate, SCFAs, and MT (Paulose and Cassone 2016). SCFAs, mainly acetate, propionate, and butyrate, should be noted (Leone et al. 2015; Parkar et al. 2019). Recently, Fawad et al. (2022) discovered that PER2::LUC enteroids exposed to SCFAs (such as acetate, isovaleric acid, propionate, butyrate) resulted in significant phase delays in the abundance of PER2::LUC compared to untreated controls in mouse enteroids. Their study demonstrated that SCFAs generated by host microbes directly alter host circadian rhythms ex vivo without involving other intestinal cell types, such as immune and vascular. Specific SCFAs induce distinct patterns of circadian entrainment in intestinal epithelial cells, affecting parameters like circadian rhythm amplitude and phase shift magnitude while maintaining a roughly 24-hour period. A similar phenomenon was observed in human enteroids, colonoids exposed to microbial metabolites basolaterally, and a human-transformed colonic cell line (Caco-2). Furthermore, SCFA alters the host clock through HDAC inhibition (Fawad et al. 2022).

The GM can influence circadian rhythms via the GBM. As previously discussed, circadian rhythm disruptions, such as LD cycle and dietary patterns, can significantly impact the GM. Disruptions in LD cycle can influence the sleep state to some extent (Sgro et al. 2022), and the GM possesses the ability to react to sleep/wake cycle via the GBM. The GM and their metabolites can impact the neurons of the enteric nervous system and interact with the afferent pathways of the vagal nerve, which in turn affects the neural circuits involved in sleep/wake regulation. Additionally, immune mediators derived from the gut can be transmitted to the brain through the bloodstream and afferent vagal pathways, influencing sleep. For instance, lipopolysaccharides (LPS) and SCFAs can modulate immune cell responses and interact with inflammatory homeostasis, triggering microglia activation that, in turn, affects sleep/wake regulation. Apart from LPS and SCFAs, the regulation of the sleep/wake cycle is also influenced by other metabolites, including serotonin (5-HT), orexin, and histamine. Their collective actions contribute to the overall orchestration of the sleep/wake cycle (Wang et al. 2022).

GM, a new frontier in human disease treatment

As we all know, unhealthy dietary practices could contribute to the development of metabolic disorders, and diet is the most critical determinant in shaping the configuration of the GM. One of the most prominent illustrations of an unhealthy eating pattern is diabetes. The presence of *Akkermansia*, *Bifidobacterium*, *Roseburia*, *Bacteroides* and *Faecalibacterium* showed a negative association with type 2 diabetes (T2D). On the other hand, the presence of *Ruminococcus*, *Fusobacterium*, and *Blautia* genera exhibited a positive association with T2D (Gurung et al. 2020). In addition, notable disparities in the composition of GM have been observed between individuals with prediabetes and those with diabetes (Wu et al. 2020).

In recent years, there has been a surge of interest in exploring the role of the GM, often referred to as the

"forgotten organ", in various diseases. This has led to many studies investigating the potential use of GM-based therapies for treating diabetes. As an illustration, fecal microbiota transplantation (FMT) is a technique that involves transferring healthy fecal microbes from a donor to the gastrointestinal tract of a patient in order to modify the GM and address the disease (Huda et al. 2021). Scientific reports indicate that FMT can improve plasma metabolic parameters, including enhanced peripheral and hepatic insulin sensitivity (Antushevich 2020). However, in a double-anonymized study involving 22 obese patients who received FMT capsules derived from a single lean donor, no significant changes in mean BMI were observed after 12 weeks.

Nonetheless, the study revealed a sustained decrease in taurocholic acid stool levels, and the patients' bile acid profiles began to resemble those of the donor more closely (Allegretti et al. 2020). This indicates that the utilization of FMT alone is insufficient for the treatment of diabetes and the reduction of body weight in diabetic patients. Moreover, we are still in the early stages of understanding how GM can be harnessed to effectively prevent the onset and progression of diabetes (Iatcu et al. 2021).

FMT has shown promising results not only in treating diabetes but also in addressing cancer and psychiatric disorders (Antushevich 2020), and GBM can provide a plausible explanation for this treatment. In recent years, the investigation of the GBM has brought to light valuable insights into epilepsy and neurodegenerative conditions, including Alzheimer's disease (AD) and Parkinson's disease (PD). For instance, it has been shown that FMT improves both motor and non-motor symptoms in patients with PD (Cheng et al. 2022). Moreover, exogenous MT can be utilized as an additional treatment to enhance cognition in patients with AD, potentially due to its ability to modulate the composition of GM (Chen et al. 2021). It is worth noting that these diseases are closely associated with circadian rhythms. The circadian clock genes in the brain, beyond being confined to the SCN, are involved in controlling a range of brain functions, including synaptic conduction of neurons (McMartin et al. 2021). This implies that the GBM facilitates the intricate bidirectional association between the GM and circadian rhythms. Overall, FMT is considered a safe therapeutic approach, although occasional short-term adverse reactions, such as diarrhea, may occur. However, some potential risks should be taken into account. The transmission of opportunistic pathogens or viruses through filtered or liquefied fecal matter directly or indirectly administered into the colon via capsules. The U.S. Food and Drug Administration (FDA) has reported two cases of infections caused by *E. coli* producing extended-spectrum beta-lactamase (ESBL), one of which resulted in death, and six cases of infections caused by *E. coli* producing Shiga toxin, one of which also resulted in death. These two cases were potentially transmitted through donor fecal matter, but the fecal matter was not screened for ESBL (Gupta et al. 2021; Park and Seo 2021). Therefore, prior to FMT treatment, it is crucial to handle these risk factors with caution, emphasizing the need for the development of comprehensive, advanced, and efficient screening methods.

Additionally, other diseases, such as 1) hypertension and 2) rheumatoid arthritis (RA), have also been shown to be closely associated with dysbiosis of the GM. 1) The GM can communicate through the enteric nervous system with the brain. Dysbiosis associated with intestinal epithelial barrier dysfunction can trigger systemic inflammation and activate mechanisms related to blood pressure regulation, such as the renin-angiotensin-aldosterone system, the autonomic nervous system, and the immune system (O'Donnell et al. 2023). This mechanism suggests that GM is likely a key factor involved in blood pressure regulation. Modulating the GM in hypertensive patients through appropriate means may enhance the effectiveness of antihypertensive medications. 2) Disease-modifying anti-rheumatic drugs, such as sulfasalazine, etanercept, and methotrexate, have been shown to modulate the GM and alleviate symptoms beneficially (Zhao et al. 2022). Furthermore, Zeng et al. (2021) successfully treated a case of refractory RA with FMT, providing strong evidence for the influential role of GM in immune system regulation.

Conclusions

In this review, we described that the circadian rhythm-GM interaction is a mutual feedback system where one participant's actions elicit a reaction from the other. Given the significant associations between circadian variations in GM and the onset of physiology and diseases, it is possible that GM could serve as a promising diagnostic tool for monitoring disease progression in humans. We have summarized the mechanisms underlying the involvement of GM in certain metabolic and neurological disorders and discussed the advantages and challenges of treatment options, including FMT. A study based on drosophila models found that even with minimal changes in the rhythmicity of their gut microbiota after timed feeding, this is entirely different from the phenomenon observed in mammalian GM that follows a day/night cycle – moreover, timed feeding compromised the flies' responses to stressors. These findings were somewhat surprising, yet there is compelling evidence that GM plays a significant role in tempering the response of the gut clock to fluctuations in the day/night cycle. As a result, it facilitates the harmonization of cir-

cadian rhythms between the gut and the brain, ensuring their synchronization (Zhang et al. 2023). The conclusions we have discussed above also serve as a reminder that it is essential to highlight that there is a future need to address the challenge of effectively tracking the dynamic fluctuations in the GM and distinguishing between changes induced by dietary factors and those influenced by external circadian rhythms in order to understand their implications in disease better.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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