Basic Biology of Rhythms and the Microbiome

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Abstract The mammalian microbiome undergoes diurnal oscillations in composition and function throughout a 24-period that are regulated by host clock and nutritional signals. These diurnal oscillations, in turn, impact the host's transcriptome and multiple other physiologic functions. Emerging evidence has begun to uncover the molecular mechanisms that underlie the coordinated meta-organismal diurnal rhythmicity with crucial implications for homeostasis and disease. Herein, we highlight current mechanistic understanding by which the diurnally oscillating commensal microbiota is regulated by the host and its environment, and how commensals diurnally modulate host biology in health and disease. Finally, current challenges, open questions, and perspectives in this exciting new field of chronobiology are discussed.

1 Introduction

1.1 Circadian Rhythms in Mammals

Created by the Earth's rotation in relation to the sun, most living beings on Earth experience a daily light/dark cycle (Kaczmarek et al. 2017). Living organisms are subject to an evolutionary pressure to develop regulatory clock networks to adapt to the circadian nature of their environment (Troein et al. 2009). Circadian rhythms are

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cycles of physiology and behavior driven by an endogenous oscillator set to a period of approximately 24 hours (Panda et al. 2002). Evolving mechanisms of diurnal homeostasis allow organisms to accommodate to rhythmic environmental challenges and, thus, provide them with a competitive survival advantage (Dodd et al. 2005; Hellweger 2010). Diurnal rhythms of varying degree of complexity are exhibited by the majority of organisms including animals, bacteria, fungi, and plants (Hastings et al. 2007). For many years, circadian clocks were conceptualized in terms of feedback loops of transcription and translation. However, more recent studies have unraveled a wealth of posttranslational circadian oscillators (Brown et al. 2012). Going beyond the "clock" metaphor, more recent research has revealed that unlike a conventional clockwork, the circadian systems of many organisms are dynamic and highly adaptive (Roenneberg and Merrow 2005). Nevertheless, certain biological rhythms persist in the absence of environmental signals (such as light and temperature) (Panda et al. 2002). A mammalian 24-h circle is typically comprised of one active and feeding as well as one resting and fasting phase. In humans, the light phase represents the active phase, while in mice, arguably the most commonly used animal model in biomedical research, the dark phase constitutes the active phase. Growing evidence suggests that the host's circadian rhythms, diet, and commensal microbiota are closely interconnected (Kaczmarek et al. 2017).

In mammals, the central oscillator, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, generates a circadian rhythm and synchronizes the periphery (Hastings et al. 2003). The SCN is normally synchronized to solar time by retinal afferents from intrinsically photoreceptive retinal ganglion cells (Mohawk et al. 2012). Peripheral tissues generate oscillations using circuitry based on clock proteins that can function cell-autonomously to generate transcriptional rhythms (Kaczmarek et al. 2017). In mice, up to 45% of the transcriptome adheres to an approximately 24-h oscillation pattern (Zarrinpar et al. 2016).

The underlying mechanism in both neurons and peripheral cells of mammals is a transcriptional-translational feedback loop oscillating with a periodicity of 24 h. It comprises the proteins CLOCK and BMAL1 that activate transcription of genes encoding the repressors PERIOD (PER) and CRYPTOCHROME (CRY). The products of these genes can form the PER/CRY repressive complex that can translocate into the nucleus and inhibit CLOCK/BMAL1 transcription activity, subsequently resulting in *PER* and *CRY* gene repression (Green et al. 2008).

Figure 1 outlines the interactions between environmental, host-related, and microbial factors in circadian regulation and its impact on physiological outcomes

1.2 Diurnal Rhythms of the Mammalian Microbiota

The human body is colonized by a diverse community of microorganisms, especially in the gut. Circadian rhythms in prokaryotes are far less understood compared to those in mammals and have primarily been investigated in light-responsive cyanobacteria (Nobs et al. 2019). Though the prokaryotic microorganisms largely

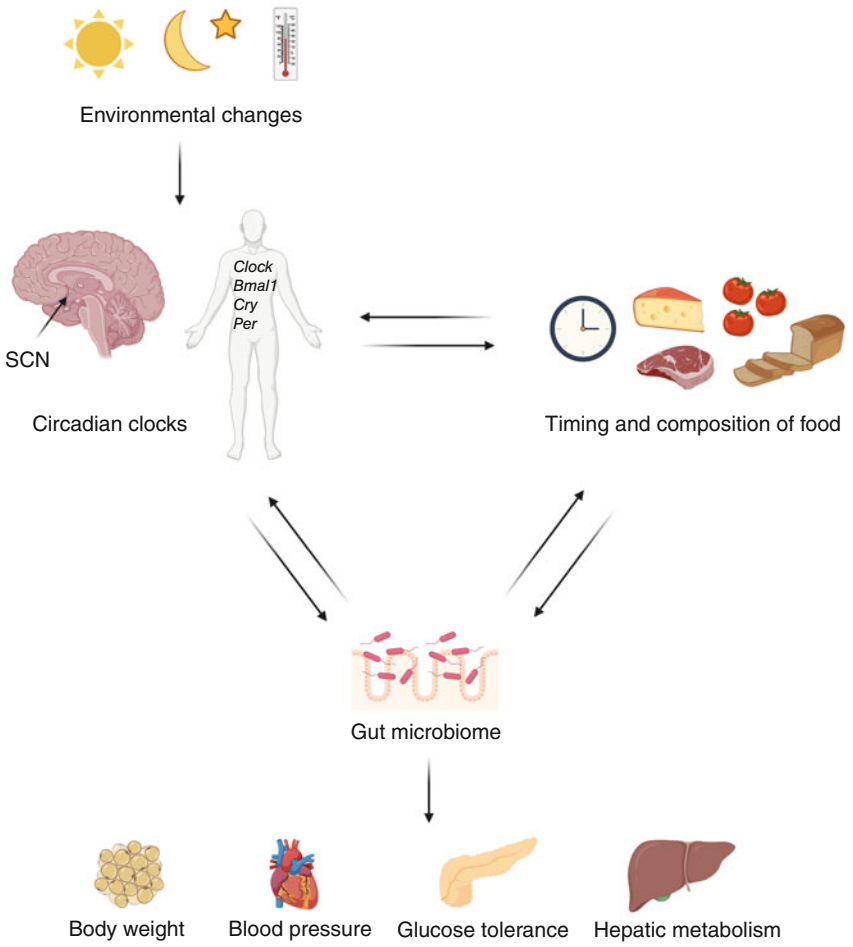

Fig. 1 Circadian rhythm in host-diet-microbiome interactions. The circadian clock oscillates with a periodicity of 24 h in neurons of the suprachiasmatic nucleus (SCN) and peripheral cells and is entrained by diurnal environmental changes. It leads to circadian oscillations in the composition and function of the gut microbiome, which in turn modulates the circadian rhythm and associated physiological functions of the host. The timing and composition of food intake is another major factor interacting with both host rhythms and circadian microbiome oscillations

constituting the mammalian gut microbiome are not exposed to light, the daily environmental changes in the intestine lead to various diurnal oscillations in the commensal microbial community (Nobs et al. 2019; Saran et al. 2020). The gut microbiome's taxonomic and functional genomic composition is highly dynamic, exhibiting cyclical fluctuations (Thaiss et al. 2014, 2016; Zarrinpar et al. 2014; Liang et al. 2015; Deaver et al. 2018; Wu et al. 2018; Godinho-Silva et al. 2019; Leach et al. 2019). In mice, the proportion of species belonging to the Firmicutes phylum was reported to peak during nocturnal feeding and to reach its nadir during daytime

fasting. Contrary, the phyla Bacteroidetes and Verrucomicrobia species peak during daytime fasting and bottom out during nocturnal feeding (Zarrinpar et al. 2014). Moreover, the absolute number of fecal bacteria also seems to be subject to diurnal oscillations. A distinction must be drawn regarding the circadian variation of the *relative* versus the *absolute* abundance of a bacterial clade. As such, no circadian oscillation was demonstrated for the relative abundance of the phylum Proteobacteria, whereas the inferred absolute abundance oscillated during the light-dark cycle (Liang et al. 2015).

The bacterial microbiome features rhythmic patterns of localization and metabolite secretion in the colon. The abundance of commensal bacterial genes implicated in chemotaxis and flagellar assembly was shown to reach their peak at the end of the resting (light) phase in mice (Thaiss et al. 2016). This may drive bacterial penetration into the intestinal mucus layer in order to utilize mucus as a nutritional source when food intake is reduced. The interconnection between anabolic and catabolic metabolism and circadian clocks is required to synchronize the energy turnover with diurnal variations in nutrient supply. Feeding in restricted periods of the light-dark cycle dissociates peripheral clocks from the central master zeitgeber. The relationship between circadian genes and feeding rhythms seems to be interdependent. Interestingly, mice with genetically altered circadian clock genes not only lose many host transcriptome oscillations but also their usual nocturnal feeding behavior. However, restricting access to food to the dark cycle partly rescues behavioral and transcriptional patterns in these mice, strongly suggesting that many circadian processes are driven by feeding rhythms independently of the central master clock (Hughes et al. 2009; Vollmers et al. 2009).

Indeed, the microbiome's circadian rhythmicity and host metabolism are intertwined. Various microbiome-derived metabolites oscillate diurnally including secondary bile acids (Zhang et al. 2011; Joyce et al. 2014). Plasma bile acids and key genes in bile acid biosynthesis are regulated by both the host's hepatic molecular clock and by food intake (Eggink et al. 2017). Alteration of microbiota-derived short-chain fatty acids (SCFAs) under high-fat diet directly modulates circadian clock gene expression in hepatocytes and other peripheral tissues (Leone et al. 2015; Parkar et al. 2019). Knockout of the important peripheral circadian rhythm orchestrating genes *Per1* and *Per2* leads to oscillatory loss in many bacterial operational taxonomic units (OTUs) under ad libitum feeding (Fig. 2a). In the mouse gut, about 23% of identified KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways and the respective underlying bacterial gene abundances display oscillations within a 24-h cycle. Among these, levels of genes encoding for pathways involved in energy metabolism, DNA repair, and cell growth show a peak during the dark (active) phase, whereas those involved in detoxification, motility, and environmental sensing reach the peak during the light (resting) phase in mice. The diurnal fluctuation of KEGG pathways in microbiota from wild-type mice is absent in mice with knockout of *Per1* and *Per2* (Fig. 2b). In humans, 10% of bacterial OTUs and around 20% of KEGG pathways show circadian oscillation patterns. Mice deficient in circadian rhythmicity because of knockout of the *Per1* and *Per2* genes feature lower alpha biodiversity. The loss of bacterial circadian oscillations in arrhythmic Per1/

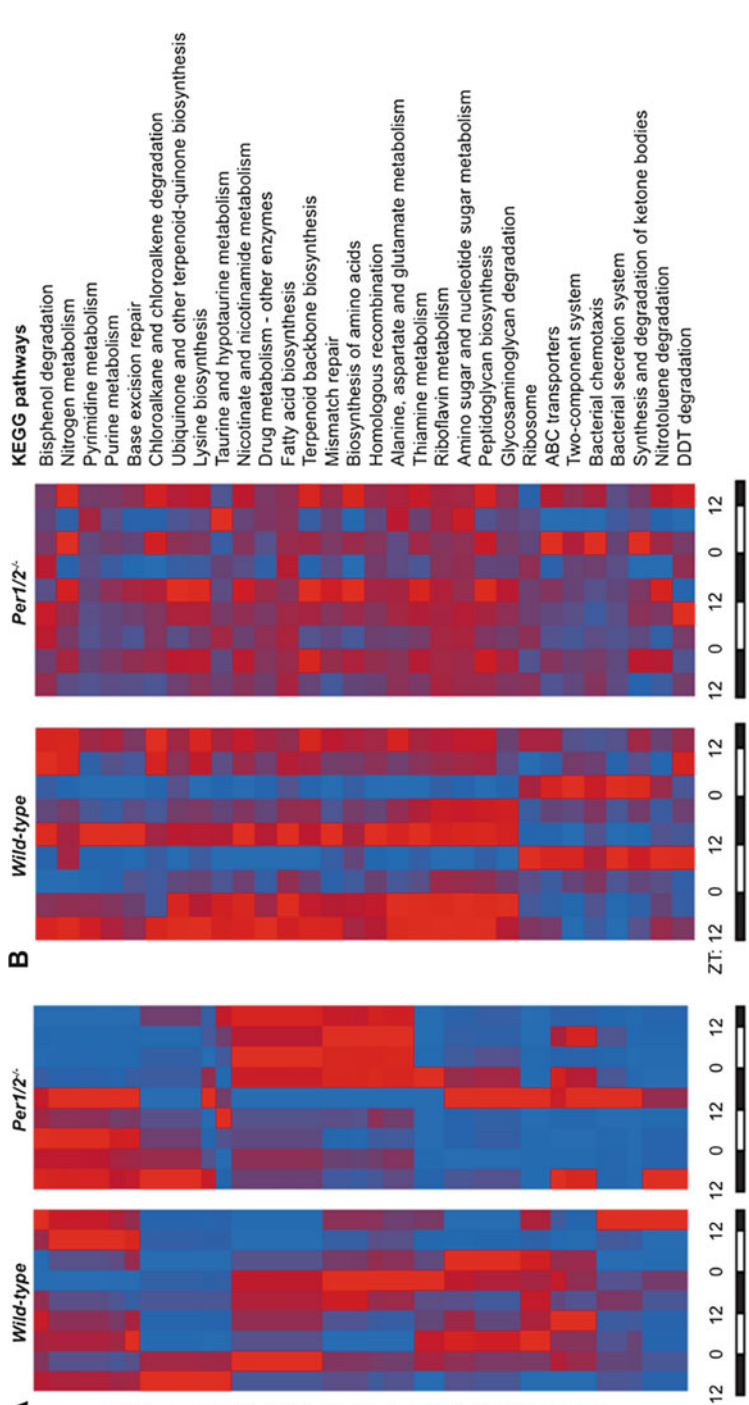

Fig. 2 Loss of taxonomic and functional microbial diurnal oscillations in mice with *Per1/2* knockout. (**a**) Taxonomic diurnal oscillation: compared to wild-type mice, mice with knockout of *Per1* and *Per2* show oscillatory loss in many bacterial operational taxonomic units. (**b**) Functional diurnal oscillation: wild-type mice show diurnal fluctuation of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways in microbiota, which is absent in mice with knockout of *Per1* and *Per2*. Samples were taken at time points of changing light conditions (Zeitgeber times [ZT] 12 and 0, i.e., "dusk" and "dawn") and the midpoint of the dark and light phases (ZT 18 and 6, respectively) (Thaiss et al. 2014)

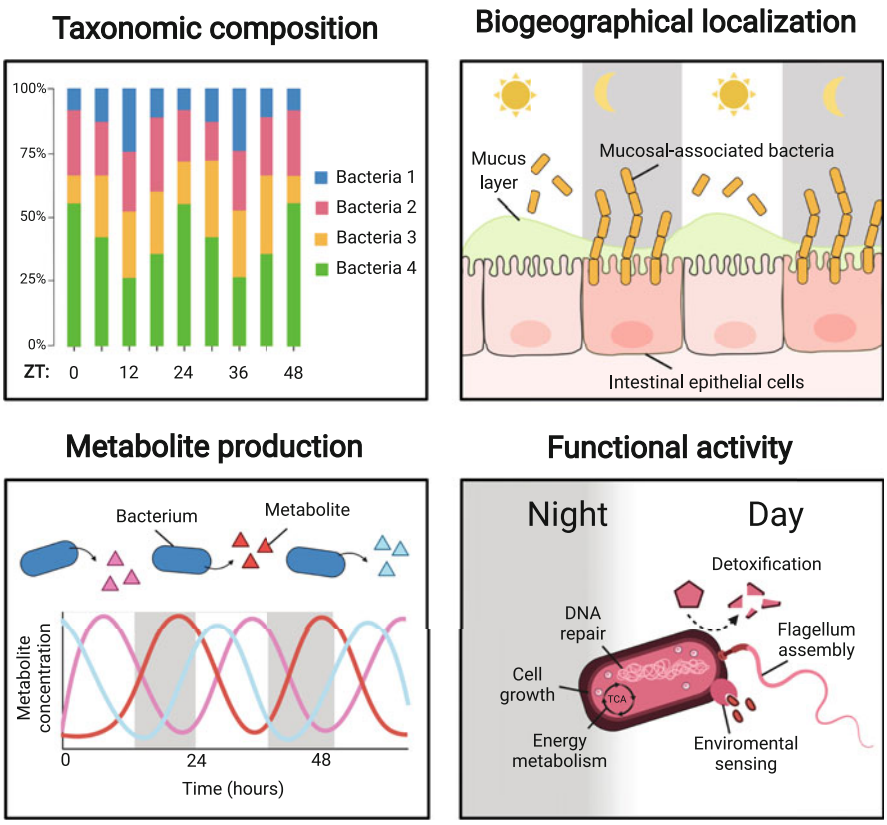

Fig. 3 Manifestations of diurnal rhythms in the mammalian microbiota. The intestinal microbiome displays cyclical rhythms over a 24-hour period in terms of taxonomic composition, biogeographical localization (rhythmic bacterial adherence to the mucosa and penetration into the mucus layer), production of various metabolites (such as short-chain fatty acids, carbohydrates, etc.), and functional activities with some genes being more expressed during the nighttime and others during daytime

2-deficient mice was rescued by introducing time-restricted feeding (Thaiss et al. 2014). Therefore, timing of feeding is a dominant orchestrator of temporal microbiome composition and functional dynamics. Although it is now evident that commensal microbial signaling affects maintenance of gut homeostasis and circadian control of intestinal and various extra-intestinal functions, it is still largely unclear through which mechanisms commensal bacteria and host tissues communicate and how the microbiome may take advantage of host circadian functions to maintain its own homeostasis. Moreover, since circadian phenomena of the host's physiology can be habituated by daily cycles of restricted feeding (Stephan 1984), it remains to be clarified whether the restoration of microbial circadian rhythmicity is explained by direct influence of feeding, restoration of the host's circadian clock, or

a combination of both. Figure 3 summarizes relevant aspects of diurnal fluctuation in microbiota.

2 Circadian System in Host-Microbiome Interactions

2.1 Host Factors Shaping Microbiota Rhythms

In addition to studies showing that the ablation of the molecular clock *Per* genes causes changes in the commensal microbiota composition (Thaiss et al. 2014; Zarrinpar et al. 2016), microbial configuration was also shown to be influenced by *Bmal1*-dependent forward limb of the clock signaling pathway (Liang et al. 2015). Interestingly, the impact of host factors on microbial circadian rhythmicity shows a sex-dimorphic pattern. Although both male and female mice display circadian behavior and physiology, circadian oscillation in females is more pronounced than in male animals. Deficiency of *Bmal1* not only abrogated circadian behavior of the fecal microbiome in both sexes, but the resulting shifts in the microbiome configuration showed similarly intriguing sex-specific patterns (Liang et al. 2015). The absence of the microbiota in germ-free mice levels hepatic rhythmic and sex-dimorphic gene expression and metabolism. Additionally, there is evidence that sex-specific diurnal rhythms of gene expression are driven by microbial metabolites (Weger et al. 2019).

Exposure to unnatural light cycles are increasingly common in modern society due to availability of electricity, long-distance travel, and shift work. In mice, perturbation of the physiological cycle through constant light or dark exposure may lead to altered abundance of several taxonomic groups in the intestinal microbiome and altered levels of certain microbiome-derived plasma metabolites subject to regulation by the microbiome, such as tryptophan (Kim et al. 2019). The induction of jet lag leads to deregulated microbiota diurnal fluctuations and altered microbiota composition (dysbiosis), driven by impaired feeding rhythmicity, in both humans and mice (Thaiss et al. 2014). Although there is growing concern that altered circadian rhythms, sleep deprivation, and related stressors may adversely impact human gut microbiota with significant health implications, evidence for this is still very scarce (Zhang et al. 2017; Karl et al. 2018) and warrants further research. At least one species commonly colonizing the human gut, *Enterobacter aerogenes*, may be sensitive to the host-derived neuro-hormone melatonin, strongly suggesting the existence of autochthonous clocks in some commensal bacterial cells synchronizing with host circadian regulators (Paulose and Cassone 2016).

The host's innate immune arm utilizes a wealth of antibacterial polypeptides, known as defensins, to regulate commensal microbiota and to combat invading pathogens. Mouse enteric defensins, also known as cryptdins, are produced and secreted constitutively but are increasingly expressed upon enteric infection or inflammation. An analysis of expression patterns of cryptdin 1 and cryptdin 4 around the circadian cycle in mice revealed a circadian oscillation of these defensins with a

peak at the end of the dark phase (Froy et al. 2005). In mice, the circadian regulator *Arntl* has been shown to be a key regulator in intestinal group 3 innate lymphoid cells (ILC3s) and contributing to regulation of the gut microbiome by ILC3s in a circadian rhythm-dependent manner (Godinho-Silva et al. 2019). Immune system parameters change according to the time of day, and disruption of circadian rhythms has been linked to inflammatory pathologies (Curtis et al. 2014). As the host's immune system is now known to be a major regulator of microbiome homeostasis (and vice versa), there is potentially an enormous wealth of circadian immunological mechanisms regulating the commensal microbiota, which are yet to be discovered.

2.2 *The Influence of Microbiota on Host Rhythms and Metabolism*

The oscillating bacterial adherence to the colonic mucus layer may regulate the circadian changes in the colonocyte epigenome and transcriptome (Thaiss et al. 2016). The host's metabolism, which is increasingly recognized to be shaped by both host-intrinsic factors and the microbiome, is entwined with circadian regulation. The integrity of the circadian clock of intestinal epithelial cells (IECs) is required to regulate the dialog between IECs and the microbiota. This is especially mediated through a rhythmic expression of Toll-like receptors (TLRs) by IECs. The importance of this crosstalk is highlighted by the finding that microbiome signaling deficiencies induce a prediabetic syndrome due to ileal corticosterone overproduction, which manifests as a consequence of IEC clock disruption (Mukherji et al. 2013). The liver is a key organ orchestrating metabolic homeostasis and maybe a primary target impacted by gut microbiome-secreted factors influxing through the portal venous system.

Indeed, the microbiome is required for integration of liver clock oscillations to regulate gene expression for optimal liver function. This has implications for the regulation of diverse metabolite levels, including glucose, cholesterol, free fatty acids, bilirubin, and lactate. Moreover, the hepatic clock-microbiome cross-talk influences xenobiotic metabolism, protein turnover, and redox balance (Montagner et al. 2016). Circadian transcriptomic changes in the liver may be regulated by timely fluctuations of microbiota-derived metabolites, including lipids, amino acids, carbohydrates, vitamins, nucleotides, and xenobiotics (Thaiss et al. 2016). The microbiome-derived SCFA butyrate may function as a histone deacetylase inhibitor in the liver, hereby exerting epigenetic control of host circadian rhythms (Leone et al. 2015).

Preventive efficacy of dietary fiber intake and microbiome-derived acetate against hypertension may be partly mediated by their influence on the expression of circadian genes in the heart and the kidney (Marques et al. 2017). Unconjugated bile acids, generated through bile salt hydrolases activity of the gut microbiota, are potentially chronobiological regulators of host circadian gene expression. This

represents an additional potential mechanism for microbe-host crosstalk regulating host circadian gene expression (Govindarajan et al. 2016).

Moreover, the microbiota modulates the diurnal variation in hepatic drug detoxification and hepatotoxicity. Acetaminophen, a potentially hepatotoxic drug undergoing hepatic metabolism, was demonstrated to exert hepatotoxicity with differing severity depending on the time of the day. This diurnal phenotype is co-regulated by the microbiome as germ-free or antibiotic-treated mice do not feature diurnal variation in acetaminophen-induced liver injury (Thaiss et al. 2016). Diurnal homeostasis is intertwined with weight maintenance and glucose tolerance, which is partially mediated by the microbiome. Jet-lag challenge induces alterations in the microbiome configuration in both humans and mice. This may confer an increased risk for metabolic disease, since obesity and glucose intolerance are transferable by fecal microbiota transplantation from jet-lagged humans and mice to germ-free mice (Thaiss et al. 2014).

Although it is increasingly clear that circadian clocks are key orchestrators of immune responses (Scheiermann et al. 2018), understanding how circadian rhythmicity of the microbiota may impact host immunity is only at its very beginning. Some clues come from studies with bacterial pathogens. For example, in murine infection with the enteric pathogen *Salmonella typhimurium*, the efficacy of colonization by the pathogen and the magnitude of the host's inflammatory response depend on the time of day of pathogen exposure (Bellet et al. 2013).

Despite these advances, the understanding of the diurnal mechanisms underlying regulation of host biology by the microbiota remains largely unknown and warrant additional research.

2.3 Perspectives and Challenges

In recent years, major progress has been achieved in unraveling the interplay between the host's and the microbiota's circadian rhythms, related environmental cues, and their concerted impact on host physiology. However, in this relatively young field, many questions on the circadian regulation of the microbiome's composition and function and associated host-microbiota mutualism remain hitherto unanswered. It is clear that more mechanistic evidence is required for a proper understanding of circadian phenomena at the host-microbiome interface. Therefore, the field presents exciting opportunities for future discoveries. Inquiries into the basic biology of circadian microbiota regulation hold great potential to deepen the understanding of inflammatory and metabolic disorders.

Many fundamental questions in this area of research need to be addressed. What are the mechanisms regulating diurnal oscillations in commensal intestinal bacteria apart from feeding rhythms? Which autochthonous cellular clockworks may exist in commensal bacteria? What is the role of host-derived regulators of neural, hormonal, or immunologic origin? Is there a direct relationship between the central circadian regulator in the SCN and gut microbiota circadian rhythms? Which mechanisms

underlie this potential relationship? Through which mechanisms are host peripheral clocks and dependent biological processes synchronized with bacterial oscillations? What is the role of circadian phenomena regarding non-bacterial members of the commensal microbiota?

It will be crucial to disentangle the role of circadian control of immune responses by the host and modulation of host immunity by microbiota rhythms, e.g., by employing animal models with knockouts for specific genes involved in circadian regulation. It is challenging to directly demonstrate causal links between diurnal changes in the microbiome and host biology in humans. Nevertheless, in addition to elaborated basic research using advanced animal models, more comprehensive observational human studies are required with sufficiently deep analysis of metagenome and transcriptome profiles to confirm that circadian alterations associated with modern life style, such as represented by shift work, truly impact the human microbiome in a way significant for human health and disease. This is of high public health relevance as it is estimated that currently up to 30% of the working population perform shift work and about one-third of adults sleep less than 6 h per night (Liang and FitzGerald 2017). Going one step further, the recent emergence of microbiota-targeted therapies (Skelly et al. 2019) may inspire novel chrono-pharmacological approaches targeting the host's peripheral clocks and microbiome rhythms in order to treat inflammatory or metabolic diseases.

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