

Gut microbiota: closely tied to the regulation of circadian clock in the development of type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM), a worldwide epidemic disease, has caused tremendous economic and social burden, but the pathogenesis remains uncertain. Nowadays, the impact of unrhythmic circadian clock caused by irregular sleep and unhealthy diet on T2DM has been increasingly studied. However, the contribution of the endogenous circadian clock system to the development of T2DM has not yet been satisfactorily explored. It is now becoming clear that the gut microbiota and the circadian clock interact with each other to regulate the host metabolism. Considering all these above, we reviewed the literature related to the gut microbiota, circadian clock, and T2DM to elucidate the idea that the gut microbiota is closely tied to the regulation of the circadian clock in the development of T2DM, which provides potential for gut microbiota-directed therapies to ameliorate the effects of circadian disruptions linked to the occurrence and development of T2DM.

Keywords: Gut microbiota; Circadian clock; Type 2 diabetes mellitus; Metabolites

Introduction

Diabetes mellitus, recognized as the “disaster of the 21st century” by the World Health Organization, has resulted in a tremendous economic and social burden.^[1] According to the latest data published by the International Diabetes Federation in 2019, there were approximately 463 million diabetes patients worldwide.^[2] Type 2 diabetes mellitus (T2DM) is the most common type of diabetes and is a collective consequence of both genetics and environment.^[1] In recent years, the prevalence of T2DM has been continuously increased due to dramatic lifestyle changes in response to the industrialization and development of modern society.^[1,3] Therefore, the pathogenesis of T2DM and more effective approaches to fight against it and its associated disorders need further exploration.

The circadian rhythm is coupled to the day-night light cycle as well as the feeding-fasting cycles through the circadian clock elements.^[4] Compelling evidence from observational studies and well-designed clinical trials has demonstrated that disruption of circadian rhythm involving irregular working schedules and unhealthy eating patterns is associated with an increased risk of T2DM via mechanisms related to impaired glucose control and compromised

insulin sensitivity.^[5-8] However, the contribution of the endogenous circadian clock system to the development of T2DM has not yet been satisfactorily explored.

The gut microbiota plays an irreplaceable role in digesting and absorbing food. It is now becoming clear that the gut microbiota and the circadian clock interact with each other to regulate the host metabolism.^[4,9] This review aims to summarize the current literature to explore the regulation of the circadian clock in the development of T2DM through the modulation of the gut microbiota and its metabolites. We propose that the gut microbiota and the alterations of its metabolites have an important impact on the circadian clock and the related regulation of the development of T2DM, which means that the gut microbiota may be a key element in the regulation of the circadian clock in T2DM. This review will help to highlight potential therapeutic strategies for T2DM.

What is the circadian clock?

In the 1980s, the periodic gene was successfully isolated from *Drosophila melanogaster*, and the molecular mechanisms controlling circadian rhythms were discovered by three scientists, Jeffrey C. Hall, Michael Rosbash, and Michael Young, whose findings explained how plants,

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animals, and humans adapt to their biological rhythms and keep pace with the earth's rotation. The circadian rhythm is an internal rhythmic pattern of approximately 24 h, which is formed by organisms based on the rotation of the earth to adapt to the periodic changes of the environment.^[9] All living organisms, including bacteria, fungi, plants, and animals, experience physiological changes regulated by endogenous circadian rhythms. These rhythms align biological functions with regular and predictable environmental patterns to optimize function and health.^[10-13] Simultaneously, the body resets its circadian rhythm by sensing cues from the outside world when the environment changes.^[14,15]

The circadian clock system is composed of a central clock and peripheral clocks. The central clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Known as the circadian master pacemaker, the SCN integrates inputs from the eyes mainly in the form of light and synchronizes circadian rhythms in the periphery through diffusible factors such as cortisol and melatonin as well as synaptic projections including sympathetic and parasympathetic signals. Widely found in all tissues of the body, including the intestines, liver, pancreas, kidney, adipose tissue, and skeletal muscle,^[16] plenty of peripheral clocks not only integrate signals from the central clock but are also entrained by environmental and behavioral factors, such as light,^[10] sleep,^[17,18] physical activity,^[19,20] and feeding,^[21] and metabolites to form their own autonomous rhythms and regulate the body's functions in a rhythmic manner.

In mammals, the intracellular circadian clock is maintained at the molecular level mainly by clock genes, most of which were confirmed to be transcription factors.^[22] A series of clock genes have been identified in humans, including circadian locomotor output cycles protein kaput (Clock), brain and muscle ARNT-like protein (Bmal1, also called Arntl), period circadian clock 1 (Per1), Per2, Per3, cryptochrome 1 (Cry1), and Cry2, which are the core components of a transcriptional-translational feedback loop (TTFL) [Figure 1].^[23,24] As the central drivers of the

molecular circadian clock, the heterodimeric transcription factors Clock and Bmal1 can trigger three Per genes, two Cry genes and reverse erythroblastosis virus α , as well as hundreds of clock-controlled genes (CCGs), by binding E-box motifs in a highly rhythmic manner, until accumulated Per and Cry proteins assemble into large heterotypic protein complexes to bind to Clock/Bmal1 and inactivate them.^[25,26] The TTFL regulates thousands of rhythmic cascades of transcriptional and post-transcriptional events throughout the body, including numerous events involved in metabolism, providing a connection between the circadian clock system and metabolic reactions.^[27]

Effects of circadian disruption on the development of T2DM

In the 1970s and 1980s, Prof. Panda explained that patients responded poorly to a glucose challenge in the evening but had no signs of diabetes when given the same challenge in the morning; even in healthy individuals, the glycometabolism associated with night-time meals was slower than that associated with morning meals, which is in line with his saying "There is a beautiful rhythm in glucose metabolism."^[28] In recent years, accumulating well-designed clinical trials and experimental studies have provided solid evidence explaining the inextricably intertwined role of circadian disruptions in the increased risk for the development of T2DM.^[29-31] This review focuses on the studies that have detected a potential relevant relationship between circadian disruption and the risk of T2DM in shift workers, the most notable representations of circadian disruption among modern people, and in the clock gene mutation models.

Evidence from clinical studies in shift workers

Increasing studies have concentrated on shift workers and their higher risk of T2DM because they are the most notable representation of circadian disruption among modern people due to their irregular working schedules and unhealthy eating patterns.^[32] The prevalence of shift work is also increasing rapidly as a result of industrialization and modernization.^[33] The past decade has seen a

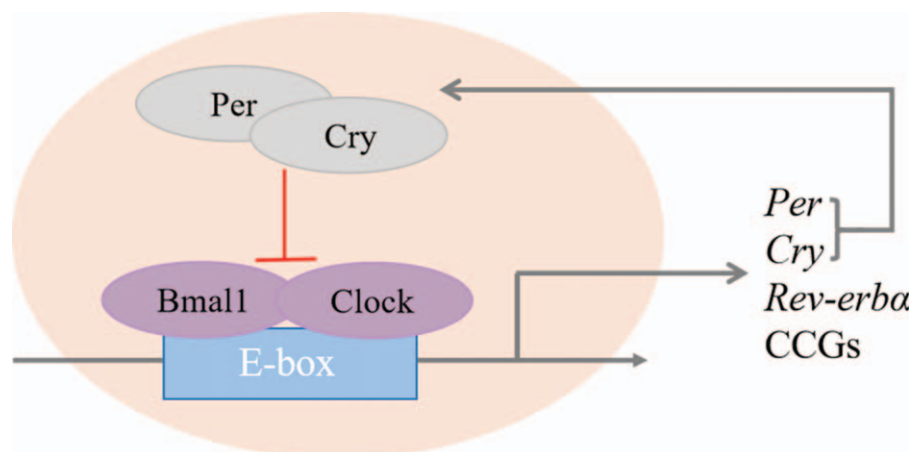


Figure 1: The molecular circadian clock. In the TTFL, positive elements are shown in purple, and negative elements are shown in gray. Clock: Circadian locomotor output cycles protein kaput; Bmal1: Brain and muscle ARNT-like protein; CCGs: Clock-controlled genes; Cry: Cryptochrome; Per: Period circadian clock; Rev-erba: Reverse erythroblastosis virus α ; TTFL: Transcriptional-translational feedback loop.

considerable increase in the literature regarding shift work.^[34-37] Several studies have verified that shift work is associated with reduced glucose tolerance,^[7,38] insulin resistance,^[39] and an increased risk of obesity,^[40] all of which are risk factors for T2DM. Subsequently, a number of epidemiological studies have investigated the direct link between shift work and T2DM.^[34-37] A recent meta-analysis of 12 such observational studies including 28 independent reports involving more than 200,000 participants reported that the risk of DM was increased by 9% for shift workers compared with individuals who had never been exposed to shift work.^[41] In fact, rotating shift work forces shift workers to adjust their body's functions according to the duty duration, thus leads them to be unable to adapt their body to the sleep pattern changes.^[42] Intriguingly, studies confirmed a stronger positive association of rotating shift work with the risk of DM than of other types of shift work (irregular shifts, night shifts, mixed shifts, and evening shifts).^[41] Moreover, because the frequency of rotating shift work is much higher than that of other types of shift work, researchers preliminarily speculated that the higher frequency of rotating shift work might be connected with a higher diabetes mellitus risk.^[41] In line with that speculation, Celine *et al*^[31] confirmed that the frequency of night shifts truly mattered; a greater average night shift frequency per month, especially rotating shift work including night shifts, was associated with an increase in T2DM odds in the comprehensive study of more than 270,000 individuals in the UK Biobank linking shift work patterns to 6770 prevalent T2DM cases. Another landmark study of rotating night shift work found a modestly increased risk of T2DM after extended periods of rotating night shift work in two prospective cohort studies with 18 to 20 years of follow-up focusing on more than 190,000 female nurses in the Nurses' Health Study (NHS) and NHS II.^[32] Two newly reported large US cohorts in the NHS and NHS II further suggested that among more than 140,000 female nurses, both rotating night shift work and unhealthy lifestyles were associated with a higher risk of T2DM after 22 to 24 years of follow-up, suggesting that most cases of T2DM could be prevented by adhering to a healthy lifestyle.^[34] Apart from studies among non-diabetic populations, researchers also found that patients with T2DM who performed night shift work had dramatically worse glycemic control with significantly higher hemoglobin A1c levels than those who performed day work or who did not work, after adjusting for multiple factors, including morning-evening preference, sleep duration, and diet, which were in accordance with earlier findings in T2DM patients.^[35]

Evidence from experimental models

Much more direct evidence demonstrating the links between circadian clock disruptions and the risk of T2DM comes from the various diabetes states and relevant metabolic abnormalities that occur in mice with targeted clock gene mutations.^[43-45] The awareness of the importance of the relationship between the circadian clock and glucose metabolism became apparent in 2005 when researchers found that homozygous *Clock* gene mutant mice not only had a severely disturbed diurnal feeding rhythm and became obese but also developed metabolic

syndrome characterized by hyperleptinemia, hyperlipidemia, hyperglycemia, and hypoinsulinemia, making individuals more prone to metabolic disorders, including T2DM.^[44] Another study also showed that a *Clock* gene mutation altered the expression of pancreatic genes, which in turn disrupted the regulation of the survival of insulin cells, and most importantly, caused diabetes mellitus due to defective β -cell function if the pancreatic clock was deleted conditionally at the very latest stage of stimulus-secretion coupling.^[46] However, different results have been discussed in other *Clock* mutant mouse models with no findings of signs of obesity or even weight loss or hyperlipidemia, but impaired glucose tolerance was tested.^[47,48] As a central transcription factor that regulates the circadian clock, *Bmal1*, when its function is lost, was also found to result in several metabolic anomalies linked to disruption in insulin and triglyceride levels.^[49] In most cases, *Bmal1* was knocked out tissue specifically in mice with the aim of determining whether the metabolic disorder was related to the disturbance of the central circadian clock in the SCN or the disruption of peripheral clocks. Deletion of *Bmal1* in the pancreas was found to make mouse models more likely to develop diabetes, suggesting the importance of peripheral circadian clocks.^[50] Intriguingly, although studies found increased accumulation of liver fat in liver-specific *Bmal1* knockout models, there still exists some uncertainty.^[45,51] Chaix *et al*^[45] showed that increased glucose clearance in hepatic *Bmal1* knockout mice was connected to high levels of fasting insulin and increased insulin sensitivity, while Jacobi *et al*^[51] revealed that hepatic *Bmal1* gene deletion led to insulin resistance. Deletion of *Bmal1* in adipocytes was also performed and not only showed a disruption in the normal feeding rhythm without alteration in the expression circadian clock genes (including *Bmal1*) in the SCN but also resulted in obesity, which was not observed with the deletion of *Bmal1* in the liver or pancreas.^[52] Glucose homeostasis was also disturbed in *Cry*-deficient mice. *Cry1* and *Cry2* double-knockout mice exhibited higher blood glucose and more severe impaired glucose clearance.^[45,53] Even mice lacking either *Cry1* or *Cry2* showed a notable disability in restoring normal blood glucose after glucose injections.^[53] The latest study also found that *Cry1* and *Cry2* double knockout mice were more prone to bodyweight loss.^[45] In contrast, *Per2*-deficient mice were vulnerable to obesity and a lack of diurnal feeding rhythm.^[54]

Collectively, evidence from both clinical trials in shift workers and experimental models has shown that chronic circadian misalignment due to disruptions in social and biological rhythms resulting from synchronizing to an irregular 24-h light/dark cycle and clock gene disruptions contributes to a higher risk of T2DM, which validates the crucial role of circadian disruption in the development of T2DM [Table 1]. Nonetheless, studies suggest several classically involved mechanisms, such as impaired glucose control and compromised insulin sensitivity, linking the role of circadian disruption to the development of T2DM; however, the specific mechanism in the process has not been satisfactorily understood. Since studies have recognized the inextricably reciprocal connection between the circadian clock and gut microbiota, this review explores

Table 1: Circadian gene mutations in mice model showing metabolic disorders.

Mutation genes	Metabolic disorders	References
<i>Clock</i>	Impaired glucose tolerance, reduced insulin secretion, hyperleptinemia, hyperglycemia, hypoinsulinemia	[44,46,47,48]
<i>Bmal1</i>	Increased glucose clearance, high levels of fasting insulin and increased insulin sensitivity or insulin resistance (liver-specific) Obesity (adipocyte-specific)	[45,49,50,51,52]
<i>Cry1/2</i>	Higher blood glucose and more severe impaired glucose clearance	[45,53]
<i>Per2</i>	Obesity	[54]

Clock: Circadian locomotor output cycles protein kaput; Bmal1: Brain and muscle ARNT-like protein; Cry: Cryptochrome; Per: Period circadian clock.

whether the gut microbiota is a key factor in the regulation of the circadian clock in the development of T2DM.

Gut Microbiota May Be a Key Element in the Regulation of the Circadian Clock in T2DM

A large number of studies have confirmed that circadian disruptions, involving the regulatory effects of light, sleep, feeding behavior, and stress, play important roles in the onset of diabetes.^[55,56] In the middle ages, Rambam, a famous philosopher and doctor, proposed the following guidelines for a healthy diet: “Eat like a king in the morning, a prince at noon and a farmer at dinner”; these guidelines remind people of the importance of feeding behavior in the nutritional state of the body.^[57] Feeding behavior consists of dietary content, food intake, and feeding time. There exists an intimate relationship between changes in feeding content and disturbance in the circadian clock, which has mainly been discussed in studies focusing on the role of the circadian clock in the abnormal glucose metabolism caused by high-fat diets (HFDs).^[58-60] Compared with normal diet-fed mice, the feeding rhythm of the mice in the HFD group was changed, which contributed to a greater food intake during the day (resting period) without increased activity, leading to the altered expression of circadian clock genes and downstream clock-control genes in peripheral clocks such as the liver, adipose tissue, pancreas, and kidney; thus, these changes led to disorders of glucose metabolism and T2DM.^[61,62] Another way, additionally, feeding time also impacts disorders of the circadian clock. The timing of food intake is largely determined by the endogenous timing mechanism of the body, as well as by food availability, sense of hunger and satiety, social habits and convenience. In recent years, growing evidence has determined that mealtime may have an effect on a variety of physiological processes, including the sleep-wake cycle, behavior, core body temperature, alertness, and energy metabolism.^[63] Studies revealed that mice fed HFDs during the day (sleeping period) accumulated much more body mass and developed worse glucose tolerance than those fed a HFD during the night (active period). Additionally, changes were observed in the expression of clock genes in peripheral clocks, including the liver and adipose tissue, leading to circadian rhythm disorder without the participation of the central clock.^[64,65] The external feeding schedule of daytime restricted feeding shifted the serum glucose rhythm without involving the SCN rhythm and altered the

expression of clock genes in streptozotocin-induced diabetic rats.^[64] Furthermore, studies found that mice that skipped breakfast had an adversely affected peripheral liver clock and expression of downstream CCGs, while those that skipped dinner had disordered lipid metabolism and adipose tissue aggregation.^[66] In line with these findings, a randomized clinical trial also revealed that breakfast-skippers showed significantly higher post-prandial blood glucose compared to those who consumed three meals per day.^[67]

Taken together, the evidence above indicates that circadian disruption induced by the irregular administration of food might be crucial in mediating glucose and lipid metabolism, which is causally linked to the development of T2DM. Indeed, feeding behavior is a powerful entrainer in metabolic tissues, particularly the intestine,^[68] which further emphasizes the role of the gut microbiota.

Gut microbiota and its own oscillation rhythm

The gut microbiota, the general term for the microbial community that colonizes the intestinal tract, is a community of up to 100 trillion bacteria containing 1000 or more species of bacteria with ten-times the number of cells as a person and 150-times more genes than the human genome.^[69] The commensal gut microbiota and the host depend on each other to maintain a dynamic biologically balanced symbiosis.^[70-72] With further research on the human microenvironment, the importance of the gut microbiota for human health has been widely recognized by researchers. The gut microbiota performs many fundamental functions in the body, such as absorbing dietary fats and fat-soluble vitamins, synthesizing the amino acids needed by the host, digesting complex plant polysaccharides and carbohydrates, and fermenting compounds into short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate.^[70,73] Additionally, the gut microbiota plays a significant role in infection control, host immunity and energy homeostasis.^[70,74] As an organic part of the human body, the composition and metabolism of the gut microbiota importantly affect the physiological functions of the host.^[67,75] In recent years, emerging studies have revealed that gut microbiota dysbiosis is associated with the development of many metabolic disorders.^[71,76] A number of microbial genomics studies have found that changes in the structure and function of the gut microbiota contribute to insulin resistance, obesity, and abnormal elevation of blood

glucose, which are inextricably related to the development of T2DM.^[77]

The gut microbiota also plays an important role in the formation and regulation of the intestinal clock.^[81] As one of the peripheral circadian clock organs, the intestine not only receives synchronization information from the central circadian clock but also has its own oscillator.^[8,74] The intestine affects the human body with its own rhythm by controlling physiological processes, such as the mechanical movement of intestinal peristalsis, secretory function, and gut microbiota, which is mainly affected by the time of eating and diet composition.^[78,79] The gut microbiota is altered according to the periodic feeding cycles of the host, and obviously, different stages of life are related to shifts in bacterial composition and function as well.^[73] A study revealed that disturbed circadian rhythmicity in the host influenced microbial populations in the intestine.^[81] Subsequently, researchers found that up to approximately 20% of the gut microbiota exhibited diurnal fluctuations in relevant abundance and activity that were controlled by host feeding time.^[80] Therefore, feeding behavior may be the zeitgeber for the peripheral intestinal circadian clock in mammals as well as for circadian rhythms in the gut microbiota. More importantly, together with emerging evidence showing that the gut microbial community is closely correlated with the circadian clock, it becomes more evident that disrupting this interaction may lead to metabolic diseases such as obesity, glucose intolerance and insulin sensitivity, which are inextricably intertwined with the development of T2DM.

Effects of the gut microbiota on the circadian clock in T2DM

Interestingly, the best way to beat jet lag is to eat with locals to adjust the diurnal oscillations of the gut microbiota, whose regulation is under the control of host feeding behavior.^[81] Accumulating evidence indicates that changes in the host's time of eating, nutritional regimes and circadian status, including time-restricted feeding (TRF), challenge by HFD, genetic mutations in the circadian clock and time shifts, extensively alter oscillations in the intestine, liver, adipose tissue and brain of clock genes and CCGs.^[45,38] Chaix *et al*^[81] previously found that a pattern of 10-h access to food during the active phase of TRF could reverse obesity and related metabolic disorders compared to the effects observed in mice fed an HFD for 24 h. Recently, the team further revealed that TRF contributed to metabolic health in mice with a disrupted circadian clock, illuminating the balance of adequate nutrition and eating state and necessary repair and restoration during fasting controlled by the circadian clock.^[45] Disruption of the circadian clock by either genetic disruption or time shifts caused dysbiosis, as well as the loss of diurnal rhythmicity in the gut microbiota; thus, metabolic diseases occurred.^[45,82] Studies have shown that HFD consumption could induce alterations in the composition of the gut microbiota, the transplantation of which led to the development of obesity in germ-free mice.^[83] Another study showed that circadian oscillations in the abundances of some bacteria, such as those in the family *Lachnospiraceae*, a SCFA-producing bacteria, were dampened by

HFD consumption in mice, while bacteria that previously had no rhythm, such as H₂S-producing bacteria, exhibited a rhythm when the host mice were fed an HFD rather than regular chow. However, circadian rhythms of the gut bacteria can be partially reversed when HFDs are consumed only during the dark phase via TRF. The absence of gut microbiota was also shown to disturb the circadian clock genes, including *Bmal1*, *Cry1*, *Per1*, and *Per2*, in the intestinal epithelial cells and in the livers of germ-free mice.^[82] A ketogenic diet was also found to activate circadian peroxisome proliferator-activated receptor α (PPAR α) signaling in the gut of mice, which was paralleled by the food intake of mice, demonstrating that the gut microbiota of the ketogenic diet mice also dramatically reprogrammed the peripheral circadian clock via PPAR α .^[78] Furthermore, the gut microbiota was shown to regulate body composition via the circadian transcription factor nuclear factor interleukin-3, which controls the expression of the circadian lipid metabolic program and regulates lipid absorption and transport in intestinal epithelial cells. Undeniably, this finding established a crucial molecular connection among the gut microbiota, the circadian clock, and host metabolism.^[84] Montagner *et al*^[85] reported that germ-free mice exhibited dynamic oscillation of circadian clock gene expression with concomitant alterations in the expression of clock output regulators, which are closely connected with daily alterations in glucose, lipids, and xenobiotic metabolism. A recent study found that intestinal epithelial cells induced histone deacetylase 3 to play a role in recruiting to chromosomes under the guidance of the circadian rhythm, leading to acetylation and deacetylation of histones and ultimately affecting the expression of metabolic-related genes, which demonstrates that the gut microbiota, the circadian clock, and the metabolic system are tightly connected and that the gut microbiota programs diurnal rhythms in host metabolism.^[4]

Therefore, in the development of T2DM, the gut microbiota takes control of the host circadian rhythm, and vice versa, the circadian clock regulates the structure and function of the gut microbiota, which results in the bidirectional communication between the gut microbiota and the circadian clock in the development of T2DM.

Metabolites Might Be Crucial Mediators That Regulate the Gut Microbiota in the Regulation of the Circadian Clock in the Development of T2DM

Accumulating studies have demonstrated that microbial metabolites might play significant roles in the crosstalk between the gut microbiota and other metabolic organs as well as in the development of metabolic diseases; particularly important metabolites are SCFAs, the main metabolic byproducts of gut microbial fermentation of non-digestible carbohydrates in the colon by specific microbial taxa.^[86,87] Butyrate, propionate, and acetate, which account for 90% to 95% of the SCFAs present in the colon, not only have anti-inflammatory effects and improve intestinal barrier function but can also play a role in the feedback mechanism by which the gut microbiota communicates with the host to regulate the circadian clock.^[88] As previously described, Leone *et al*^[82]

found that HFD consumption led to alterations in gut microbial structure and circadian oscillations, and the bacterial metabolic products, SCFAs and H₂S, also exhibited a rhythm when the host mice were fed an HFD rather than regular chow. Furthermore, researchers revealed that either 5 mmol/L acetate or butyrate *in vitro* caused a significant change in the hepatic expression of the clock genes *Bmal1* and *Per2*, which at least partially explained the impact of metabolites in the gut microbiota-circadian rhythm link.^[82] Furthermore, oral administration of a mixture of SCFAs (butyrate, propionate, and acetate) and organic acid lactate or single administration of each SCFA or lactate resulted in phase alterations in peripheral clocks with stimulation timing dependency, while this effect was not tested in cultured fibroblasts or liver slices with SCFAs *in vitro*, demonstrating that SCFAs mediate indirect regulation of circadian clocks *in vivo*.^[87]

Studies have suggested that SCFAs mediate the activation of orphaned G protein-coupled receptor 43 (GPR43), one of the specific receptors of SCFAs, and suppress insulin signaling in adipocytes, which further inhibits fat accumulation in adipose tissue and accelerates the metabolism of unincorporated lipids as well as glucose in other tissues, leading to a subsequent increase in insulin sensitivity.^[89] Additionally, SCFAs were found to be involved in the management of inflammatory processes by controlling neutrophil chemotaxis and T regulatory cell proliferation. Once SCFAs activate GPR43, they may act on the recruitment of immune cells and regulate inflammatory processes at the intestinal site.^[90] In addition, butyrate and propionate were also found to fight against diet-induced obesity and modulate gut hormones.^[91] The oral administration of acetate plays a role in improving glucose tolerance and suppressing obesity.^[92] In light of the indispensable involvement of insulin sensitivity, inflammatory response and glucose metabolism in the development of T2DM, the regulation via GPR43 might be a crucial metabolic effect exerted by SCFAs.^[86]

Conclusions and Prospects

As one of the severest chronic diseases and the ninth major cause of shortened life expectancy, T2DM is unstoppable in the short term with the trend of “blowout” outbreaks. At present, the recognized inherent genetic factors, as well as traditional environmental factors, do not align with the continuous rapid increase in the prevalence of T2DM. It is necessary to uncover more novel perspectives and targets for fighting against T2DM and associated metabolic disorders.

Over the past few decades, the rapid development of modern society due to the industrialization has driven great changes in the way people choose to live. With the increasing prevalence of shift work and social jet lag, the role of circadian disruption in relation to metabolic disorders, including a higher risk of T2DM, has gained much more interest. The role of circadian disruption in the development of T2DM was indicated most profoundly in the clinical trials in shift workers. Studies have verified that shift work, especially rotating night shift work linking an irregular working schedule with unhealthy eating patterns

by synchronizing irregularly to the 24-h light/dark cycle, is inextricably intertwined with impaired glucose tolerance, insulin resistance, and an increased risk of obesity, all of which are risk factors for T2DM. Animal studies in mice with targeted clock gene mutations, which were conducted in the laboratory without behavioral or environmental influences, have provided direct evidence demonstrating the linkages between circadian clock disruptions and the risk of T2DM. It is worth mentioning that the effects of *Clock* gene mutations as well as tissue-specific *Bmal1* knockout vary in different tissues in rodent studies, which encourages researchers to perform further in-depth studies to underpin the tissue-specific contributions that will help in future precise therapeutics.

It is highly recognized that the gut microbiota not only triggers the development and progression of T2DM in a direct way due to altered microbial community structure and activity, but also involved in the conversation with the host metabolism controlled by endogenous circadian system, external eating pattern, and other factors. The gut microbiota serves to regulate the circadian system mainly by altering the expression of circadian genes. Studies have demonstrated that the gut microbiota plays a role in governing the expression of circadian genes

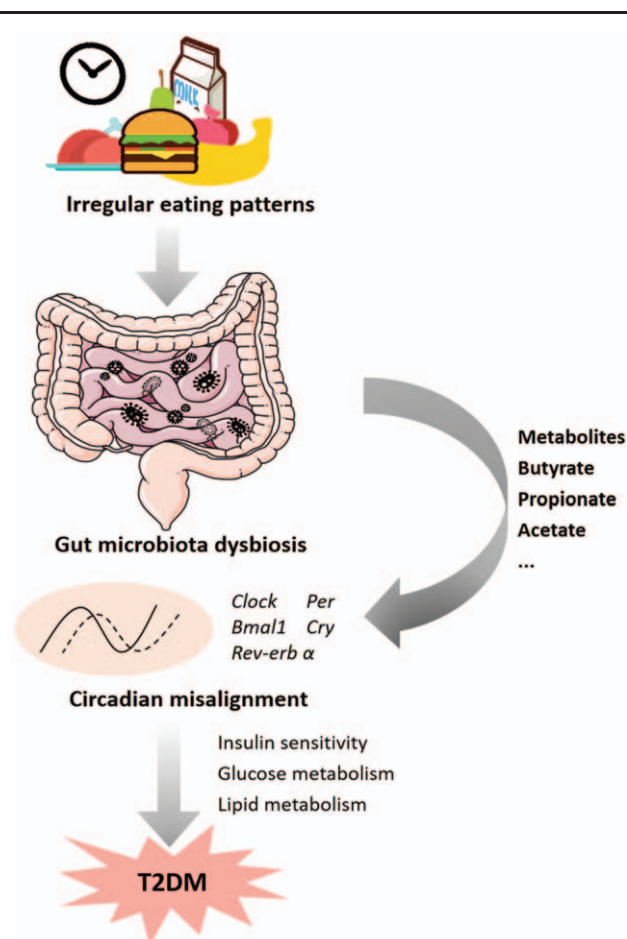


Figure 2: The gut microbiota plays a key role in the regulation of the circadian clock in the development of T2DM. Clock: Circadian locomotor output cycles protein kaput; Cry: Cryptochrome; Bmal1: Brain and muscle ARNT-like protein; Per: Period circadian clock; Rev-erb α : Reverse erythroblastosis virus α ; T2DM: Type 2 diabetes mellitus.

involved in metabolic pathways such as lipid and glucose regulation to mediate the development of T2DM. Intriguingly, microbial metabolic activity at least partially acts through the production of SCFAs, which activate its specific receptor to take part in the process of insulin sensitivity, inflammatory response, and glucose metabolism, which are all involved in the development of T2DM. As such, not only the gut microbiota itself but also SCFAs may be considered key components in the regulation of the circadian clock in T2DM. However, studies directly clarifying the specific mechanism of the gut microbiota in the regulation of the circadian clock in T2DM and its related effects are still limited, although they are of great significance for new targets to treat T2DM.

Overall, this review makes it more clear that the gut microbiota dysbiosis induced by irregular eating patterns contributes to circadian misalignment mainly through metabolite availability. Alterations of circadian oscillation make individuals more prone to T2DM by regulating insulin sensitivity, glucose metabolism, and lipid metabolism [Figure 2]. We expect that the bidirectional relationship of gut microbiota and circadian clock provides a potential for gut microbiota-directed therapies such as probiotics and targeted prebiotics to ameliorate the effects of circadian disruptions linked to the occurrence and development of T2DM.

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Conflicts of interest

None.

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