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REVIEW

immunology
Insights into immunity in health and disease

Circadian rhythm regulation in the immune system

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Abstract

Circadian rhythms are a ubiquitous feature in nearly all living organisms, representing oscillatory patterns with a 24-h cycle that are widespread across various physiological processes. Circadian rhythms regulate a multitude of physiological systems, including the immune system. At the molecular level, most immune cells autonomously express clock-regulating genes, which play critical roles in regulating immune cell functions. These functions encompass migration, phagocytic activity, immune cell metabolism (such as mitochondrial structural function and metabolism), signalling pathway activation, inflammatory responses, innate immune recognition, and adaptive immune processes (including vaccine responses and pathogen clearance). The endogenous circadian clock orchestrates multifaceted rhythmicity within the immune system, optimizing immune surveillance and responsiveness; this bears significant implications for maintaining immune homeostasis and resilience against diseases. This work provides an overview of circadian rhythm regulation within the immune system.

KEYWORDS
circadian regulatory factors, circadian rhythms, immune cell functions, immune system

INTRODUCTION

The cyclical environmental changes resulting from the Earth's rotation have a profound impact on the physiological activities of organisms. Human physiological functions also exhibit ~24-h rhythmic variations, referred to as circadian rhythms. Circadian rhythms represent an organism's adaptive response to environmental changes, a concept first proposed by Halberg et al. in 1959 to describe this intrinsic physiological regularity [1, 2].

Abbreviations: ARNTL, aryl hydrocarbon receptor nuclear translocator like; ATP, adenosine triphosphate; BMAL1, brain and muscle aryl hydrocarbon *r*eceptor nuclear translocator like 1; CCL2, C-C motif chemokine ligand 2; CCR7, C-C motif chemokine receptor 7; CD80, cluster of differentiation 80; CLOCK, Circadian locomotor output cycles kaput; COX4, cytochrome c oxidase subunit 4; CRY, cryptochrome circadian regulator; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor type 4; DBP, albumin D-box binding protein; DCs, dendritic cells; DHFR, dihydrofolate reductase; DRP1, dynamin-related protein 1; E4BP4, E4 promoter-binding protein 4; IL-17, interleukin 17; IL-1β, interleukin 1 beta; LECs, lymphatic endothelial cells; LYVE-1, lymphatic vessel endothelial receptor 1; MAPK, mitogen-activated protein kinase; NAD, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyl transferase; NFIL3, nuclear factor interleukin-3; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain containing 3; NRF2, nuclear factor erythroid 2-related factor 2; OVA, ovalbumin; PER, period circadian regulator; REV-ERB, nuclear receptor subfamily 1 group D member 1; RORE, retinoic acid receptor-related orphan receptor response element; SCN, suprachiasmatic nucleus; SIRT1, Sirtuin 1; TCR, T-cell receptor; TH17, T helper 17 cells; TLR9, toll-like receptor 9; VSV, vesicular stomatitis virus; ZAP70, zeta chain-associated protein kinase 70; γδT17, gamma delta T 17 cells.

Jun Ding and Pengyu Chen contributed equally to this work.

Circadian rhythms are generated by biological clocks, with the core region of the mammalian biological clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, also known as the central clock [3]. The stability of an organism's overall rhythmicity requires the coordinated action of the SCN and peripheral clocks, involving the participation of both the autonomic nervous system and the endocrine system (such as steroid hormones) [4]. Research indicates that the circadian rhythms driven by the biological clock play a crucial role in regulating the immune system [5, 6]. Various aspects of the immune system, from molecular to cellular to organelle levels, are regulated by the circadian rhythms of the organism (Figure 1). Disruption of these circadian rhythms can lead to immune system dysfunction, increasing the likelihood of conditions such as tumour development, exacerbated inflammatory responses, and autoimmune diseases [7]. Given the regulatory role of circadian oscillations on the immune system, this article provides a review of the latest research progress on circadian rhythm regulation within various aspects of the immune system. This review can aid in clinically determining optimal treatment times and exploring new immune therapies based on these rhythmic patterns.

KEY REGULATORY FACTORS OF CIRCADIAN RHYTHMS AND THEIR ROLES IN THE IMMUNE SYSTEM

Circadian rhythms at the molecular level stem from a transcription–translation oscillatory feedback loop comprised of a set of clock genes [8]. At the core of this loop are the central genes BMAL1 (also known as ARNTL) and CLOCK, whose transcription products form a heterodimer. This heterodimer binds to E-box sites and induces the expression of inhibitory factors PER and CRY. These inhibitors, in turn, can suppress the expression of BMAL1 and CLOCK by interfering with the heterodimer. When the expression of central genes is downregulated, the inhibitory effect of these factors weakens, allowing the expression cycle to begin anew with another 24-h period. The second loop is composed of the genes REV-ERB and ROR; they are activated by the BMAL1-CLOCK heterodimer binding to E-box sites and can bind to the retinoic acid receptor-related orphan receptor response element in the BMAL1 promoter region upon translocation into the cell nucleus. When RORs are activated, REV-ERBs inhibit the expression of BMAL1. Meanwhile, a third loop is formed by the albumin D-box binding protein (DBP) and the transcriptional repressor nuclear factor interleukin-3 (NFIL3, also known as E4BP4), which regulates the transcription of genes containing D-box sequences, including the PER gene [9, 10]. These three loops constitute the foundation of the organism's circadian rhythm regulation.

Role of the key circadian gene BMAL1 in immune system regulation

Studies have reported that BMAL1 is involved in regulating the circadian clocks of lymphatic endothelial cells (LECs) and dendritic cells (DCs) in the skin, which is

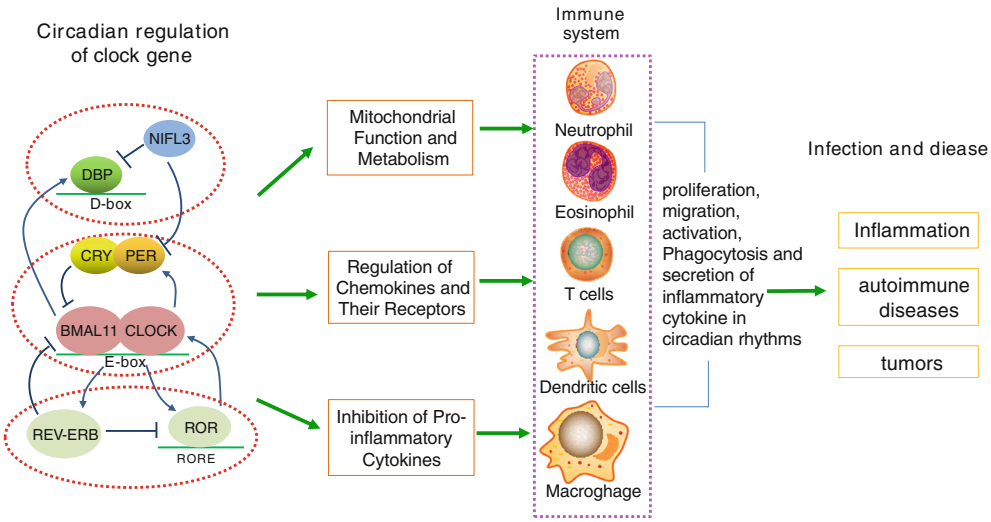

FIGURE 1 The translation–transcription loop comprising components of the circadian rhythm genes, which govern the transcription and expression of genes associated with mitochondrial structural function, chemokines and receptors, as well as pro-inflammatory factors within immune cells. This regulatory mechanism subsequently influences immune cell proliferation, migration, phagocytosis, metabolism, secretion of inflammatory factors, and immune response efficacy. Ultimately, this intricate process modulates the body's inflammatory response and the development of diseases such as autoimmune conditions and tumours.

crucial for DC entry into the skin's lymphatics. BMAL1 regulates the circadian expression of the chemokine receptors CCR7 and CXCR4 on the surfaces of these immune cells by influencing the internal clocks of skin LECs and DCs [11, 12]. This rhythmic expression is essential for the migration of white blood cells and DCs from peripheral tissues to the lymphatic system.

Additionally, BMAL1 can directly bind to the promoter regions of chemokine genes such as CCL21, CCR7, and LYVE-1, thereby regulating their transcriptional activity. This induction of circadian expression of chemokines in LECs guides immune cells to enter the lymphatic system in a time-dependent manner. Specific knockout of BMAL1 in endothelial cells leads to a reduced ability of immune cells to enter lymph nodes, and complete loss of BMAL1 disrupts the rhythmic migration activity of immune cells between lymph nodes and nonlymphatic tissues [13].

Beyond its role in immune cell migration, studies have shown that BMAL1 can directly bind to the promoter regions of target genes, including pro-inflammatory and antioxidant factors, to regulate their circadian expression, thereby influencing the inflammatory responses of immune cells. BMAL1 expression and activity also exhibit clear circadian rhythmicity, and its absence leads to abnormal inflammatory responses in immune cells [14–16]. Therefore, BMAL1 plays an important role in maintaining immune system homeostasis by regulating the circadian genes of immune cells and the circadian expression of inflammatory factors.

The immune regulatory role of circadian gene REV-ERB in inflammation and diseases

REV-ERB is a crucial member of the nuclear receptor superfamily, with two main subtypes identified: REV-ERBα and REV-ERBβ. As important transcriptional regulators, REV-ERBs are widely expressed in various immune cells, including DCs, macrophages, and T cells [17]. They not only participate in the regulation of normal circadian rhythms and physiological processes but also serve as key modulators of immune system function, connecting innate and adaptive immunity. Increasing evidence suggests that REV-ERB is involved in regulating the pathogenesis of various autoimmune diseases. For example, in diseases such as psoriasis, REV-ERB can inhibit the production and release of IL-17, negatively regulating TH17-mediated inflammatory responses [18, 19]. Mechanistic studies have shown that gene knockout of REV-ERB leads to a significant increase in γδT17 cells in the skin of mice, while the REV-ERB-specific agonist SR9009 can directly act on γδT17 cells, significantly alleviating skin inflammation [18].

In addition to regulating IL-17 expression, REV-ERB can suppress the production of other pro-inflammatory factors, exerting a broader immunomodulatory effect [20, 21]. In macrophage inflammation models, activating REV-ERB can inhibit the production of pro-inflammatory cytokines such as IL-1β. Mechanistic studies have revealed that activated REV-ERB can suppress the formation of the NLRP3 inflammasome, reduce intra-cellular caspase-1 protein levels, and consequently reduce IL-1β generation [22]. This pathway is applicable not only to acute inflammation models but also to various chronic inflammatory diseases, such as rheumatoid arthritis. Additionally, as an essential component of REV-ERB, REV-ERBα can directly inhibit the expression of inflammatory factors such as CCL2 in immune cells, negatively regulating the inflammatory functions of macrophages, among others [23]. REV-ERBα expression exhibits significant circadian rhythmicity, and it, along with BMAL1, participates in regulating the rhythmicity of various immune cell physiological processes. The loss of REV-ERBα also leads to abnormal inflammatory responses in immune cells [24].

Therefore, the development of small molecule agonists targeting REV-ERB, harnessing its ability to regulate the body's immune and inflammatory responses, offers new hope for the treatment of immune-related diseases such as psoriasis and rheumatoid arthritis. However, the precise molecular mechanisms by which REV-ERB is involved in the pathogenesis of autoimmune diseases require further investigation, serving as a crucial foundation for the development of targeted REV-ERB-based therapies.

The impact of the circadian genes *PER* and *CRY* on disease occurrence

PER and *CRY* genes encode a protein family that is a core component of the primary circadian regulation network in mammals. As previously mentioned, this network mainly consists of PER, CRY, and the CLOCK/BMAL1 transcription complex, forming a loop through a complex series of membrane feedback mechanisms capable of generating ∼24-h autonomous oscillations [25]. The PER protein family mainly includes members such as PER1, PER2, and PER3, all of which exhibit distinct circadian rhythmic patterns in their expression and activity [26]. At the molecular level, PER proteins form heterodimers with CRY, inhibiting the transcriptional activity of CLOCK/BMAL1 and achieving rhythmic feedback regulation [27].

Increasing evidence suggests that abnormal expression or activity of PER and CRY can lead to the development of various diseases, including cancer, inflammatory diseases, metabolic disorders, and more; this indicates that they not only participate in the regulation of normal circadian rhythms but also serve as crucial links between circadian disruption and disease occurrence. Studies show that in immune-related inflammatory diseases such as allergic rhinitis, disrupted expression of PER2 can disturb the circadian rhythms of immune cells such as Th cells, altering the day–night pattern of allergic rhinitis symptoms [28]. In various tumours, including lung adenocarcinoma, PER1 and PER2 often show reduced expression, making the PER genes tumour suppressor genes [27, 29]. Furthermore, the polymorphisms of PER and CRY genes can also affect susceptibility to diseases and clinical prognosis. In colorectal cancer, the polymorphism of PER3 influences patient treatment response [30].

Circadian rhythms in immune cells

Many important immune cells in the immune system exhibit highly autonomous circadian rhythms in both their quantity variations and functional activities. This includes neutrophils, eosinophils, lymphocytes, DCs, and more. Research has shown that immune cells themselves also express core clock genes such as BMAL1, and their circadian physiological rhythms are not directly governed and regulated by the central clock of individuals [31, 32]. Even when these immune cells are isolated and cultured in vitro, processes such as migration capacity, proliferation cycles, metabolic activity, and more can maintain continuous near 24-h autonomous oscillations [33].

The generation of circadian rhythms in immune cells is related to the operation of their internal core clock gene networks. For instance, knocking out the BMAL1 gene in DCs can disrupt the circadian rhythms of their metabolism and function [34]. Additionally, different immune cells exhibit significant circadian rhythmic differences in their peak quantities, which is crucial for the coordinated immune surveillance and initiation of immune responses among various cell populations. Disrupting this autonomous rhythm in immune cells can lead to disturbances in the immune response and surveillance processes, potentially worsening disease outcomes. The molecular mechanisms behind this autonomous circadian rhythm in immune cells are not entirely clear; it may be related to the circadian changes in mitochondrial metabolism within cells or the time-dependent expression of signalling pathways that promote immune activity [35].

Circadian rhythms in neutrophil marrow mobilization and tissue homing

Neutrophils are vital effector cells in the innate immune system. After being released from the bone marrow into the bloodstream, neutrophils can infiltrate infected or inflamed tissues to participate in immune responses. Research has revealed significant circadian variations in the mobilization of neutrophils from the bone marrow into the blood and their entry into peripheral tissues [36–38]. During the daytime, neutrophil numbers in the blood are relatively low; however, their release increases significantly during the beginning of the night, peaking in quantity [39]. This rhythmic mobilization of neutrophils from the bone marrow into the blood is regulated by adrenergic neural transmission and circadian expression changes in the bone marrow stromal cell chemokine CXCL12 [40]. On the other hand, neutrophil infiltration into peripheral tissues such as the lungs, liver, and skin also exhibits distinct circadian rhythms, with higher levels during the active phase. Tissue-level rhythmic homing is regulated by cell surface receptors and the diurnal release of glucocorticoids. Deletion of the core circadian gene BMAL1 significantly weakens these circadian migratory patterns of neutrophils, indicating that this migration process is controlled by the endogenous molecular clock [4]. Thus, from marrow mobilization to homing in peripheral tissues, neutrophil migration is marked by significant circadian rhythms that critically influence the timing and intensity of their involvement in immune and inflammatory responses.

Circadian rhythms in lymphocyte migration in lymph nodes

Studies indicate that lymphocytes exhibit significant circadian rhythms in their flow and quantity variations within lymph nodes. During the daytime, lymph nodes contain relatively fewer lymphocytes [41]. However, when the night-time active phase begins, a large number of lymphocytes rapidly enter the lymph nodes, causing a rapid accumulation of lymphocytes within the lymph nodes, reaching peak numbers [36, 37]. Further research has found that this circadian pattern of lymphocytes massively entering lymph nodes is not influenced by external environmental day–night changes and is not disrupted by brief light conditions; instead, it is predominantly regulated by an individual's endogenous molecular clock mechanisms. Experimental deletion of the core circadian gene BMAL1 or its inhibition can disrupt these circadian patterns of lymphocyte flow within lymph nodes [41].

Additionally, during the time window when lymphocyte numbers peak daily, immunizations or exposure to

vaccines can induce stronger immune responses [37, 41]. This response further confirms the significant physiological regulatory role of circadian rhythms in lymphocyte entry into lymph nodes in modulating the body's immune responses. In summary, lymphocytes entering lymph nodes, as well as their quantity and flow within lymph nodes, exhibit autonomous periodic fluctuations, which provides important insights for deeper exploration of the intrinsic regulatory mechanisms of the immune system's rhythms and the development of personalized treatment approaches for adaptive immune diseases.

Circadian rhythms in myeloid monocyte and eosinophil

Myeloid monocytes and eosinophils, including macrophages and DCs, are crucial effector cells in the innate immune system, and their numbers and functional activities also display significant circadian rhythms. Studies show that the release of these immune cells from the bone marrow into the peripheral blood exhibits regular day–night fluctuations; their numbers are lower during the daytime but significantly increase at the beginning of the active phase, reaching peak numbers during the day [41, 42]. Furthermore, myeloid monocytes and eosinophils also enter peripheral tissues such as the skin, liver, lungs, lymph nodes, and spleen in a rhythmic manner, participating in immune surveillance. This rhythmic homing to tissues relies on the regulation of core circadian genes such as BMAL1, and its loss significantly weakens the circadian patterns of migration of these immune cells [12, 14, 23]. Moreover, some studies have also revealed time-dependent variations in the phagocytic activity of myeloid monocytes and eosinophils, the intensity of the inflammatory response of these cells to pathogens varies throughout the day [13, 43].

Circadian rhythms in immune cell mitochondrial function and metabolism

An increasing body of research suggests that immune cell metabolism exhibits significant circadian rhythm patterns closely related to the endogenous biological clock. The endogenous biological clock system affects immune cell mitochondrial function by regulating oxidative phosphorylation, ATP production, mitochondrial structure, and more, thus participating in metabolic regulation.

Studies show that mitochondrial respiratory chain activity and ATP production levels oscillate within a day [31, 44]. This oscillation is regulated by the expression of the mitochondrial structure protein DRP1. DRP1, through its impact on mitochondrial fission and fusion processes, participates in regulating mitochondrial morphology and metabolic activity [33]. Furthermore, the mitochondrial membrane potential in immune cells also undergoes clear diurnal changes. Mechanistic research indicates that the circadian regulation of mitochondrial metabolic activity relies on the normal functioning of core clock genes. These clock genes influence the expression of proteins related to mitochondrial structure and function, thus rhythmically controlling mitochondria and cellular metabolism [45]. For instance, the BMAL1 gene can directly regulate DRP1 expression, while the SIRT1 gene is involved in regulating the NAMPT-NAD axis, both of which are closely related to mitochondrial activity. Specifically, DRP1 is phosphorylated during the day, promoting its separation from the mitochondrial surface and resulting in reduced fragmentation of the mitochondrial network. At night, DRP1 becomes dephosphorylated and associates with mitochondria, leading to increased fragmentation of the mitochondrial network [33, 46]. SIRT1, as a key regulator of mitochondrial metabolism and function, exhibits diurnal variations in its activity, further influencing the expression of NAMPT. NAMPT, as the crucial rate-limiting enzyme for NAD+ synthesis, reaches its peak in protein and mRNA expression levels and enzyme activity at night. Increased NAMPT activity leads to enhanced NAD+ synthesis, subsequently increasing the activity of SIRT1, an NAD+-dependent deacetylase [35, 47]. The protein expression levels and enzyme activity of cytochrome c oxidase IV (COX4) in the mitochondrial respiratory chain complex also display distinct circadian rhythms, peaking during the daytime active phase and declining during the nighttime resting phase [31]; this indicates that mitochondrial oxidative phosphorylation activity is under clock control. However, the peak activity of dihydrofolate reductase in the folate cycle occurs at night [31]. Additionally, the circadian clocks also regulate aerobic glycolysis, and recent studies have found that the knockout of BMAL1 gene leads to decrease WNT/β-catenin pathway activity and then in the absence of initiation of aerobic glycolysis [48, 49].

CIRCADIAN RHYTHMS IN IMMUNE SYSTEM RECOGNITION

Circadian rhythms in innate immune recognition pathways

Several components of the innate immune recognition pathways exhibit distinct circadian rhythm patterns, including the expression, activity, and downstream signal

transduction of immune recognition-related receptors and effector molecules [50]. For instance, Toll-like receptor 9 (TLR9) gene expression and the production of mRNA and protein peak in the early active period, resulting in rhythmic changes in its ability to recognize pathogens due to the receptor's own daily fluctuations in expression [51]. Moreover, the ability of these receptors to activate downstream MAPK and NF-κB signalling pathways also displays diurnal dependence, ultimately affecting the rhythmic release of proinflammatory cytokines and chemokines [1]. It is worth noting that different immune cells may exhibit different rhythm patterns, which are crucial for their organized immune responses [52].

Disruptions in the circadian rhythms of immune recognition pathways can severely impair the body's ability to mount immune responses. Studies have found that mutations in core clock genes such as PER2 can alter mouse immune responses to pathogen stimuli [51], highlighting the importance of circadian regulation in immune recognition for timely and effective immune responses. BMAL1 can directly bind to target gene promoters in the e-box region and regulate the expression of downstream immune factors, thus modulating immune cell function. Deficiency in BMAL1 results in reduced activity of the oxidative stress-related transcription factor NRF2, promoting the generation of pro-inflammatory cytokines [14]; this reveals possible mechanisms through which core clock genes participate in regulating innate immunity by influencing immune recognition and effector processes. Maintaining and stabilizing this rhythmic regulation is crucial for ensuring that immune cells respond promptly and effectively to pathogenic invasions in the environment [52].

Circadian rhythms in adaptive immune recognition

In recent years, increasing research has indicated significant circadian rhythm patterns in the adaptive immune system, including processes such as vaccine response, pathogen clearance, and immune cell circulatory migration. Studies show that elderly individuals receiving flu vaccines in the morning exhibit stronger antibody responses than those receiving vaccinations in the afternoon [53], which suggests a time-dependent response of the immune system to vaccines. Further research has revealed that the CD8+ T-cell response to DC vaccines carrying OVA antigens follows circadian rhythms, dependent on the integrity of the CD8+ T-cell intrinsic clock gene BMAL1 [54]. Similarly, T-cell responses to T-cell receptor (TCR) triggering also vary in a circadian manner, mainly depending on diurnal changes in TCR-related kinase ZAP70 protein levels [55]. Additionally, the survival rate of mice infected with vesicular stomatitis virus varies with the time of infection, indicating a time-dependent antiviral immune response [23]. This time dependence mainly arises from the regulatory role of the internal biological clock system on the immune system.

Relationship between disease and the circadian rhythms of the immune system

There is increasing evidence suggesting that the occurrence and progression of infections and diseases are closely related to the circadian rhythm regulation of the host's immune system. The rhythmic oscillations in the numbers, phenotypes, and functions of immune cells affect their efficiency in clearing pathogens such as viruses and bacteria. Studies have shown that mice infected with encephalitis virus at the end of their active phase exhibit significantly reduced survival rates, possibly due to the aggregation of pro-inflammatory immune cells and an increase in cytokine levels during this phase [23]. Furthermore, the onset of immune-related diseases and the intensity of symptoms also display diurnal variations. Research has demonstrated that morning stiffness in rheumatoid arthritis is higher, as proinflammatory cytokines such as IL-6 and tumor necrosis factor alpha secretion peak at this time, indicating that the symptoms of arthritis exhibit circadian changes due to rhythmic oscillations in inflammatory cytokine levels [56]. In mouse models, researchers have even found that the time of tumour cell implantation directly affects the final tumour size, with tumours formed from daytime implantation being smaller than those from night-time implantation. This difference is due to the circadian response of DCs transported to tumour-draining lymph nodes to prime tumour antigen-specific CD8+ T cells, a response dependent on the diurnal expression of the costimulatory molecule CD80 [57].

Clock genes play a central role in maintaining the rhythmic oscillations of immune cells, ultimately affecting the circadian regulation of the immune system's response to infections and disease occurrence. For example, the BMAL1 gene is a key transcription factor driving circadian rhythms. In specific knockout mouse models in which BMAL1 was deleted in myeloid cells, the T-cell polarization cytokine response was significantly enhanced compared with that in control mice; this results in increased inflammation and higher susceptibility to autoimmune diseases [58]. Furthermore, BMAL1-deficient DCs cannot generate normal antigen presentation and T-cell activation rhythms, promoting tumour growth in tumour-bearing mice [57]. In summary, the disruption of circadian rhythms in the immune

system can weaken the body's ability to recognize and respond to pathogens and tumours, affecting the timing and severity of disease symptoms.

CONCLUSIONS

Circadian rhythms regulate a multitude of physiological systems, including the immune system. Research into the circadian regulation of the immune system presents a promising avenue with broad applications. The endogenous circadian clock orchestrates multifaceted rhythmicity within the immune system, optimizing immune surveillance and responsiveness; this is critical for maintaining immune homeostasis and resilience against diseases. In this review, we summarize the regulatory mechanisms of circadian rhythms within the immune system. The transcription–translation feedback loop of circadian rhythm genes controls immune cell gene expression and function, subsequently participates in the regulation of the immune system, and thereby regulates inflammation and disease pathogenesis (Figure 1). Continuous efforts from multiple angles are needed to develop comprehensive clinical applications for the treatment of immune-related diseases. Treatments based on circadian rhythms can enable immune cells to perform at their optimal times, thus aiding in the design of more rational and effective immune therapy strategies.

Although the research on circadian regulation of the immune system has important prospects, there is still a long way to go before practical application. First, further clarification is required regarding the mechanisms by which key clock genes in immune cells, such as BMAL1 and REV-ERB, specifically regulate the circadian release of inflammatory cytokines and metabolic activity, which is essential for a comprehensive understanding of the timing regulation of the immune system. Second, based on the relationship between infection, disease, and the circadian rhythms of the immune system, optimal times for vaccine administration can be explored, as well as the best time for immune therapy, to maximize therapeutic efficacy. Additionally, different diseases may be associated with the loss of normal circadian rhythms in specific immune cells, requiring relevant studies that could provide new approaches for targeted therapy of related diseases. Building upon this, the design of small molecule compounds targeting key genes and proteins such as BMAL1 can be considered, allowing precise control of their activity to improve immune-related disorders.

AUTHOR CONTRIBUTIONS

JD, PC, and C Qi conceived the review. JD and PC drafted the article. CQ initiated the study and revised and finalized the article. The author(s) read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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