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REVIEW

Immunological and inflammatory effects of infectious diseases in circadian rhythm disruption and future therapeutic directions

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Abstract

Background Circadian rhythm is characterised by daily variations in biological activity to align with the light and dark cycle. These diurnal variations, in turn, influence physiological functions such as blood pressure, temperature, and sleep–wake cycle. Though it is well established that the circadian pathway is linked to pro-inflammatory responses and circulating immune cells, its association with infectious diseases is widely unknown.

Objective This comprehensive review aims to describe the association between circadian rhythm and host immune response to various kinds of infection.

Methods We conducted a literature search in databases Pubmed/Medline and Science direct. Our paper includes a comprehensive analysis of findings from articles in English which was related to our hypothesis.

Findings Molecular clocks determine circadian rhythm disruption in response to infection, influencing the host's response toward infection. Moreover, there is a complex interplay with intrinsic oscillators of pathogens and the influence of specific infectious processes on the CLOCK: BMAL1 pathway. Such mechanisms vary for bacterial and viral infections, both well studied in the literature. However, less is known about the association of parasitic infections and fungal pathogens with circadian rhythm modulation.

Conclusion It is shown that bidirectional relationships exist between circadian rhythm disruption and infectious process, which contains interplay between the host's and pathogens' circadian oscillator, immune response, and the influence of specific infectious. Further studies exploring the modulations of circadian rhythm and immunity can offer novel explanations of different susceptibilities to infection and can lead to therapeutic avenues in circadian immune modulation of infectious diseases.

Keywords Chrono-immunology · Circadian rhythm · Infectious diseases · Molecular clocks · Melatonin · Inflammation · Immune response

Abbreviations

CK	Casein kinase
PP	Protein phosphatase
SCN	Suprachiasmatic nucleus
BMAL1	Brain and muscle ARNT-like 1
CLOCK	Circadian locomotor output cycles kaput
CCL2	Chemokine (C–C motif) ligand 2
TNF	Tumour necrosis factor
IL6	Interleukin 6
IL12	Interleukin 12
CXCL5	C-X-C motif chemokine ligand 5
CXCR4	C-X-C chemokine receptor type 4
IL-7R	Interleukin-7 receptor
Rev-erbα	Reverse orientation c-erbA gene α
miR-155	MicroRNA-155
LPS	Lipopolysaccharide
IL-1β	Interleukin 1β
NRF2	Nuclear factor erythroid 2-related factor 2
S. Typhimurium	*Salmonella enterica*
CXCL12	C-X-C motif chemokine ligand 12
NADPH	Nicotinamide adenine dinucleotide phosphate

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PER	Period circadian regulator
CRY	Cryptochrome circadian regulator
SCD	Stearoyl-CoA-desaturase
HBV	Hepatitis B
HCC	Hepatocellular carcinoma
HCV	Hepatitis C
HSV	Herpes simplex virus
HIV	Human immunodeficiency virus
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ACE2	Angiotensin-converting enzyme 2
T. Brucei	*Trypanosoma brucei*
P. falciparum	*Plasmodium falciparum*
S. Mansoni	*Schistosoma mansoni*
FRQ	Frequency protein
WC1-2	White Collar-1 and 2
MEME	Multiple EM for motif elicitation
B. cinere	*Botrytis cinerea*
BcFRQ1	Botrytis cinerea frequency protein
RNA	Ribonucleic acid
ROR	Retinoic acid-related orphan receptor
RBC	Red blood cell

Introduction

Daily variations of biological activity can characterise the circadian rhythm to align with the 24hours light and dark cycle, a concept that originates from our biological clock [1]. The role of circadian oscillations underlies the physiology of the human body, such as the variations in blood pressure, temperature, and sleep–wake cycle [2]. The circadian system modulates all cellular and physiological functions of our body and synchronises them to the light–dark environmental cycle. The multi-factorial pathways that regulate the circadian rhythm impact the molecular clock through interactions with the immune system, controlling and adjusting oscillations in response to infection [3].

From pathogens to humans, almost all living things have adjusted their behaviour and physiology to the daily cycle. Circadian rhythms affect almost every aspect of physiological architecture daily (i.e., gene expression to organismal behaviour). Our sleep–wake cycle is influenced by the time of day due to our internal physiological clock and can affect the circulation of immune cells and cytokines. The discipline of chrono-immunology has expanded significantly over the past ten years. Studies have shown that the circadian clock is connected to various aspects of microbial infection and that a functioning molecular clock is essential for viral infection. At the organismal and molecular levels, clock disruption has been accomplished utilising mutants with clock gene deletions and disruption of the light–dark cycle, respectively. The stability and position of circadian clock proteins are impacted by protein phosphatase (PP) and casein kinase (CKI) family members [4]. Along with the central clock system in the suprachiasmatic nuclei (SCN), peripheral clocks have also been found in the kidney, skeletal muscle, pancreas, liver, heart, and immune cells [5, 6]. The circadian clock influences the immune system in various ways, including immunological trafficking, activation of innate and adaptive immunity, and microbe-host interactions [7]. Emerging evidence links how fluctuations in circadian rhythm influence host responses. Molecular clocks of the human body are known to impact two aspects of host defence: Microbe-host interactions and immune responses [8]. Research in this area is still rapidly evolving, as emerging studies focus on the mechanisms of clock rhythms of microbes and how circadian fluctuations impact host immune responses against infectious diseases. For example, mortality in nocturnal rats is known to be rhythmic in response to bacterial infection or endotoxic shock, with more fatalities during late rest time [9, 10].

Commendable research has been done in the field of circadian rhythms since associated molecular mechanisms were first discovered in 1729 through plant studies [11]. The genetic influence of endogenous clocks synchronised by external signals was extensively studied in *Drosophila* fruit flies in the early twentieth century, and since then marked the beginning of the interconnection between circadian rhythms with immune system functions, behavioural mechanisms, and inflammatory responses [12]. Leukocyte trafficking was one of the first uncovered immune cells to escalate under the control of the circadian clock rhythms [13, 14]. Often, the strong association between circadian clocks and immune responses is what commonly defines the concept of "shift-work" due to life-style changes and relates to the intensity of certain inflammatory-mediated conditions, such as cardiovascular disease and auto-immune rheumatological disorders. The tie-in of immunology and chronology is linked to inflammation, and has been corroborated in early studies demonstrating that inflammatory mediators are often higher during rest, and further elucidating leukocyte trafficking to pro-inflammatory states [15]. The secretion of mediators and cytokines that cause inflammation are attributed to different immune cells, such as macrophages and neutrophils, which are also key regulators for pathogen recognition [16]. Infectious diseases are rising to dysregulated circadian rhythm as a result of different immune processes attributed to different types of pathogens [15].

The intricacy has been previously alluded to in various studies, and only continues to increase our knowledge on circadian disruption from infection. This in-depth review aims to examine research on the impact of circadian regulation on infectious diseases brought on by bacterial, parasitic, viral, and fungal pathogens. Because infectious causes

can exacerbate immune regulation, it is crucial to deepen research on circadian modulation and develop time-based therapy for infected patients.

The circadian rhythm: clock genes, transcriptional regulation, and immunity

Chronobiology is a field of research analysing the relationship between biological clocks and clock genes. It has been observed that the circadian regulation of these processes leads to the differentiation, maturation, activation and functioning of different immune cells with clinical relevance [11]. The integration of immune signals has been widely researched and focused on the hierarchical roles of the peripheral clock and central clock. The human body's primary pacemaker is the central clock, which is housed in the SCN of the hypothalamus [17]. The main goal of the central clock is to sense light, allowing the body to adjust to day and night cycles through molecular pathways, gene expression, and intracellular signalling [18]. Rhythmic adjustments and circadian rhythm control in response to external stress depend on feedback loops produced by transcription factors of these clocks [19]. Brain and muscle ARNT-Like 1 (BMAL-1), a core clock gene, has been reported to interact with circadian locomotor output cycles kaput (CLOCK) to bind with clock-controlled genes [20, 21]. To control the complex in a feedback loop, the transcription factors BMAL1 and CLOCK can additionally express transcription repressor genes like Cryptochrome (CRY) and Period (PER).

Similarly, the role of nuclear receptor REV-ERB has been determined in vivo to play a crucial role in circadian rhythms through the BMAL1:CLOCK pathway as a transcriptional repressor [22]. REV-ERB proteins are key regulators of RRE-mediated oscillations, and have been reported to exert tissue-specific functions in the brain and liver in vivo [23]. Depending on the sub-type, it is shown that different motifs in REV-ERBa binding sites broadly interact with clock genes in all tissues, whereas REV-ERBb can highly expressed in specific organs such as the brain cortices, thyroid, and pituitary glands [24]. In a secondary feedback loop, BMAL1 and CLOCK interactions induce the expression of REV-ERBα and REV-ERBβ, which go on to repress the expression of BMAL1 by competitively binding to retinoid-related orphan receptor (ROR)-response elements (RRE) against RORα and RORγ [22, 25]. While REV-ERBa represses transcription in the BMAL1:CLOCK pathway through the recruitment of NR corepressor/histone deacetylase three complexes, the role of REV-ERBb in circadian rhythms and metabolic processes is not fully elucidated compared to its counterpart [26]. Recent studies have demonstrated that the reason may be because the DNA-binding domain of REv-ERBb is closely related to its REV-ERBa subtype and functions together to hinder the expression of the BMAL1 and CRY clock genes [27]. However, REV-ERB knock-out was found to result in mitochondrial biogenesis in muscle metabolism by increasing genes implicated in fatty acid b-oxidation and strongly associated with cardiometabolic fibrotic changes via macrophages, which may explain the functional differences of REV-ERB subtypes in circadian rhythm feedback loops [28, 29]. In comparison, RORs are known as activators of transcription, and separate studies have corroborated deletions of RORα and RORγ to dampen circadian oscillation in core clock genes amongst liver tissue [25]. A summary of the circadian rhythm and its influence on human immunity is represented in Fig. 1.

The peripheral clock is another entity directly synchronised by the central clock and sets a common rhythm in virtually all cell forms [16]. Compared to the central clock, the peripheral clock is implicated by catecholamines and glucocorticoids released through the hypothalamic–pituitary–adrenal axis [30, 31]. The literature has suggested that the axis gains input from the SCN, leading to the regulation of adrenal gland activity. Glucocorticoids are a key hormone in the peripheral clock, as it exerts anti-inflammatory effects, while catecholamines regulate the levels of natural killer cells as well as neutrophils circulating in the body [32]. These epigenetic pathways have been widely studied in the literature to have an immense impact on our circadian rhythm, with immunological implications.

In addition to adrenal glands, various peripheral clocks are expressed in all mammalian cells. Lamia et al. conducted a study to understand the function of liver as a peripheral tissue clock. The study revealed that hepatic Bmal1 function is essential for the circadian regulation of genes responsible for glucose homeostasis [33]. Other studies also revealed that the liver can significantly affect the circadian rhythm of peripheral tissues leading to the alteration of glucose homeostasis [34, 35]. Sadacca et al. revealed that the pancreas having Bmal 1 and Per 1 genes in beta-cells, can function as a peripheral tissue clock that can alter glucose homeostasis [36]. Stomach with circadian food-entrainable oscillators in oxyntic cells can also affect the food intake, thus functioning as a peripheral clock [37]. Studies have revealed that CLOCK gene mutation in peripheral tissue can alter the tissue clocks, and can lead to the development of obesity and metabolic syndrome [38, 39].

Immune cells are also regulated by circadian clocks, which can affect the risk of infection. Though the exact relation is yet to be identified, studies have revealed a significant association between the timing of exposure and the risk of developing infection [40]. One of the major immune cells expressing intrinsic circadian rhythm are macrophages. Macrophages can function as a circadian clock affecting the development of infection [16, 41]. Kiessling et al. revealed the role of the macrophage-regulated circadian clock in

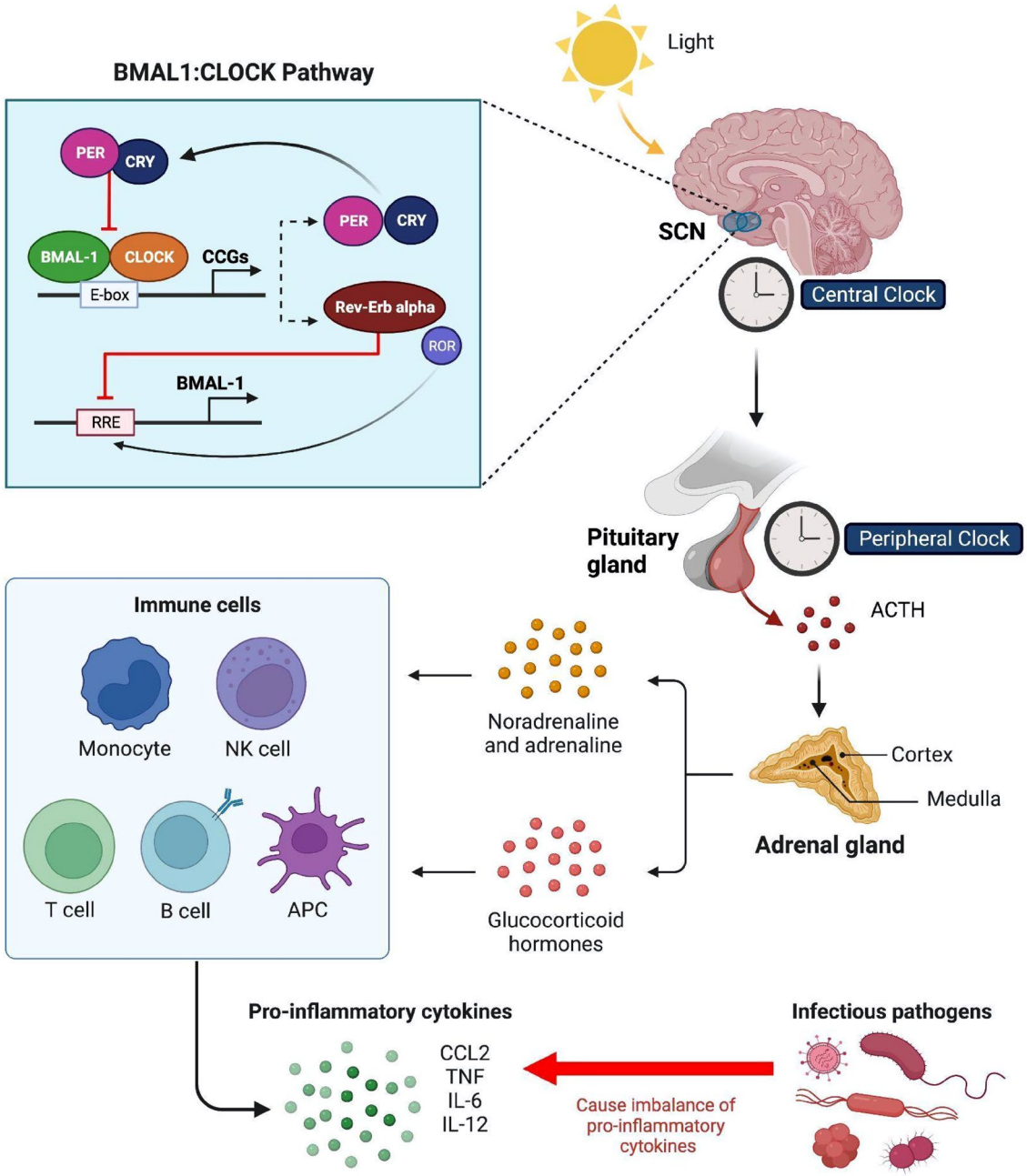

Fig. 1 Schematic representation of the influence of Central and Peripheral Clocks on BMAL1-CLOCK Pathway and Immune Response. (Created with biorender.com by HH). SCN suprachiasmatic nucleus, BMAL-1 brain and muscle ARNT-like 1, CLOCK circadian locomotor output cycles kaput, CCGs clock controlled genes, PER period circadian regulator, CRY cryptochrome circadian regulator, Rev-Erb reverse orientation c-ErbA gene α, ROR retinoic acid-related orphan receptor, RRE rev response element, ACTH adrenocorticotropic hormone, NK cell natural killer cell, APC antigen-presenting cell, CCL2 C–C motif chemokine ligand 2, TNF tumour necrosis factor, IL-6 interleukin-6, IL-12 interleukin-12

influencing Leishmania infection. Macrophages can influence the appearance and severity of infection by Leishmania parasite [42].

The disruption of the circadian rhythms by environmental or genetic manipulations triggers substantial modifications in the immune response, both in experimental and human models. The level of immune cells circulating in the peripheral blood fluctuates daily, with evidence indicating that circadian-regulated signals can increase leukocyte recruitment during inflammatory responses [43, 44]. However,

pro-inflammatory cytokines are best documented to describe the association between clock rhythms and immune function. Scheiermann et al. identifies CCL2, TNF, IL6, IL12 and CXCL5 to be the key cytokines and chemokines that are genetically impacted by oscillating circadian rhythms [7]. Normalizing the circadian rhythm depends on maintaining a balance between pro-inflammatory cytokines during sleep and anti-inflammatory mediators during awake hours. However, this balance can be dysregulated in the context of inflammation and host invasion of pathogens, causing major disruptions in clock genes and their pathways.

Immunological responses to infectious disease susceptibility modulated by circadian rhythms

Research into the circadian oscillations of the immune functions could account for the daily fluctuation in the symptoms of many pathologies and the severity of many inflammatory processes. Immune system cells, such as B and T lymphocytes, monocytes, and neutrophils, exhibit circadian oscillations in circulation and migration from the blood to tissues, with numbers maximum during the rest period of the organism. This rhythmicity keeps going as lymphocytes are sent to the lymph nodes [45].

The immune system's cells respond to circadian changes to attain maximum ability to combat infection. The immune cell rhythmic pattern is linked with glucocorticoid's regulation of chemokine receptor CXCR4 expression [46]. Abe et al. claim that glucocorticoids also activate the Interleukin-7 receptor (IL-7R), which aids in the survival, proliferation and development of T cells [47]. TCXCR4 expression is increased by the daily rhythmic induction of IL-7R, which also aids T cell survival. T cell diurnal variation enhances not only immune responses to infections by systemic bacteria at night but also to soluble antigens [48]. The interplay between immune system functions and clock proteins such as the effects of REV-ERBα and BMAL1 in anti-inflammation and elimination of cytokine storm against endotoxins by Bmal1 ablation in macrophages is evident [49]. It also abolished the daily protection in mice against sepsis in the rest phase [50]. In wild mice, miR-155 induction was inhibited by BMAL1 leading to protection against (LPS)-induced sepsis [51]. Sutton et al. explained the association of autoimmune disease and circadian disruption by the multiple sclerosis model, where the myeloid BMAL1 loss leads to inflammation by IL-1β-secreting monocytes infiltration in the central nervous system [52]. The BMAL1 which controls the Nrf2, antioxidant-encoding gene, levels suggest that the regulation of NRF2 in immune cells to control the inflammatory response is a potential role of the molecular clock [53].

The Circadian rhythms have a significant influence on not only the outcome of infection but also on susceptibility to invading pathogens. The impact of infection largely depends on the time of the day [54]. During Leishmania parasite infection, Bmal1 in monocytes is responsible for influencing the magnitude of infection, which is circadian in nature [42]. Similarly, the mice infected by Trichuris muris at the active phase depicted delayed resistance to the infection [54]. *Salmonella enterica (S. Typhimurium)* infection during the rest phase shows high microbial levels compared to infection in the active phase in mice. The CLOCK functional copy causes this difference [55]. When the disruption of the Bmal1 gene impacts the host circadian rhythms, the infections of Influenza A, herpes and the Paramyxoviridae family respiratory virus are enhanced. Thus, the circadian clock regulates cellular immunity against viruses, parasites and bacteria [56]. The interdependent relationship is present between circadian rhythm, infections and inflammation, where the disruption of the host circadian clock by a dramatic decrease in the levels of circadian rhythms by infections and inflammation is also evident in infections with *Trypanosoma cruzi* (Chagas disease), *Trypanosoma brucei* and *Plasmodium* (Malaria) [57, 58]. This downregulation of clock gene expression appears to be a massive immune response to the infectious invasion, as the pro-inflammatory cytokines decrease the magnitude of the rhythms in vitro [59]. This can be highly applicable to humans, as a study concludes that the parasite may disturb the sleep of patients by the modification of their circadian clocks. This occurs by a systemic signal secreted by the host or parasite molecule and can shorten the period of the circadian clock. Thus, the infections can impact the circadian rhythm [58].

When clock genes in the host are disrupted, the microbiota rhythms appear to be affected, which leads to metabolic interactions between the gut and host microbiome [60]. The absence of gut microbes also disturbs the circadian clock gene expression in the mouse liver [61]. When clock genes in the host are disrupted, the microbiota rhythms appear to be affected, which leads to metabolic interactions between the gut and host microbiome [62].

Immune-modulation of circadian rhythms in anti-bacterial immunity

Circadian rhythm and its influence on physiological processes is well documented [63]. Circadian rhythm is a network of transcription factors that drives rhythmic gene expression and metabolic activity over a ~ 24 h cycle synchronised by the suprachiasmatic nucleus (SCN) in the hypothalamus and non-SCN cues [64]. These rhythms

are driven by a transcriptional-translational feedback loop involving transcription activators CLOCK and BMAL1 which regulate the expression of repressor proteins period and cryptochrome which in turn inhibits CLOCK/BMAL-1 generated transcription in virtually all tissues [63]. Of particular interest is the possible role of circadian rhythms in regulating intestinal microbiota. Approximately 100,000 billion microbes constitute the intestinal microbiota and contribute to intestinal integrity and defence against pathogenic microbes. The microbiota composition may differ according to age and nutrition and is also subject to disruptions in circadian rhythms, subsequently leading to dysbacteriosis and intestinal infections [65]. Compelling evidence also suggests the modulation of bacterial immunity by circadian rhythms, first observed in the 1960s with response to infection by Gram-negative bacteria varying according to times of the day [9].

Circadian rhythms also influence neutrophil activity in a slightly different manner [66, 67]. Neutrophil expression of CXCR4 and morphological attributes such as side-scattering properties and nuclear segmentation, distribution of young and aged cells within the peripheral blood all demonstrate daily rhythms. Plasma levels of the CXCR4 ligand CXCL12, significant modulators of cell trafficking in the bone marrow, also fluctuate synchronously during the day. Studies have evidenced that NADPH oxidase activity also changes depending on the time of the day [67]. As reported by Hriscu, studies on mice and rats demonstrate basal phagocytosis in neutrophils peaks in the second part of the dark phase, dependent on nocturnal melatonin surge by the pineal gland [66]. As a result, phagocytosis and antimicrobial activity of neutrophils show time-dependent differences, further substantiating the role of circadian rhythm in antibacterial immunity [67]. Circadian rhythms possibly influence humoral adaptive immunity, such as B-lymphocytes and subsequent antibody production. When studied on rat lymph nodes, B-lymphocytes which play a pivotal role in humoral immunity show fluctuations according to the day-night cycle with peaks observed during the night [68]. The circadian cycle is also a significant driver for B cell maturation, with BMAL1 knockout (KO) mice demonstrating impaired B lymphocytes [69]. Therefore, the function of key players in immune defence against bacterial infections is modulated by circadian rhythm and disturbances in circadian rhythms or melatonin activity can potentially influence immunity. The circadian rhythm may also play a role in the does timing for antibiotics however, that effect has currently not been explored showing the need for further knowledge on the matter.

Further research exploring the complex interplay between diurnal changes in melatonin, cortisol activity and antibacterial immunity could provide a novel explanation for different susceptibilities to infection and open therapeutic pathways in infectious disease control.

Interactions between viral infection and circadian rhythms

The Circadian clock in mammals functions based on a transcriptional/ translational feedback loop primarily involving four clock proteins, two activators (CLOCK and BMAL1), and two repressors (PER and CRY) [70]. Mure et al. found that more than four-fifths of the protein-encoding genes in primates showed diurnal rhythmic variation [71]. Viruses are obligate anaerobes and depend on their host to complete their life cycle [72]. They are expected to adapt to the host's circadian rhythm. The role of different viruses in circadian rhythm is demonstrated in Fig. 2.

Dengue virus

Dengue is a significant public health threat caused by the dengue virus, transmitted by Aedes aegypti, and is endemic to more than 100 countries across the globe [73]. In dengue viruses, REV-ERB significantly contributes in regulating the circadian rhythm through metabolic pathways [74] and inhibits the transcription by repressing the stearoyl-CoA-desaturase (SCD) expression [75]. Another study by Lima-Camara et al. reported a significant increase (10.3–48%) in the locomotor activity of female Aedes aegypti infected by Dengue compared to controls [76]. Though the mechanism of dengue viruses causing circadian fluctuations is poorly understood, multiple in-vitro studies have postulated that the infection modulates vector locomotor activity, as circadian clock neurons are known to regulate the activity of *Drosophila* and its ability to fight infection under circadian control [76].

Viral hepatitis infection

Chronic Hepatitis B and Hepatitis C virus infection through the deleterious effect on the liver, such as cirrhosis and hepatocellular carcinoma, can lead to significant mortality and morbidity [77]. Yang et al. found that in HBV infection, PER 1 and PER 3 genes were downregulated in 90% of cases, and mRNA levels of PER genes were significantly lower in HCC tumour cells compared to peritumoral tissues [78]. PER genes are responsible for inhibiting transcriptional activity [79], and the downregulation of tissues can lead to increased activity of CLOCK-BMAL 1 genes and ultimately to increased transcriptional activity. This may explain the association of HBV with hepatocellular carcinoma [80]. A study by Benegiamo et al. found that HCV RNA levels were

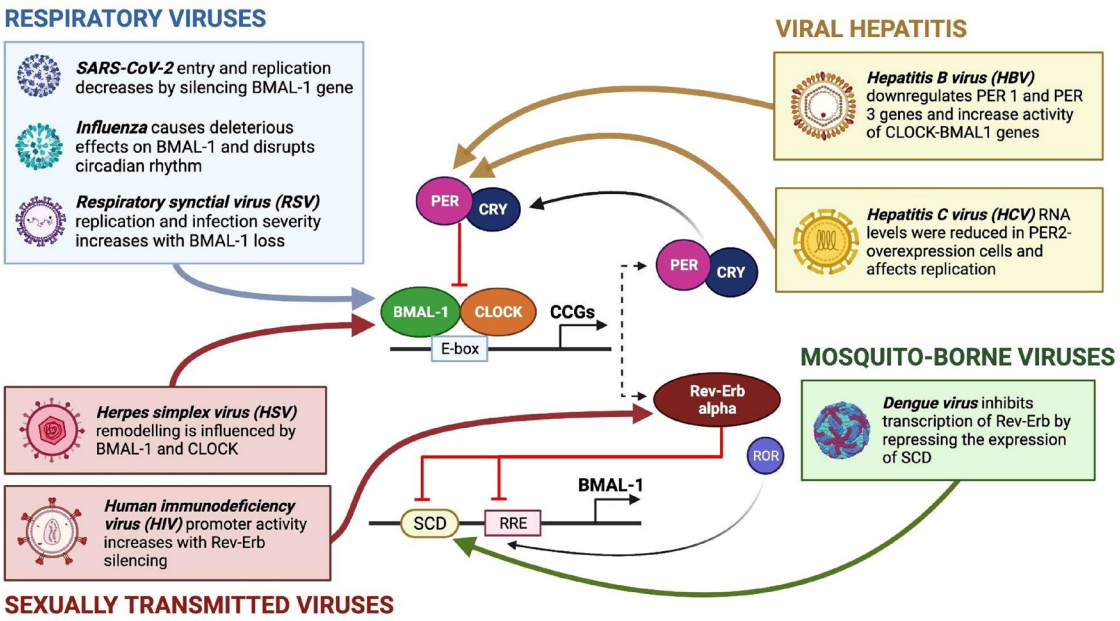

Fig. 2 A summary of the association between viral infection and the CLOCK:BMAL1 pathway. (Created with biorender.com by HH). SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, BMAL-1 brain and muscle ARNT-like 1, CLOCK circadian locomotor output cycles kaput, CCGs clock controlled genes, PER period circadian regulator, CRY cryptochrome circadian regulator, Rev-Erb reverse orientation c-erbA gene α, ROR retinoic acid-related orphan receptor, RRE rev response element, SCD stearoyl-CoA-desaturase

significantly reduced by approximately 27% in PER2-overexpressing cells. This shows that PER 2 genes can significantly affect HCV replication. Also, Zhuang et al. showed that REV-ERBα could lead to dose-dependent inhibition of HCV entry and replication [75]. These findings suggest a complex interplay between Hepatitis viruses and the circadian rhythm.

Sexually-transmitted viral infections

Herpes simplex virus (HSV) and human immunodeficiency virus (HIV) are the two most common viruses that cause sexually-transmitted infections: Herpes simplex viruses (HSV) and human immunodeficiency viruses (HIV). Herpes simplex virus can lead to primary and recurrent infection, and the biological properties such as neuroinvasiveness and neurotoxicity can lead to significant mortality [81]. Kalamkovi et al. established the link between circadian genes and HSV. They found that BMAL 1 and CLOCK are involved in remodelling herpes simplex viral chromatin [82]. In addition, HIV is an evolving epidemic and public health concern, leading to a wide range of systemic manifestations [83, 84]. Various studies have been conducted to identify the association between the circadian rhythm and HIV infection. Borrmann et al. reported that silencing REV-ERB leads to increased HIV 1 promoter activity [85], and Chang et al. found a significant association between the BMAL1 gene and HIV RNA level. Furthermore, Clark et al. revealed that HIV Tat could alter the host's circadian rhythm [86]. Also, Tat, through BMAL 1 gene can alter circadian rhythms [87, 88] and decrease the locomotor activity and consequently, the amplitude of the circadian clock in mice [89].

Viral respiratory infections

Influenza is an acute respiratory infection with pulmonary and extrapulmonary manifestations caused by the influenza virus [90]. Sundar et al. studied the interaction between influenza virus and circadian rhythm and showed that influenza virus infection leads to circadian disruption, with a particularly deleterious effect on BMAL knockout mice [91]. In addition, immune cells demonstrated a significant increase in number for wild-type infected mice [92]. Other studies supported that the cellular circadian clock significantly impacts herpes virus infection, and BMAL 1 expression is different based on the timing of infection [93, 94]. Moreover, Majumdar et al. found that BMAL 1 loss resulted in more replication and enhanced severity of infection in parainfluenza virus-3 and RSV [56]. With SARS-CoV-2 being at the forefront of research, studies have that circadian disruption often correlated with acute-COVID-19 complications. COVID-19 disease is an acute respiratory illness due to SARS-CoV-2 infection. It has transformed into a pandemic and a global public health issue, with significant mortality rates in high-risk groups [95]. Moreover, post-COVID-19 manifestations

can also have deleterious effects on global public health. Studies have been done to identify its association with the circadian clock. Zhuang et al. studied the effects of circadian clock genes and found that silencing the BMAL 1 gene or treatment of lung epithelial cells by REV-ERB agonist reduced ACE2 expression and inhibited SARS-CoV-2 entry and replication [96]. However, other pathways may contribute to this as COVID-19 remains unexplored [97].

The influence of circadian rhythm on the life cycle of parasites

It is well known that as humans we have a circadian rhythm that interplays with the immune system to defend and attack pathogens that become a threat to our organism. It is still under research with rodent experiments that Circadian clocks are a fundamental part of parasites because they allow them to live longer and grow rapidly. It has been studied that Trypanosoma Brucei, the organism that causes African Sleeping Sickness, has shown circadian daily patterns regulated by transcription and translation feedback mechanisms [98]. It is known that the main problem in the disease is the reversal of sleep and awakenings cycles, the person sleeps during the daytime and experiences insomnia at night time [58]. From mouse blood samples infected with *T. Brucei*, it was noted that these possessed oscillating transcripts which allows the parasite to have its own ability to generate rhythmicity independently from the host rhythm thus making it easier to adapt and also facilitating access to the brain which disrupt sleep pattern, temperature and damages endocrine signals. It is observed that inflammation affects the circadian rhythm in the host when infected and that an adaptive immune response with Lipopolysaccharide and interferon-gamma with the trigger of the suprachiasmatic nuclei affects the sleep–wake cycle [99]. Malaria is an infectious disease caused mainly by four parasites in humans: Plasmodium Vivax, Ovale, falciparum and malaria. It invades red blood cells as schizont to asexually reproduce and to continue to infect other cells as merozoites [100]. It was noted through mice experiments with *Plasmodium Chabaudi* infection that the parasite created its rhythmicity during the outburst periods of the asexual reproduction cycle and was not affected by the feeding pattern in mice [100, 101]. It does remain unclear however if the same process applies in the human host and the intraerythrocytic development cycle [102]. In another in-vitro study with *P. falciparum*, it was concluded that in fact, *P. falciparum* needs to possess an intrinsic oscillator which means that it follows its own circadian rhythm and is not affected by external cues and that as *T. Brucei* it is regulated by transcription [101, 103]. There is still a lot to unfold for Plasmodium species because their correlativity with the human circadian rhythm it's undergoing investigations. Another parasite that continues to be under research is Schistosoma Mansoni, it has been observed through studies in rodent hosts that their circadian clock and function are influenced by white blood cell count, oxygen, glucose and thermoregulation [99]. In another study, it was also noted that both host and parasite matched their circadian clock. During The waking phase of the host, the parasites were under stress and laying eggs. During the sleeping cycle, the parasite would be undergoing metabolism and interacting with the host immune system showing this way the similar clock shared among both and that perhaps because of this, S. Mansoni can live for so long in the host [104, 105]. Host and parasites' interactions with the circadian clock is an interesting discovery that with no doubt we will be able to know more about in the future.

Emerging evidence of circadian disruption in fungal infections from plant-based studies

Unlike the influence of bacterial, viral and parasitic pathogens on the circadian rhythm, less is known about the effect seen in fungal infections. The information about the circadian clock circuits of fungal infection and its effects stemmed from studies conducted on the *Neurospora* species [106]. The circadian effects of *Neurospora* stem from several proteins including the Frequency (FRQ) proteins as well as White Collar-1 and 2 (WC1-2). Stuart Brody discovered that of the 13 FRQ homologues studied using MEME analysis, at least four different regions of FRQ were maintained across all species [107]. This is consistent with an earlier work by Salichos et al. on the development of circadian clock proteins in fungus [108]. The commonality discovered in this research allows us to generalize that the circadian proteins and effects of Neurospora fungus proteins may be detected in other fungal infections. However, due to a lack of understanding about the real circadian rhythm of these pathogens and few investigations outside of plant-fungal interactions, generalizing the consequences of fungal infections in humans is extremely challenging. New research is being carried out to determine if fungal infections have intrinsic oscillators and how the circadian clock regulates host relationships. Botrytis cinerea was found as one of the first necrotrophic fungal diseases to include internal circadian clocks and to play a role in BcFRQ1 (a Botrytis ortholog of Neospora core clock). When the oscillator of *B. cinere* is disrupted through mutations of BcFRQ1 or suppression of rhythmicity, circadian regulations of virulence become absent [109]. As a result, the circadian clock of fungal pathogens influences light-to-dark interactions of the plant *Arabidopsis-Botrytis* [110]. Additionally, Bluhm et al. identified the circadian rhythm to regulate hyphal melanisation

in *Cercospora Kikuchi* and its persistent growth after the colonies were transferred to darkness from the absence of external light [111].

The predominant fungal infections seen in humans stem from *Aspergillus fumigatus* and *Candida Albicans* [106]. However, because the expression of wc-1 and wc-2 varies amongst the aforementioned infections, it is unknown how the circadian clock system is structured in human fungal diseases [112]. These proteins can operate in a feedback loop which allows for different protein interactions as well as phosphorylation [106]. Despite this information, detailed studies and knowledge about the specific effects of these proteins are both lacking. Assumptions have been made that fungal infections interact similar to how bacterial infections impact the body with effects on macrophages and neutrophils. However, no studies have been able to confirm this as of yet. In 2018, Chen et al. conducted a study on Aspergillus fumigatus to try to illuminate some of the effects and found a time-of-day influence on its clearance in mice models, but the methods behind the effect remained unclear [113]. Future work on this subject is needed as the expansion of knowledge that can come from these studies could also potentially help the treatment of these ailments.

Therapeutic intervention and avenues for circadian rhythm disruption from infectious diseases

The immune system and the circadian cycle have a complex relationship. In some infectious disorders, this interaction can be disrupted, resulting in a reduced immune response. To treat this type of disturbance, different types of therapies including a mixture of chronotherapy and pharmacotherapy have been developed and continue to be developed to treat these circadian rhythm disruptions. Several therapies focus on targeting different receptors involved with circadian machinery because infectious diseases use these receptors to further their effects. Figure 3 shows a general schematic demonstrating the possible sites of therapeutic intervention already established in the field of chronotherapy. An example of this includes synthetic REV-ERB agonists. REV-ERB is a nuclear receptor that participates in a variety of functions, including immunology and circadian rhythm [114]. These agonists can bind to the REV-ERB receptor and prevent RNA replication, infectious particle release, and HCV entrance [70]. This causes a decreased expression of stearoyl-CoA-desaturase which is a rate-limiting step in the viruses' replication. By decreasing promoter activity, these agonists were also found to suppress HIV replication and transcription [85]. Similarly, ROR inverse agonists can be used to limit viral replication because they were found in vivo to compete and bind to the same DNA response elements as REV-ERB agonists [115].

Melatonin regulation is another example. The pineal gland produces melatonin, which is regulated by the suprachiasmatic nucleus (SCN). As a result, the CLOCK:BMAL pathway can regulate the melatonin cycle through various methods [116, 117]. There are multiple receptors for melatonin both in the SCN and in other non-SCN sites in the brain but primarily can prompt circadian rhythm-induced proliferation through the interaction of CLOCK genes with c-Myc [117]. Multiple recent reviews found that melatonin and its possible analogues can resynchronise circadian rhythm disturbances [116]. Regimens involving exogenous melatonin administration or melatonin agonists/analogues were found to treat circadian disruptions and have been seen in murine models to improve low-grade infections. These experimental studies demonstrated that melatonin administration during the day induced a powerful inflammatory response against infection, as host immune response mechanisms were more effective during the night [117–119]. As a result, prospective studies were able to establish that melatonin could accelerate therapy for septic patients, as they experienced higher levels of cortisol and a weakened inflammatory response during circadian disruptions [120]. Melatonin agonists are promising for the treatment of circadian disruption caused by parasitic infection, such as the suppression of *Trypanosoma cruzi*. Macias et al. also reported melatonin to increase RBC invasion of *Plasmodium Chabaudi* and affect parasitic maturation, making agonists a therapeutic strategy [121, 122]. Melatonin therapy should be explored as a treatment option for patients experiencing circadian disruption while also deepening our understanding of the efficacy of melatonin analogues in the treatment of circadian dysregulation from infectious diseases.

Another therapy route that has been briefly mentioned is the use of hormonal therapies. Patients with untreated or undertreated adrenal insufficiency had a greater risk of infection and a fivefold increase in infection mortality [123]. This may be seen in a number of circumstances. Cushing's syndrome is a frequent example. Cushings syndrome, also known as chronic hypercortisolism, has been linked to higher levels of interleukin-1 (IL-1) and interleukin-6 (IL-6) as well as adipose tissue invasion by immune cells, resulting in a persistent, nonresolving inflammatory state [124]. It has been shown that being prone to prolonged inflammation renders one more vulnerable to infectious illnesses such as aspergillosis and cryptococcal infections. Replacement regimens have been shown to reduce infection susceptibility in people with adrenal insufficiency by improving mortality and restoring normal glucocorticoid secretion patterns insufficiency [123].

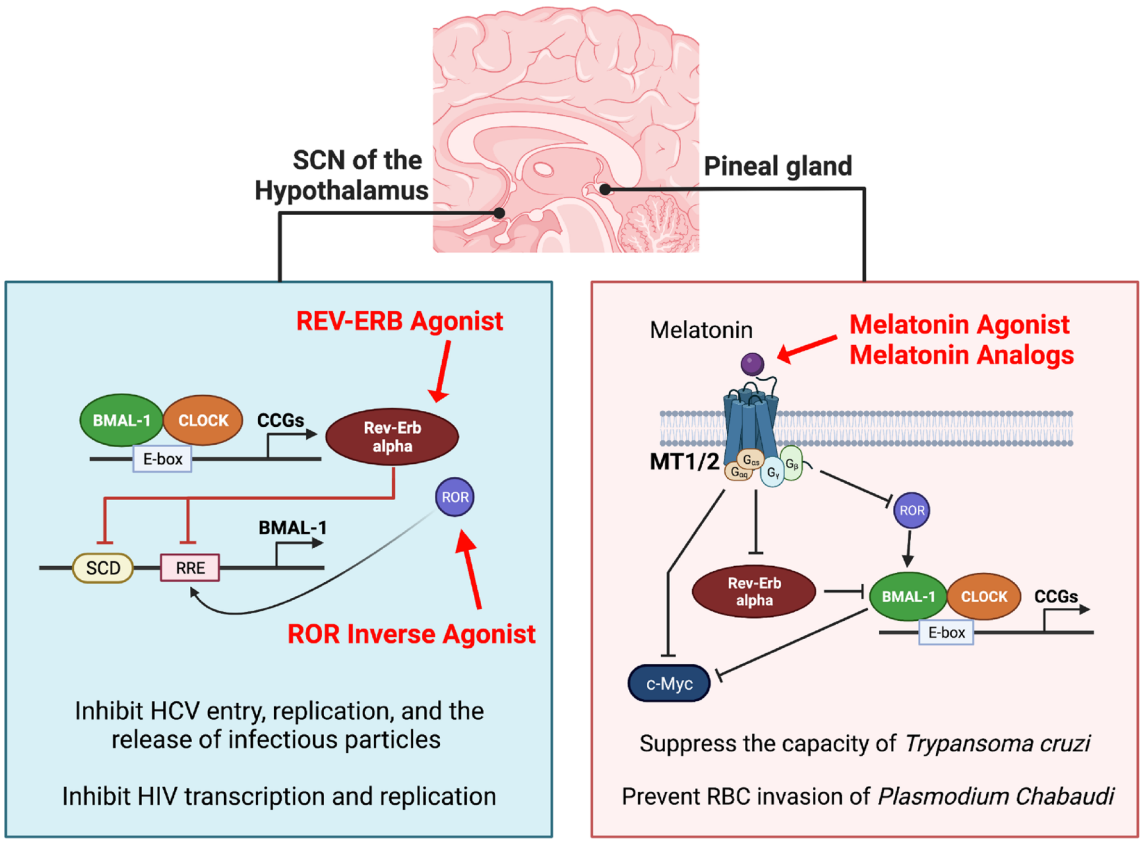

Fig. 3 Sites for therapeutic intervention to modulate Rev-Erb and ROR expression in the suprachiasmatic nucleus (SCN) of the hypothalamus and the role of melatonin agonists on the CLOCK:BMAL1 pathway. (Created with biorender.com by HH). BMAL-1 brain and Muscle ARNT-like 1, CLOCK circadian locomotor output cycles kaput, CCGs clock controlled genes, Rev-Erb reverse orientation c-erbA gene α, ROR retinoic acid-related orphan receptor, RRE rev response element, SCD stearoyl-CoA-desaturase, c-Myc cellular Myc; MT 1/2, melatonin receptors, HCV hepatitis C virus, HIV human immunodeficiency virus

Though the discussed treatments are only a few potential therapeutic interventions used to correct circadian rhythm disruption, further studies should focus on overcoming the disruption of homeostasis caused by bacterial and fungal infections. Several studies that were carried out to determine the susceptibility of antibiotics in pathogens determined that circadian rhythm disruption in those pathogens led to different periods of sensitivity of pathogens toward antibiotics and thus to antibiotic resistance in several cases [125]. In addition to this, the specific timing of antibiotic usage has been subject to debate. In viral interventions, it was found that acyclovir administration in HSV-2 infected murine models should be timed, as a higher dosage was needed when infected at ZT18 [126], However, it is not known whether the synchronisation of antibiotics would have an effect on bacterial infection at different time-points of the day and whether the timing of antibiotic administration is related to circadian rhythms. The emergence of chronopharmacology may shed better insight on the effects of therapeutic intervention at different-time points and will eventually open the way to new antibiotic administration strategies to enhance their efficacy and overcome antibiotic resistance [127].

Conclusions of several studies regarding the role played by circadian rhythm in the host immune response toward pathogens have made circadian rhythm a new instrument for assessing and determining infectious disease outcomes as well as improving anti-infectious medication administration strategies [8]. This would allow for better use of current therapies and a potential increase of new ones which could lead to an improvement in patient outcomes. While there are promising avenues to develop novel treatments for circadian disruption, the lack of literature delineating the association between fungal infections and the circadian clock presents challenges in the future direction of treatment for infectious fungal diseases.

Conclusion

Circadian rhythm disruption in response to infection is now well known and established. It is determined by molecular clocks and does influence the host's response toward infection. Such mechanisms vary between bacterial pathogens and viral infections, both of which are well studied in the literature. However, less is known of the association of parasitic infections and fungal pathogens with circadian rhythm modulation. It is paramount that further in-vitro studies are conducted to fully understand the influence of common human fungal infections on circadian rhythm modulation to improve treatment options in these patient groups. Though the discussed regimens are only a few potential therapeutic interventions used to correct circadian rhythm disruption, further studies should focus on overcoming the disruption of homeostasis caused by bacterial and fungal infections. Regardless, conclusions of several studies regarding the role played by circadian rhythm in the host immune response toward pathogens have made circadian rhythm a new instrument for assessing and determining infectious disease outcomes as well as improving anti-infectious medication administration strategies. This would allow for better use of current therapies and a potential increase of new ones which could lead to an improvement in patient outcomes.

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Declarations

Conflict of interest Authors have no conflicts of interest to declare.

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