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Review

Basic helix–loop–helix ARNT like 1 regulates the function of immune cells and participates in the development of immune-related diseases

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Abstract

The circadian clock is an internal timekeeper system that regulates biological processes through a central circadian clock and peripheral clocks controlling various genes. Basic helix–loop–helix ARNT-like 1 (*BMAL1*), also known as aryl hydrocarbon receptor nuclear translocator-like protein 1 (*ARNTL1*), is a key component of the circadian clock. The deletion of *BMAL1* alone can abolish the circadian rhythms of the human body. *BMAL1* plays a critical role in immune cell function. Dysregulation of *BMAL1* is linked to immune-related diseases such as autoimmune diseases, infectious diseases, and cancer, and vice versa. This review highlights the significant role of *BMAL1* in governing immune cells, including their development, differentiation, migration, homing, metabolism, and effector functions. This study also explores how dysregulation of *BMAL1* can have far-reaching implications and potentially contribute to the onset of immune-related diseases such as autoimmune diseases, infectious diseases, cancer, sepsis, and trauma. Furthermore, this review discusses treatments for immune-related diseases that target *BMAL1* disorders. Understanding the impact of *BMAL1* on immune function can provide insights into the pathogenesis of immune-related diseases and help in the development of more effective treatment strategies. Targeting *BMAL1* has been demonstrated to achieve good efficacy in immune-related diseases, indicating its promising potential as a targetable therapeutic target in these diseases.

Keywords: *BMAL1*; ARNTL1, Immune response; Autoimmune diseases; Infectious diseases; Cancer

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Background

With the environmental changes of the 24-h Earth rotation, adaptive physiological rhythms have been observed in animals, plants, fungi, and bacteria [1]. These rhythms, known as circadian rhythms, couple organismal and cellular activities and have evolved a complex regulatory mechanism in synchrony with the solar cycle [2]. Circadian rhythms regulate the mammalian sleep–wake cycle, body temperature, metabolism, and immune function, coordinating the physiological behaviour of all organs to maintain whole-body homeostasis [3–5]. These processes are orchestrated by the circadian clock, an internal oscillator built on several interconnected feedback loops [3, 6] that temporally regulate organism physiology, behaviour, and metabolism [7–9]. At the molecular level, the circadian clock consists of self-regulatory transcription–translation feedback loops of multiple sets of transcription factors [9].

Misalignment of the circadian clock has been linked to several clinical disorders, including immune system imbalance [10], inflammation [11], and cancer [4]. Previous studies have shown that almost all components of the immune system involved in adaptive and innate immunity exhibit circadian rhythm variation [9]. As a major clock gene, the circadian clock system directly controls the expression of basic helix–loop–helix ARNT-like 1 (*BMAL1*), also referred to as aryl hydrocarbon receptor nuclear translocator-like protein 1 (*ARNTL1*) [12]. In autoimmune disorders, this modulation is important for controlling inflammatory pathways and immune cell differentiation [5]. For example, genetic variations in *BMAL1* and circadian locomotor output cycles kaput (*CLOCK*) contribute to an increased risk of multiple sclerosis [13]. Depletion of *BMAL1* specifically in bone marrow cells induced monocyte chemokine expression and disrupted the rhythmic cycling of Ly6C (hi) monocytes [14].

The regulation of immune cells by *BMAL1* and its involvement in immune-related diseases have not been comprehensively investigated. This review explores the current understanding of the physiological functions of *BMAL1* in immune cells and its implications for immune-related diseases, aiming to inform the development of innovative management strategies for these conditions.

Review

Overview of the regulatory relationship between circadian clocks and the immune system

Since the 1970s, the regulation of immune function by circadian clocks has garnered significant attention from the scientific community. Halberg *et al*. first reported that mice exhibit circadian variation in sensitivity to *Escherichia coli* endotoxin, revealing rhythmic regulation of the innate immune system by circadian clocks [15]. Fernandes *et al*. reported that the number of plaque-forming cells (reflecting B-cell quantity) in the spleens of mice injected with sheep red blood cells also exhibited circadian rhythms, further demonstrating the rhythmic regulation of adaptive immune responses by circadian clocks [16].

Research has revealed that circadian clocks affect the quantity, migration, and function of immune cells. Specifically, the number of immune cells and the levels of inflammatory markers demonstrate a significant circadian rhythm [17]. Circadian clocks regulate immune cell migration patterns through migration factors and affect both internal functions (such as metabolism and the production of inflammatory mediators) and external functions (such as pathogen sensing and phagocytosis) of immune cells [11, 18, 19]. Conversely, the immune system can also impact circadian clocks. For example, tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) inhibit the expression of clock genes, thereby regulating circadian rhythms [20, 21].

The mutual regulation between circadian clocks and immune rhythms is an evolutionary mechanism enabling organisms to defend against pathogens. Under the regulation of circadian clocks, the immune system self-adjusts during rest periods, redistributing, activating, and proliferating immune cells in various tissues to ensure optimal immune protection during active periods. Moreover, the presence of pathogens can influence the circadian regulation of the host's daily activity patterns.

Molecular mechanism of circadian clocks and the central role of *BMAL1*

The molecular mechanism of circadian clocks involves multiple highly interconnected transcription factors, including *BMAL1*, *CLOCK*, Period Circadian Regulator 1/2/3 (*PER1/2/3*), and Cryptochrome Circadian Regulator 1/2 (*CRY1/2*) [22]. These transcription factors interact through transcription–translation feedback loops to maintain stable circadian rhythms. Specifically, *BMAL1* and *CLOCK* form heterodimers that bind to the E-box DNA sequences of *PER1/2* and *CRY1/2*, inducing the expression of the negative regulators *PER* and *CRY*. When the *PER* and *CRY* protein complexes enter the nucleus, they inhibit the transcriptional activity of *BMAL1* and *CLOCK*, resetting the cycle once their concentrations sufficiently decrease. Furthermore, *BMAL1* regulates other factors, such as RAR-related orphan receptor A (*RORA*), nuclear receptor subfamily 1 group D member 1/2 (*NR1D1/2*), and sirtuin 1 (*SIRT1*), further influencing circadian rhythms.

BMAL1 is particularly crucial to the circadian clock system, whose deletion alone can abolish the circadian rhythm [23]. Therefore, *BMAL1* has become a focal point in studies exploring the mechanisms by which circadian clocks regulate immune functions. Under physiological conditions, *BMAL1* regulates the development, differentiation, migration, homing, metabolism, and effector functions of immune cells. In immune-related pathological processes, the dysregulation of *BMAL1* is also a key factor (Table 1).

Role of clock genes in the immune system

Numerous studies have demonstrated that the immune response has a circadian rhythm, with clock genes playing crucial roles in regulating immune system function. These genes influence both the timing and intensity of the immune response and interact bidirectionally with immune components [24]. For example, *BMAL1* functions primarily as an anti-inflammatory factor, whereas its heterodimer partner *CLOCK* activates the immune system, positively regulates nuclear factor κB (NF-κB) [25], modulates T-cell and mast cell function [11, 26], influences cytokine production [27], and promotes inflammation [28]. Moreover, mutations in *CLOCK* are associated with various inflammation-related changes, reinforcing its involvement in proinflammatory processes [27, 29].

CRYs are significant anti-inflammatory genes that modulate the intensity of the immune response by downregulating

Table 1. Immune phenotypes in clock-specific global and conditional knockout systems

Clock gene	Model	Effect	Tissue/cells	Reference
BMAL1	*Arntl$^{fl/fl}$ mice*	Regulated the expression of the chemokine CXC motif chemokine ligand 2 Modulated neutrophil migration	Neutrophil	[45]
BMAL1	*Myeloid-specific Bmal1 knockout mice were generated by crossing Bmal1$^{fl/fl}$ mice with Lyz2-Cre mice*	Exacerbated mitochondrial dysfunction Exacerbated energetic stress Exacerbated hypoxia-inducible factor-1 alpha-dependent metabolic reprogramming	Bone marrow–derived macrophages Peritoneal macrophages Splenic macrophages Mouse embryonic fibroblasts RAW264.7 macrophages B16-F10 melanoma cells Supernatants containing retroviruses	[50]
BMAL1	*Bmal1$^{fl/fl}$ ER^{cre} mice* *Bmal1$^{-/-}$ murine fibroblasts*	Suppressed NF-κB activity Limited C-X-C motif chemokine ligand 5 production Limited neutrophil recruitment	Bone marrow cell Immortalized lung fibroblasts Primary lung fibroblasts	[44]
BMAL1	*Arntl* $^{fl/fl}$ mice	Increased atypical inflammasome-mediated pyrodeath and lethality	Mouse bone marrow cells Alveolar macrophages Resident peritoneal macrophages Mouse lungs Spleen tissues Renal	[39]
BMAL1	*Mouse embryonic fibroblasts from Bmal1$^{-/-}$ mice*	Inhibited NF-κB expression		[54]
BMAL1	*Bmal1$^{fl/fl}$ mice*	Increased the expression of programmed death-ligand 1 Aggravated the sepsis phenotype	THP-1 cells (no. TIB-202) Bone marrow–derived macrophages Peritoneal exudate cells Mouse neutrophils	[48]
BMAL1	*Bmal1$^{LoxP/LoxP}$ Lyz2^{Cre} (Bmal1$^{-/-}$) mice*	Decreased activity of NF-E2-related factor 2 Increased production of IL-1beta		[52]
BMAL1	*MOP3* $^{-/-}$ mice T-cell depleted *MOP3*$^{+/+}$ mouse bone marrow cells T-cell depleted *MOP3*$^{+/-}$ mouse bone marrow cells T-cell depleted *MOP3*$^{-/-}$ mouse bone marrow cells	Impaired B-cell development	Mouse splenocytes, immune cells in peripheral blood, T-cell depleted MOP3 mouse bone marrow cells, MOP3$^{+/+/+/-}$ mouse bone marrow cells, MOP3$^{-/-}$ mouse bone marrow cells, BALB/c mouse bone marrow cells	[40]

(*Continued*)

Table 1. Continued

Clock gene	Model	Effect	Tissue/cells	Reference
BMAL1	*Bmal1* $^{LoxP/LoxP}$; *Lyz2*^{Cre} mice	Promoted the production of IL-1beta	Mouse bone marrow–derived macrophages	[49]
BMAL1	*Bmal1* $^{-/-}$ mice	Reduced interleukin-10 transcription	Human umbilical vein endothelial cells 293T cells	[53]
BMAL1	*Immunoprecipitation was performed using a BMAL1 antibody*	BMAL1 regulates the activity and expression of toll-like receptor 9	Per2Brdm1 macrophages Splenic macrophages Dendritic cells B cells	[55]
BMAL1	*RAW264.7 cells were transfected with a Bmal1 overexpression plasmid*	Promoted the glycolytic pathway Accelerated the occurrence of M1 macrophage polarization	RAW264.7 cell line	[47]
CLOCK	*Clock* $^{mut/mut}$ mice	Loss of the circadian rhythm of T-cell proliferation following T-cell receptor stimulation	T cells	[11]
CLOCK	C57BL/6 *Clock*$^{\Delta19/\Delta19}$ mice	Modulated mast cell responses to interleukin-33	Mast cells	[26]
CLOCK	C57BL/6 *Clock*$^{\Delta19/\Delta19}$ mice	Loss temporal variations in immunoglobulin E-mediated degranulation in mast cells	Mast cells	[156]
CLOCK	*Clk* $^{\Delta19/\Delta19}$ mice *Clk*$^{\Delta19/\Delta19}$ *Ldlr*$^{-/-}$ mice *Clk*$^{\Delta19/\Delta19}$ *Apoe*$^{-/-}$ mice Bone marrow–derived macrophages from *Clk*$^{\Delta19/\Delta19}$ *Apoe*$^{-/-}$ mice	Accelerated inflammation	Intestines Macrophages	[157]
CLOCK	*Clock* $^{\Delta19/\Delta19}$ mice	Attenuated γ/δ T-cell responses to interleukin-23	Splenic γ/δ T-cell	[27]
CLOCK	*Clock* $^{-/-}$ mice	Reduced NF-κB activity	HEK-293T cells L929 cells Mouse embryonic fibroblasts	[25]
CLOCK	*Clock* $^{\Delta19}$ mutant mice	Promoted intestinal dysbiosis		[29]
CLOCK	*Clock* $^{\Delta19}$ mice	Increased the number of macrophages	Human primary renal proximal tubule epithelial cells RPTEC/TERT1 or immortalized human renal proximal tubule epithelial cells Mouse primary kidney cells	[158]
CLOCK	Expressed *CLOCK* and/or *BMAL1* in the human cell lines HCT116 and HeLa	*CLOCK/BMAL1* represses GR-induced transcriptional activity	HCT116 cells (human colon cancer) HeLa cells (human cervical cancer) HepG2 cells (human hepatoma)	[28]
CLOCK	*Clock* ^{mutant} mice	Reduced inflammatory cytokines after LPS	Bone marrow–derived macrophages	[159]
CRY	*Cry1* $^{-/-}$*Cry2* $^{-/-}$ mice *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mouse embryonic fibroblasts	Increased tumour necrosis factor alpha	Inflammatory synovial cells Spleen cells	[160]
CRY	*Cry1* $^{-/-}$*Cry2* $^{-/-}$ mice *Cry1*$^{-/-}$*Cry2*$^{-/-}$ fibroblasts	Increased NF-κB activity	Immortalized fibroblasts 293T cells	[30]

(*Continued*)

Table 1. Continued

Clock gene	Model	Effect	Tissue/cells	Reference
CRY	*Cry1* $^{-/-}$*Cry2* $^{-/-}$ mice *Cry1*$^{-/-}$ mice *Cry2*$^{-/-}$ mice *Cry1*$^{+/-}$*Cry2*$^{+/-}$ mice	Increased infiltration of neutrophils	Human primary renal proximal tubule epithelial cells Immortalized human renal proximal tubule epithelial cells Mouse primary kidney cells	[158]
PER1	*Per1* $^{-/-}$ mice	Loss of the circadian rhythm of IFN-γ, perforin, and granzyme B	Splenic NK cells in mice	[161]
PER1	*mPer2* $^{-/-}$ mice	Downregulated the mRNA expression of Ly49C receptor and natural killer group 2 member D	NK cells Natural killer T cells T cells	[162]
PER1	*Per1* $^{-/-}$ mice	Enhanced the recruitment of macrophages Increased C-C chemokine receptor 2 expression levels	Peritoneal macrophages	[32]
PER1	*Per1* $^{\text{knockdown}}$ in H69 cells *Per1*$^{\text{overexpression}}$ in Mz-ChA-1 cell	PER1 is regulated by microRNA-34a	Human cholangiocarcinoma cell lines (Mz-ChA-1, TFK-1, CCLP-1, HuCC-T1, SG231, and HuH-28) Mz-ChA-1 cells HuH-28 cells TFK-1 cells HuCC-T1 and SG231 cells The human immortalized cholangiocyte line MMNK-1 The human immortalized, nonmalignant cholangiocyte cell line H69	[163]
PERs	*Per1* $^{-/-}$ *Per2*$^{-/-}$ mice	Induced ferroptosis in spleen lymphocytes	Spleen lymphocytes	[164]
PER2	*Per2* $^{-/-}$ mice	Impaired the capacity of macrophages to clear pathogens	Macrophages The murine macrophage cell line Raw 264.7 cells	[33]
PER2	*Per2* $^{-/-}$ mice	Reduced IFN-γ, IL-1beta after LPS	Splenocytes	[34]
PER2	*Per2* $^{\text{mBrdml}}$ mice	Loss of the daily rhythm of IFN-γ		[165]
PER2	*mPer2* $^{\text{Luc}}$ IFN$\alpha\beta\gamma$R$^{-/-}$ mice *mPer2*$^{\text{Luc}}$ IFN$\alpha\beta\gamma$R$^{+/-}$ mice *Per2*$^{\text{Luc}}$ cells	Proinflammatory signals suppress PER2 rhythmicity, while anti-inflammatory signals enhance the amplitude of PER2 expression	Bone marrow–derived macrophages Peritoneal macrophages	[35]
REV-ERBα	*Rev-erbα* $^{-/-}$ mice	Reduced interleukin 6, C-X-C motif chemokine 11, C-C motif ligand 2, C-X-C motif chemokine ligand 6, and interleukin-19	Peritoneal exudate cells Macrophages	[166]
REV-ERBα	*Rev-erbα* $^{-/-}$ mice	Activation of the NF-κB/NLRP3 axis Increased the severity of colitis	Macrophages	[36]

(*Continued*)

Table 1. Continued

Clock gene	Model	Effect	Tissue/cells	Reference
REV-ERBα	Myeloid-specific *Nr1d1* gene with DNA-binding domain mutation in mice	Loss of regulation over NLRP3 expression Loss of the regulation of inflammatory cytokines occurred	Bone marrow–derived macrophages Human monocyte-derived macrophages	[37]
REV-ERBα	Agonist	Upregulated OD-like receptor family pyrin domain containing 6 transcription Increased the severity of infection	Intestinal epithelial cells MCF7 cells 293T cells Caco-2 cells	[167]
REV-ERBα	*Rev-erbα* $^{+/-}$ mice *Rev-erbα* $^{-/-}$ mice	Increased the expression of C-C motif ligand 2	Peritoneal macrophages The murine macrophage cell line RAW264 (RCB0535)	[168]
REV-ERB	*REV-ERBα* knockout scenarios	Inhibited the production of IL-6 and interleukin-10		[169]
REV-ERBα	Agonist	Suppressed LPS-induced macrophage M1 polarization	U937 cells	[170]
REV-ERBα	Agonist	Suppressed IL-1beta production in macrophage	Bone marrow–derived macrophages	[171]
REV-ERBs	Agonist	Inhibited immunoglobulin E- and interleukin-33-mediated mast cell activation	Bone marrow-derived mast cells Foetal skin-derived mast cells	[172]
REV-ERBα	Agonist	Inhibited inflammatory signalling	Bronchiolar epithelial cell Lung	[173]
REV-ERBα	Agonist Antagonist	Regulated NLRP3 expression	THP-1 human monocyte/macrophage cell line	[174]
REV-ERBα	Antagonist	Increased C-C motif ligand 2 mRNA levels		[175]
RORα	*RORα* $^{-/-}$ mice	Increased immunoglobulin G, IFN-γ, tumour necrosis factor alpha, and IL-6	Spleen	[38]
RORα	Adenovirus encoding *RORα1*	Inhibited inflammation	Primary human aortic smooth muscle cells Primary human coronary artery smooth muscle cells Primary smooth muscle cells from saphenous veins	[176]
RORα	Staggerer	Increased IL-1beta, IL-6, and macrophage inflammatory protein 2 after LPS	Lung	[177]

fl, floxed; NF-kappaB, nuclear factor-kappaB; IL-1beta, interleukin-1beta; IFN-gamma, interferon-gamma; NK, natural killer; LPS, lipopolysaccharide; IL-6, interleukin-6; NLRP3, NLR family pyrin domain containing 3

inflammatory cytokines [30]. The role of the *PER* gene family is complex [31]; *PER1* has an anti-inflammatory effect [32], whereas *PER2* has both proinflammatory and anti-inflammatory effects [33, 34]. Additionally, *PER2* is regulated by both proinflammatory and anti-inflammatory signals [35].

REV-ERBα has both proinflammatory and anti-inflammatory effects [36, 37]. *RORα* plays a significant anti-inflammatory role within the immune system by negatively regulating the inflammatory response and the production of proinflammatory factors [38]. Both *RORα* and *REV-ERBα* are regulated by *BMAL1*, which exerts direct anti-inflammatory effects through these receptors [39]. In summary, clock genes are crucial in regulating immune responses.

Physiological functions of *BMAL1* in immune cells

The development and differentiation of immune cells involves a complex transformation from stem cells to mature immune cells with diverse functions, primarily recognizing and responding to various pathogens. *BMAL1* plays a crucial regulatory role in this process. Studies have shown that in *BMAL1*-deficient mice, the number of mature B cells in the peripheral blood, spleen, and bone marrow is significantly reduced, whereas the number of pre-B cells is similar to that in control mice, highlighting the key role of *BMAL1* in B-cell development and differentiation; furthermore, experiments using irradiation combined with bone marrow cell transplantation have confirmed that BMAL1 influences B-cell development through the bone marrow microenvironment [40].

The process by which immune cells migrate to specific sites, such as the lymph nodes, the spleen, or areas of inflammation, to respond to immune challenges is referred to as immune cell homing. Conversely, the process by which immune cells exit these tissues is termed egress. The migration, homing, and egress of immune cells enable their effective distribution within the body, thus allowing efficient pathogen combat while minimizing damage to host tissues [41]. *BMAL1* plays a crucial regulatory role in these processes, forming a dimer with *CLOCK*, which binds to the promoter regions of chemokines, including C-C motif chemokine ligand 2 (CCL2), C-C motif chemokine ligand 8 (CCL8), and S100 calcium-binding protein A8 (S100a8), recruiting polycomb repressive complex 2 (PRC2), inducing the circadian expression of these chemokines, and consequently leading to the rhythmic migration, egress, and homing of monocytes and macrophages [14]. Furthermore, *BMAL1* can influence lymphocyte homing and egress by regulating the expression of migration molecules, such as C-C chemokine receptor type 7 (CCR7) and sphingosine-1-phosphate receptor 1 (S1pr1), on lymphocytes [42]. *BMAL1* influences neutrophil migration between the bone marrow and peripheral blood by modulating the chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) [43]. Additionally, *BMAL1* inhibits the activity of NF-κB, thereby suppressing the production of C-X-C motif chemokine ligand 5 (CXCL5) during inflammatory responses and reducing neutrophil homing [44]. Moreover, *BMAL1* regulates the topological structure of neutrophils by controlling C-X-C motif chemokine ligand 2 (CXCL2), promoting their egress from blood vessels and thereby protecting the vasculature from immune cell damage during the host's remaining phase [45].

The metabolism of immune cells is vital for their survival and function, with *BMAL1* playing a critical role in this process. *BMAL1* negatively regulates glycolysis through the isocitrate dehydrogenase 1 (IDH1)/alpha-ketoglutarate (α-KG) pathway and its interactions with S100 calcium-binding protein A9 (S100A9). Specifically, *BMAL1* upregulates IDH1, thereby promoting the conversion of isocitrate to α-KG. As a critical intermediate in the tricarboxylic acid cycle, α-KG facilitates this cycle progression; concurrently, α-KG inhibits hypoxia-inducible factor-1 (HIF-1), thereby reducing the expression of glycolysis-related enzymes such as pyruvate kinase muscle isozyme M2 (PKM2) and hexokinase 2 (HK2) [46, 47]. PKM2 enhances glycolysis, leading to increased lactate production, and augments the expression of inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), thereby amplifying the inflammatory response. Additionally, elevated PKM2 levels enhance programmed cell death 1 ligand 1 (PD-L1) expression via the phosphorylation of signal transducer and activator of transcription 1 (STAT1), thereby resulting in immunosuppression [48, 49]. Research has indicated that the absence of *BMAL1* results in mitochondrial dysfunction and increased mitochondrial reactive oxygen species in macrophages, leading to HIF-1α-dependent metabolic reprogramming, which shifts macrophage metabolism towards glycolysis and amino acid metabolism, ultimately increasing inflammation and metabolic imbalance [50]. Furthermore, studies have shown that *BMAL1* induces neutrophil ageing by regulating CXCL2 [45].

BMAL1 is important for regulating immune cell effector functions. Nuclear factor erythroid 2-related factor 2 (NRF2) is crucial for maintaining the cellular redox balance and modulating immune and inflammatory responses [51]. *BMAL1* directly binds to the NRF2 promoter region, increasing its expression and activity, thereby increasing antioxidant responses in macrophages and suppressing the production of proinflammatory cytokines, such as IL-1β and interleukin-6 (IL-6) [52]. *BMAL1* can directly promote the transcription of the anti-inflammatory cytokine interleukin-10 (IL-10) by binding to its promoter region, thereby exerting anti-inflammatory effects [53]. *BMAL1* modulates immune function at the protein level. For example, *BMAL1* interacts with RelB (a subunit of NF-κB) to inhibit NF-κB expression, thereby exerting anti-inflammatory effects, which are further enhanced by *CLOCK* [54]. The *BMAL1–CLOCK* dimer binds to the promoter region of the proinflammatory cytokine CCL2, suppressing its expression and consequently reducing the recruitment of inflammatory monocytes and the inflammatory response [14]. Moreover, the *BMAL1–CLOCK* dimer enhances dendritic cell antigen presentation capabilities and promotes the activation of specific immune cells by binding to the Toll-like receptor 9 (TLR9) promoter region, thereby increasing its transcription [55]. Research has suggested that *BMAL1* exerts anti-inflammatory effects by upregulating or downregulating other clock genes. For example, *BMAL1* upregulated the expression of the clock genes *NR1D1* and *RORA*, contributing to its anti-inflammatory actions [39, 56]. Conversely, *CLOCK* independently enhances NF-κB-mediated gene transcription, promoting inflammation, whereas *BMAL1* inhibits this proinflammatory action of *CLOCK* on NF-κB [25] (Figure 1).

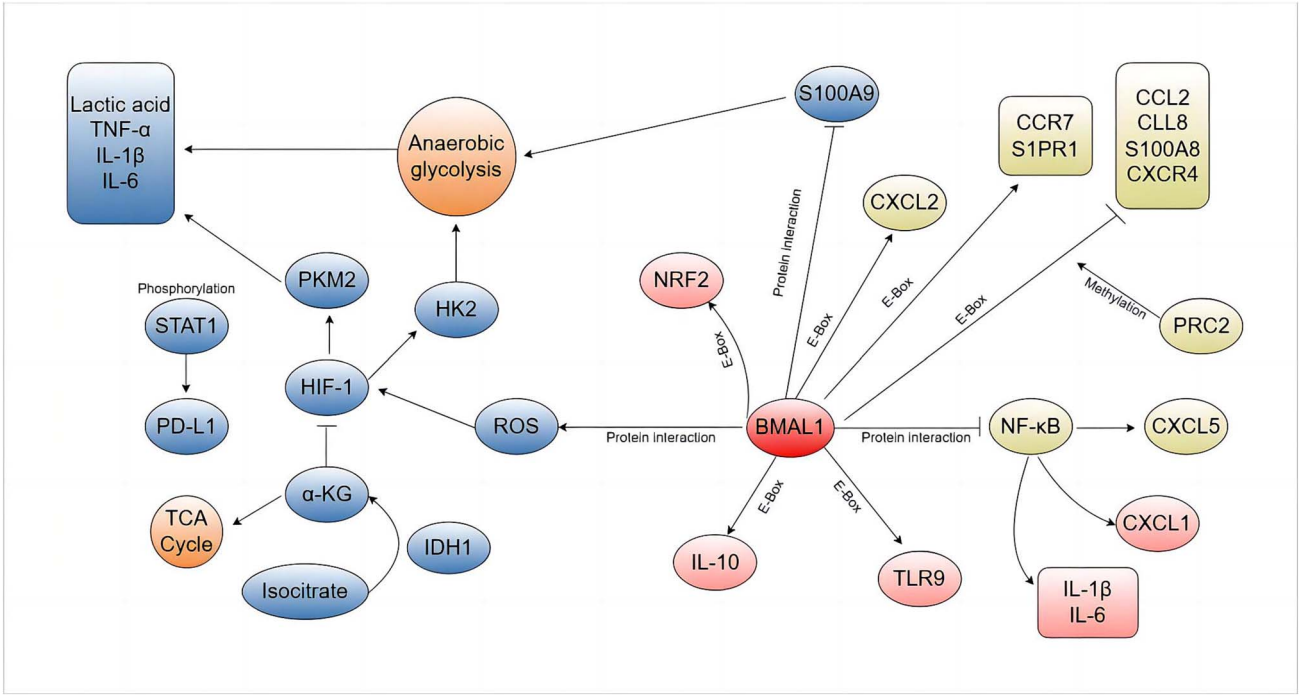

Figure 1. *BMAL1* plays a key regulatory role in immune cell migration and metabolism. *BMAL1* negatively regulates glycolysis and influences immune cell metabolism, contributing to its anti-inflammatory effects by enhancing the antioxidant response and inhibiting the production of inflammatory cytokines. Additionally, *BMAL1* regulates the migration, homing, and expulsion of immune cells. TNF-α, tumour necrosis factor alpha; IL-1β, interleukin-1β; IL-6, interleukin-6; STAT1, signal transducer and activator of transcription 1; PD-L1, programmed cell death 1 ligand 1; TCA, cycle tricarboxylic acid cycle; PKM2, pyruvate kinase muscle isozyme M2; HIF-1, hypoxia-inducible factor-1; α-KG, alpha-ketoglutarate; IDH1, isocitrate dehydrogenase 1; HK2, hexokinase 2; ROS, reactive oxygen species; NRF2, erythroid 2-related factor 2; IL-10, interleukin-10; S100A9, S100 calcium-binding protein A9; BMAL1, basic helix–loop–helix ARNT like 1; CXCL2, C-X-C motif chemokine ligand 2; TLR9, toll-like receptor 9; CCR7, C-C chemokine receptor type 7; SIPR7, sphingosine-1-phosphate receptor 1; NF-κB, nuclear factor kappaB; CCL2, C-C motif chemokine ligand 2; CLL8, C-C motif chemokine ligand 8; S100A8, S100 calcium binding protein A8; CXCR4, C-X-C chemokine receptor type 4; PRC2, polycomb repressive complex 2; CXCL5, C-X-C motif chemokine ligand 5; CXCL1, C-X-C motif chemokine ligand 1

Dysregulation of *BMAL1* in immune-related pathological processes

Impact of *BMAL1* disorders on autoimmune diseases

Autoimmune diseases are characterized by the body's immune response attacking its own antigens, leading to tissue damage [57]. *BMAL1* is implicated in the pathogenesis of autoimmune diseases, with dysregulation noted in conditions such as rheumatoid arthritis (RA) and multiple sclerosis (MS). This dysregulation leads to the abnormal production and release of inflammatory cytokines. Furthermore, autoimmune diseases can impact the expression of *BMAL1*, potentially creating a feedback loop of inflammation.

RA is a chronic autoimmune disease characterized by changes in the circadian rhythm, presenting clinical features such as morning stiffness and joint pain [58]. It is considered one of the most prevalent chronic inflammatory diseases, affecting ~1% of the global population [59]. The clinical symptoms of RA follow a distinct circadian rhythm, with morning stiffness and joint pain being prominent [60]. A significant association between shift work and an increased risk of RA (specifically in women) was first reported in 2010 [61]. The circadian clock influences not only the symptoms of RA but also its pathogenesis.

Compared with non-RA controls, patients with RA exhibit dysregulation of *BMAL1*, as demonstrated by a reduced amplitude of *BMAL1*-luciferase bioluminescence in RA patients [62]. *BMAL1* plays a role in the pathogenesis of RA by influencing inflammation and is implicated in the production of matrix metalloproteinase-3 (MMP-3), CCL2, and IL-6 in the fibroblast-like synoviocytes of individuals with RA [63]. The expression of *BMAL1* is influenced by immunoinflammatory mediators. TNF-α was found to increase *BMAL1* expression by upregulating *ROR*α. Targeting *BMAL1* expression may represent a potential novel approach for treating RA [64]. Moxibustion has been proposed as a treatment for RA at the molecular level, potentially regulating the circadian rhythm of RA by influencing core clock genes such as clock and *BMAL1* [65]. Additionally, melatonin has been shown to impact cartilage destruction and regeneration by directly or indirectly modulating the expression of key clock genes such as *BMAL1*, *CRY*, and *DEC2* [66]. Dysregulation of the *BMAL1* gene was identified in RA patients, with chronic inflammation associated with the pathophysiology of RA affecting *BMAL1* and its role in maintaining circadian rhythms. Further insights into the clock gene and its altered expression in RA could provide insight into treatment strategies for individuals with RA.

MS is a chronic autoimmune disease affecting the central nervous system. Under these conditions, the immune system targets the myelin sheath surrounding the nerves, leading to disruptions in nerve signalling. This disruption results in a variety of symptoms, including paraesthesia, muscle weakness, vision problems, and coordination difficulties [67]. The increased incidence of MS has been linked to disruptions in circadian rhythms. Studies have shown that the risk of

MS is influenced by genetic variations in circadian rhythm genes, such as *BMAL1* and *CLOCK* [13]. *BMAL1* has the potential to protect against autoimmune diseases, as its deficiency in myeloid cells worsened T-cell-mediated experimental autoimmune encephalomyelitis by promoting pathogenic IL-17$^+$/IFN-γ^+ T cells [68]. Moreover, *BMAL1* loss in the medullary system triggers inflammation through central nervous system infiltration through monocyte secretion of IL-1β [69]. Oligodendrocyte *BMAL1* loss leads to abnormal myelination and sleep disturbances, which are linked to increased MS incidence [70]. Considering the role that *BMAL1* plays in the pathophysiology of MS, regulating its expression could be a helpful therapeutic approach. Melatonin has shown promise in MS treatment because it influences the expression of circadian rhythm genes such as *BMAL1* and *CLOCK* [71]. However, not all studies have shown that MA is associated with abnormal *BMAL1* expression. In a case–control study of a Spanish population, polymorphisms in *BMAL1* and *CLOCK* were not associated with multiple sclerosis in the Spanish population [72].

Type 1 diabetes mellitus (T1D) is a chronic condition primarily characterized by the immune system's attack on insulin-producing beta cells in the pancreas. This autoimmune response results in reduced or ceased insulin production, subsequently impairing the regulation of blood sugar levels [73]. T1D is an autoimmune disorder that is associated with genes and circadian rhythms [74]. T1D has been shown to disrupt the circadian rhythm of the corneal epithelium, leading to decreased expression levels of *CLOCK*, *BMAL1*, and *PER2* while simultaneously increasing the expression of *CRY1* and *REV-ERB*α. These alterations are implicated in immune regulation and contribute to the increased recruitment of white blood cells to the cornea [75].

Autoimmune thyroiditis (AIT) is a chronic thyroid disease in which the immune system mistakenly attacks thyroid tissue, causing damage and reduced function [76]. Patients with AIT exhibit reduced expression of the clock genes *BMAL1* and *PER2* in their thyroid tissue, leading to chronic circadian rhythm disturbance and increased inflammation [77]. In polyglandular autoimmune syndrome (PAS) type III, patients often experience thyroid disease and adrenocortical hypofunction due to immune system attacks on their own tissues. Additionally, other autoimmune diseases, such as diabetes, may also be present [78].

In patients with PAS type III, all four genes—*GR-a*, *CLOCK*, *BMAL1*, and *PER3*—were significantly upregulated at night compared with those in healthy individuals, leading to a reversal in circadian patterns. Disruption of the daily expression patterns of clock-related genes in PAS type III patients is linked to disease pathogenesis [79]. Autoimmune hepatitis is a rare, chronic inflammatory condition in which the immune system targets liver tissue, causing liver damage [80]. *BMAL1* plays a role in regulating M1 macrophage activation through Junb–AKT/ERK signalling pathways, impacting immune-mediated hepatitis [81].

Impact of *BMAL1* disorders on infectious diseases

Circadian rhythms and host vulnerability to infection are closely related. The deletion of *BMAL1* in macrophages leads to alterations in the cytoskeleton that are dependent on RhoA, resulting in increased cell motility and enhanced phagocytosis. These changes ultimately improve the defence against pneumococcal pneumonia [82]. *BMAL1* is essential for controlling the innate immune response of cells to RNA viruses. Cells lacking *BMAL1* are more vulnerable to infection by RSV and PIV3, the two main respiratory viruses of the *Paramyxoviridae* family. Research on animals supports these conclusions by showing that when infected with respiratory syncytial virus, *BMAL1*(−/−) mice exhibit more severe illness and morbidity [83]. Furthermore, by interfering with the host circadian rhythm, the loss of the transcription factor *BMAL1* aggravated herpes and influenza A virus infections [84]. The circadian rhythm of ageing susceptibility governs antiviral immunity in the skin, with *BMAL1* and *CLOCK* regulating the rhythmic expression of antiviral proteins. Additionally, circadian-enhancing treatments have been shown to reverse the susceptibility of aged murine skin and human primary keratinocytes to viral infections [85].

BMAL1 plays a crucial role in preventing the onset of a sepsis phenotype in cases of severe infection by modulating PD-L1 expression and preventing T-cell depletion. These results suggest that interventions targeting the circadian clock and immune metabolic pathways could offer potential treatments for infectious diseases that result in fatal sepsis. *BMAL1* efficiently suppresses the development of a sepsis phenotype after severe infection by opposing T-cell exhaustion and PD-L1 expression. These findings suggest that targeting the immunometabolism pathway and circadian clock may be useful in treating infectious disorders that cause deadly sepsis [48].

BMAL1 is the primary clock gene responsible for regulating viral replication and transcription [83]. This gene plays a crucial role in orchestrating the immune response of the lung to viruses. In mice infected with influenza A virus and Sendai virus, deletion of the core clock gene *BMAL1* was associated with exacerbated acute viral bronchiolitis [86]. Inhibiting *BMAL1* or treating lung epithelial cells with the *REV-ERB* agonist SR9009 was shown to decrease ACE2 expression, thereby hindering the entry and replication of SARS-CoV-2 [87]. *REV-ERB* plays a crucial role in regulating the entry of hepatitis B virus. When *BMAL1* was inhibited by the *REV-ERB* ligand, the secretion of pregenomic RNA and newborn particles decreased. Furthermore, *BMAL1* directly binds to HBV DNA and activates viral genome transcription [88]. Both *BMAL1* and *REV-ERB* also impact flavivirus replication. These proteins influence various stages of the hepatitis C virus (HCV) life cycle, including particle entry into liver cells and RNA genome replication [89]. The basal level of HIV transcription during antiretroviral therapy can vary significantly and is influenced by factors such as the circadian rhythm regulator *BMAL1*. The inhibition of ART by HIV transcription in HIV-infected individuals may be linked to the direct actions of *BMAL1* [90].

During infection, the host's central and peripheral circadian rhythms may be altered. *Helicobacter pylori* activates LIN28A by transcription, disrupting circadian rhythms and inducing *BMAL1* expression both *in vitro* and *in vivo*. *BMAL1*, a transcription factor, subsequently increases the expression of the proinflammatory cytokine TNF-α, ultimately leading to inflammation [91].

The role of *BMAL1* in both innate and adaptive immune responses suggests its potential impact on susceptibility, clinical presentation, and the prognosis of infectious diseases. Given that the circadian rhythm of *BMAL1* shows promise as a biomarker for assessing the prognosis of patients with infectious diseases, new tools to study changes in host *BMAL1* are

needed. Analysing circadian rhythm alterations in infectious diseases at the individual level could lead to the development of time-based treatment strategies and the targeted administration of molecules.

Impact of *BMAL1* disorders on cancer immunology

Disruptions in circadian rhythms have been associated with an increased risk and progression of cancer [92]. The International Agency for Research on Cancer classifies shift work, which disrupts circadian rhythms, as a probable carcinogen (group 2A carcinogen), placing it in the same category as ultraviolet radiation, benzopyrene, and acrylamide [93]. Maintenance of circadian homeostasis is crucial for the clock to fulfil its protective and tumour suppressor functions [4]. Dysregulation of *BMAL1* is linked to cancer development through its impact on cellular processes such as the cell cycle, apoptosis, metabolism, and immune function.

Circadian rhythm alterations have implications for breast cancer prognosis. Circadian oscillations of *BMAL1* and *PER2* were observed in low-grade MCF7 cells but not in high-grade MDA-MB-231 cells, with further disruption of the *BMAL1* rhythm in malignant breast cancer cells. Furthermore, increased expression of the clock gene *BMAL1* was associated with improved overall survival in melanoma patients, highlighting its potential as a clinically relevant prognostic factor [94].

This study revealed a positive correlation between the expression of the clock gene *BMAL1* and the overall survival of melanoma patients. Additionally, a relationship was found between *BMAL1* expression and the levels of markers associated with T-cell activity and exhaustion within the tumour. These findings suggest that *BMAL1* could serve as a valuable prognostic factor and biomarker for T-cell-based immunotherapy [95]. Immune checkpoint blockade therapy has emerged as a significant treatment strategy for tumours [96]. Early clinical trials have demonstrated the potential of using small molecules that target circadian receptors to modulate *BMAL1* expression, thereby enhancing the efficacy of anti-PD-L1 immunotherapy. Additionally, OLFML3, a novel chemokine, was shown to recruit immunosuppressive microglia into the tumour microenvironment. The *CLOCK–BMAL1* complex was found to directly regulate OLFML3, which plays a role in driving glioma stem-like cell self-renewal and metabolism, as well as promoting microglial infiltration [97]. Furthermore, a previous study revealed that *CLOCK* and *BMAL1* are involved in driving immunosuppression in glioma [98]. The regulation of immune checkpoint signals in the tumour microenvironment by the circadian clock is intricate, highlighting *BMAL1* expression as a potential predictive biomarker and a promising enhancer for anti-PD1 immunotherapy. *BMAL1* is a potential therapeutic target for malignancies because it influences PD-1 receptor expression, which enhances antitumour immunity by upregulating cytokines, effector cells, and memory cells [99, 100].

The downregulation of the circadian clock gene *BMAL1* in cancer cells is frequently associated with hypermethylation of promoter regions, contributing to various cancer phenotypes [101]. Examples include epigenetic silencing of *BMAL1* in ovarian cancer and hypermethylation of clock gene promoters (*PER1*, *PER2*, *CRY1*, *BMAL1*) in breast cancer cell lines [102]. The downregulation of *BMAL1* was linked to increased cell migration and invasion. Hypoxic-induced acidosis in breast cancer facilitates metastasis by reducing *BMAL1* levels [103]. Furthermore, knockout of the *BMAL1* gene disrupted the circadian rhythm, resulting in increased invasion of breast cancer cells [104].

Dysregulation of *BMAL1* contributed to tumour growth by affecting the cell cycle. c-MYC, a crucial clock control gene, regulates cell cycle progression and plays a significant role in maintaining cellular changes during transformation by controlling cell growth and metabolism [105]. Tumours with mutations in *PER2* and *BMAL1* exhibit notable increases in c-MYC protein levels [106]. In unfolded C-MYC-driven tumours, c-MYC-dependent activation of the unfolded protein response inhibited *BMAL1* in Burkitt lymphoma, thereby hindering circadian oscillation and protein synthesis to promote tumour progression. The activation of the UPR by c-MYC inhibited *BMAL1* in Burkitt lymphoma, disrupting circadian oscillation and protein synthesis to drive tumour progression [107]. In malignant haematologic diseases, inactivation of *BMAL1* contributes to disease progression by disrupting cellular circadian rhythms and altering the expression patterns of clock-related genes, such as c-MYC, catalase, and p300 [108].

The interaction of TNF-α with the biological clock influences the proliferation and migration of Hodgkin lymphoma cells. Upon TNF-α stimulation, there is a general increase in the expression levels of core clock elements such as *BMAL1*, *PER2*, and *REV-ERB*α [109].

Compared with PER2 mutant cells, mammary epithelial cells with *BMAL1* mutations exhibit increased apoptosis when treated with the chemotherapeutic drugs cisplatin and doxorubicin [104]. These findings suggest that disrupting *BMAL1* expression and abolishing circadian rhythms could offer protection against tumour development following DNA damage. The overexpression of *BMAL1* in tongue squamous cell carcinoma and colorectal cancer cells has been shown to increase their sensitivity to paclitaxel and oxaliplatin, respectively [110, 111]. These findings suggest that *BMAL1* may function as a novel tumour suppressor gene by increasing cancer cells' susceptibility to chemotherapy.

The biological clock regulates numerous cellular functions, including the cell cycle, apoptosis, DNA repair, epithelial–mesenchymal transition, metabolism, and inflammation. Maintaining cellular homeostasis helps protect against cellular transformation and tumour development. Conversely, various biological processes can influence the clock, creating a complex network of interconnected pathways. Increasing evidence underscores the critical role of the biological clock in cancer biology, revealing a correlation between tumour development and circadian clock disruption. Furthermore, the importance of *BMAL1* as a target in immune disorders is increasingly recognized and studied. The immune system's cellular and molecular mechanisms are intricately regulated by the biological clock, with *BMAL1* serving as a key player in immune cell function and immune response modulation. Evidence suggests that *BMAL1* plays a role in modulating the circadian rhythm of immune cells, such as T cells, dendritic cells, and macrophages. This modulation influences several critical functions within these cells, including antigen presentation, the release of inflammatory factors, and cellular migration processes. The impairment of these functions could contribute to the development and progression of immune-related disorders.

Additionally, there is a growing body of research on the importance of *BMAL1* as a target in immunological diseases. The progression and development of immune-related illnesses may be aided by the weakening of these systems (Figure 2).

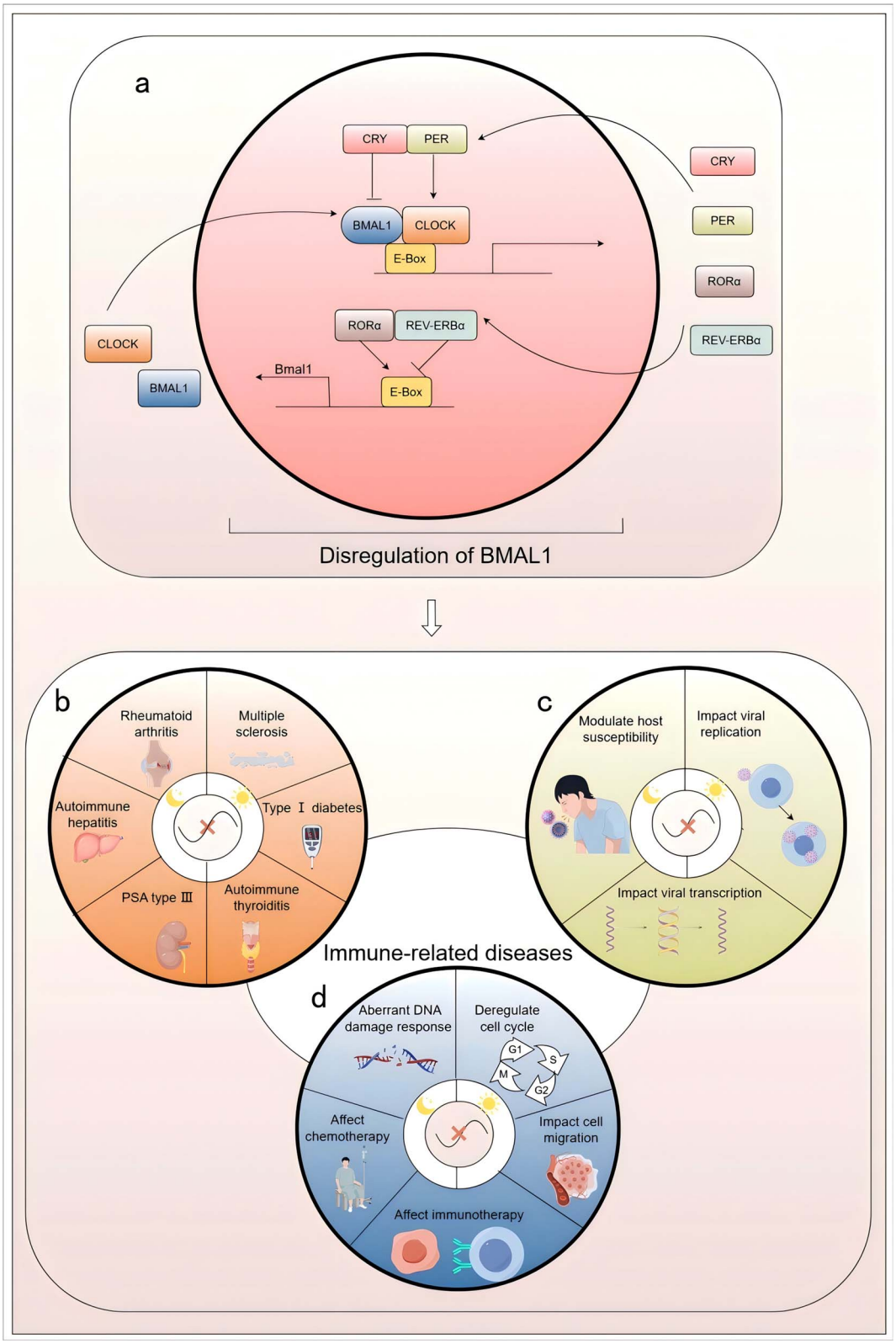

Figure 2. Association of *BMAL1* with immune-related diseases. (**a**) BMAL1 is a key component of the circadian clock and plays a crucial role in the immune system as well as the pathogenesis of various diseases. (**b**) Disruption of BMAL1 influences a range of immune-related diseases, including rheumatoid arthritis, multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, and PAS type III. (**c**) Alterations in BMAL1 impact infectious diseases by modifying host susceptibility, viral replication, and transcription. (**d**) Furthermore, alterations in BMAL1 are significantly linked to cancer development, resulting in DNA damage responses, cell cycle dysregulation, and uncontrolled cell migration, which in turn affect the efficacy of immunotherapy and chemotherapy. PAS, polyglandular autoimmune syndrome

Impact of *BMAL1* disorders in sepsis and trauma

Sepsis is a potentially life-threatening condition that arises when the body's response to infection triggers widespread inflammation and tissue damage [112]. The impact of *BMAL1* on sepsis is evident across multiple dimensions. Immunosuppression plays a significant role in the occurrence and development of sepsis. *BMAL1* plays a significant role in sepsis, preventing the progression of sepsis by inhibiting PD-L1 expression and reducing T-cell depletion [48]. *BMAL1* deficiency disrupts the liver's feeding cycle-related transcriptional response and increases LPS sensitivity [113]. In H9c2 cell models, *BMAL1* mitigates LPS-induced iron-mediated cytotoxicity via the AKT/p53 pathway [114]. In addition, loss of *BMAL1* in macrophages alters CXCL2 expression, enhances neutrophil recruitment and exacerbates acute lung injury caused by sepsis [115].

Traumatic brain injury (TBI) disrupts normal brain function and is associated with high rates of morbidity and mortality [116]. TBI results in the dysregulation of *BMAL1* expression, affecting the expression patterns of circadian rhythm genes, such as *BMAL1* and *CRY1*, which in turn disrupts the transcription–translation feedback loop [117]. Patients with TBI-related sleep disorders also exhibit abnormal expression of *PER2*, *CLOCK*, and *BMAL1* [118]. Acute subdural haematoma significantly disturbs the mRNA expression of circadian rhythm genes in peripheral white blood cells [119]. Significantly impaired *BMAL1* expression may affect the recovery of patients. Decreased *BMAL1* levels are associated with increased TBI, which may aggravate pathological symptoms by activating the phosphorylation mechanism of p38 MAPK [120].

However, reductions in *BMAL1* can have positive effects in some cases. For example, *BMAL1*-deficient mice presented lower myocardial tension, reduced total peripheral resistance, improved cardiac function, and reduced infarct expansion after myocardial infarction [121]. In addition, *BMAL1* loss improves the prognosis of patients with spinal cord injury, alleviating blood–spinal barrier breakdown, cytotoxic neuroinflammation, and chronic oligodendrocyte loss [122]. In a haemorrhagic rat model, a short period of blood loss resulted in increased *BMAL1* mRNA and erythropoietin levels, suggesting that *BMAL1* regulates EPO early in acute hypoxia/ischaemia [123]. *BMAL1* also plays a protective anti-radiation role, defending against radiation-induced DNA damage and skin toxicity through circadian mechanisms while protecting the heart from radiation-induced toxicity [124, 125]. These studies highlight the dual role of *BMAL1* in multiple pathological states and suggest directions for further investigation of the potential impact of *BMAL1* regulation on the prognosis of TBI and related diseases.

Targeting role of *BMAL1* in the treatment of immune-related diseases

Targeting the regulation of *BMAL1* could offer new treatment strategies for these immune-related diseases. Understanding the dysregulation of *BMAL1* in immune diseases is essential for the development and optimization of treatment options to maximize patient benefits. The application of *BMAL1* in immunotherapy involves two main aspects: chronotherapy and drug development targeting biological clock mechanisms. Chronotherapy focuses on optimizing drug administration timing to reduce toxicity and enhance drug efficacy by achieving optimal pharmacokinetics. Additionally, *BMAL1* serves as a promising drug target, as pharmacological manipulation of circadian signals has the potential to reset rhythms in organisms with dysfunctional circadian rhythms.

The application of chronotherapy in the medical field has been extensively documented in pharmacology. Chronotherapy enhances drug efficacy and reduces drug toxicity by considering the circadian rhythm of drug absorption, metabolism, and elimination. Evaluating circadian rhythms through clock gene expression analysis is crucial for identifying immune diseases. Monitoring circadian variations in biological and clinical markers can lead to improved patient stratification. In patients with type III PAS, all four genes—*GR-a*, *CLOCK*, *BMAL1*, and *PER3*—showed significant upregulation at night compared with those in healthy individuals. The pathophysiology of PAS type III patients is associated with disruptions in the daily expression patterns of clock-related genes [79]. Given the correlation between changes in circadian rhythm and increased symptom severity in patients with RA, chronotherapy has emerged as a promising treatment approach for RA. Administering therapy that optimizes drug release in a timely manner has also demonstrated positive effects in RA patients [126].

Chronotherapy is still in the early stages of practice, and further research into its mechanisms is needed to improve the current level of treatment. Abnormal expression of *BMAL1* is an important factor in the occurrence of immune diseases. Therefore, targeting the regulation of *BMAL1* may become a new strategy for treating these immune-related diseases. For example, *BMAL1* and *REV-ERB* control flavivirus replication in infectious illnesses. Gene knockout of *BMAL1* and synthetic agonist overexpression or activation of *REV-ERB* inhibits the replication of HCV and related flaviviruses, such as dengue and Zika viruses, by interfering with lipid signalling pathways [89]. Furthermore, *BMAL1* and *CLOCK* regulate the rhythmic expression of antiviral proteins in the skin. Treatment with the circadian enhancers nobiletin and SR8278 results in a reduction in HSV-1 infection in epidermal explants and human keratinocytes, demonstrating a *BMAL1*/*CLOCK*-dependent mechanism [85].

Targeting *BMAL1* can improve tumour prognosis. The overexpression of *BMAL1* in tongue squamous cells and colorectal cancer cells made these cells sensitive to paclitaxel and oxaliplatin, respectively [110, 111]. Additionally, overexpression of the clock gene *BMAL1* increased the sensitivity of colorectal cancer patients to oxaliplatin [111]. These findings suggest that the regulatory effect of *BMAL1* on the induction of apoptosis may vary depending on the type of chemical drug used. Interference with *BMAL1* expression and disruption of the circadian rhythm may protect against tumour development after DNA damage. Furthermore, the apoptosis of *BMAL1*-mutant breast epithelial cells is increased when these cells are exposed to chemotherapeutic drugs such as cisplatin and adriamycin [104]. The combination of *BMAL1* silencing with bevacizumab synergistically reduces angiogenesis, glycolysis, and M2 polarization while enhancing M1 polarization *in vivo*, ultimately inhibiting glioblastoma formation [127]. In trastuzumab-resistant HER2-positive gastric cancer, glycolysis oscillates with the circadian rhythm regulated by the *BMAL1*–*CLOCK*–*PER1*–HK2 axis. One potential method of counteracting trastuzumab resistance is to interfere with the circadian rhythm PER1–HK2 axis [128]. When Lewis lung cancer mice are treated with doxorubicin, significant

changes in the expression of F4/80 and CD11c in tumour tissues, as well as circadian rhythm genes such as *BMAL1*, *CLOCK*, *REV-ERBα*, *PER2*, NF-kB, and IL-6 in peritoneal macrophages, are observed [129].

Perspective

The circadian clock is an internal timekeeping system that regulates biological processes through a central circadian clock and peripheral clocks controlling various genes. Studies have demonstrated a significant circadian rhythm in the immune response. Since earlier descriptive studies, the bidirectional molecular relationship between clock genes and components of the immune system has gradually become clearer [24]. The biological clock not only regulates immune system function but also influences circadian rhythms through direct interactions between components of the biological clock and the immune system. Specifically, the circadian clock affects the immune system by directly regulating the expression of circadian clock proteins that function as transcription factors, driving or suppressing the expression of immune-related genes. Additionally, the mRNA expression levels of clock genes play crucial roles in immune function [52]. Clock genes can physically interact with key inflammatory pathway components, such as members of the NF-κB protein family, via a mechanism that does not depend on transcription, thereby facilitating mutual regulation between the clock and the immune system [54]. Clock genes are essential for regulating the immune response. Evidence from various knockout models indicates that disruptions in clock genes can lead to severe disease manifestations and immunopathology [25, 32, 45]. Complex relationships exist among ageing, circadian rhythms, and cancer [130]. Dysfunctional circadian rhythms may heighten the risk of cancer, with factors such as sleep deprivation and shift work potentially linked to cancer. As cells age, their repair capabilities and immune surveillance functions gradually decline, increasing their susceptibility to cancer [131]. The disruption of circadian rhythms often worsens with ageing, leading to a vicious cycle in which ageing impacts the stability and function of circadian rhythms. Exploring the intricate relationships among circadian rhythms, ageing, and cancer could pave the way for more effective cancer prevention and treatment approaches [132, 133]. For example, disruptions in circadian rhythm and the ageing process may contribute to tumour development through oxidative stress–related signalling pathways [134]. Targeting oxidative stress mechanisms to counteract ageing or restore circadian rhythms could enhance antitumour effects. Melatonin has been shown to inhibit cancer by inducing oxidative stress [135]. Moreover, melatonin plays a role in regulating clock genes, including those present in cancer cells, which could be crucial for cancer suppression. For example, tumour hypoxia-induced acidosis can increase metastatic potential by reducing *BMAL1* levels, but melatonin has been found to counteract this effect by inhibiting lactate dehydrogenase-A during hypoxia [103].

BMAL1, a key gene in the circadian clock system, plays a crucial role in maintaining the body's daily rhythms and in the development and progression of immune-related diseases. There are several limitations associated with studies that analyse *BMAL1* in total knockout mice, especially in contexts where mechanistic insights are limited. Although these studies provide a broad perspective on immune function, they may not fully elucidate the direct role of *BMAL1* in specific immune cell types. This is because the observed effects in total knockout mice may involve indirect or compensatory mechanisms across different cell populations.

Elucidating the specific mechanisms through which *BMAL1* operates in immune-related diseases is vital for advancing new therapeutic strategies. Fortunately, contemporary methodologies such as single-cell sequencing, organoid culture, multiomics analysis, and 3D printing can be harnessed to investigate these mechanisms [136–138]. For example, single-cell transcriptomic analysis revealed disruptions in circadian rhythms associated with adverse outcomes and drug resistance in lung adenocarcinoma [139]. Traditional two-dimensional cell cultures are limited in their ability to replicate the key characteristics of the original tumour in vivo. Bioprinting offers a way to recreate the three-dimensional structure of tumour tissue, providing a more accurate model. By enabling the creation of complex three-dimensional models of the immune system, bioprinting allows researchers to better understand how immune cells interact with tumour cells and to optimize immunotherapy strategies [140]. Furthermore, advanced biomaterials significantly enhance immunotherapy and play a crucial role in cancer treatment, establishing them as a prominent research focus within the biomedical field. A deeper comprehension of these processes could pave the way for integrating clock-based anticancer strategies into precision medicine protocols. In clinical diagnosis, developing biomarker detection methods based on *BMAL1* is highly important. By measuring the expression levels of *BMAL1* and its downstream target genes, clinicians can assess a patient's circadian clock function and its impact on the immune system. This approach can be particularly beneficial for diagnosing immune-related diseases associated with circadian clock disorders [63]. Furthermore, the application of genomic technologies can identify mutations or abnormalities in the expression of the *BMAL1* gene, serving as a powerful tool for disease risk prediction and personalized diagnosis. For example, genomic analysis has revealed the potential of *BMAL1* as a clinically relevant prognostic factor and a biomarker for T-cell immunotherapy in metastatic melanoma [94]. Furthermore, genetic polymorphisms, including variants of the clock gene *BMAL1* (such as rs2290035, rs2278749, and rs969485), have been associated with an increased risk of breast cancer [141]. Genetic testing for clock gene polymorphisms can serve as an additional screening tool for immune-related diseases, aiding in the understanding of disease risk and the development of personalized treatment plans [142].

Dysregulation of *BMAL1* has been associated with changes in the immune response in cancer, affecting the capacity of immune cells to recognize and eradicate cancer cells. Additionally, disturbances in *BMAL1* may impact the efficacy of immune checkpoint inhibitors. Not only does radiation directly destroy tumour cells, but it also serves as an immune modulator. Radiotherapy can increase the sensitivity of tumour cells to PD-L1 inhibitors, thereby increasing the effectiveness of immunotherapy [143]. Additionally, radiotherapy changes the tumour microenvironment by reducing the number of immunosuppressive cells and increasing the number of effector immune cells, helping the immune system fight against tumours. For example, stereotactic body radiation therapy improves the priming of tumour-specific T cells in poorly immunogenic tumours, and combining it with immune checkpoint blockade can further increase the frequency of these T cells [144].

BMAL1 is a promising target for drug development, with the potential for realigning circadian dysregulation in organisms through pharmacological manipulation of circadian signalling. Researchers are currently exploring drug delivery systems as a means of intervention in immune-related diseases [145, 146]. Specifically, circadian drug delivery systems are being investigated to synchronize drug release with the body's circadian rhythm, aiming to increase drug efficacy, reduce side effects, and improve patient compliance [147]. A nanoparticle (NP) is a small structure capable of carrying drugs, and NP drug delivery systems have shown controlled delivery and the ability to target specific tissues [148–150]. NPs have shown promising potential as drug delivery systems, enhancing drug delivery efficiency to immune cells and tissues through the manipulation of surface properties and drug release mechanisms [151–153]. Moreover, NPs can modulate immune responses and influence immune system activity via interactions with immune cells [154, 155].

Conclusions

Numerous studies have demonstrated a correlation between *BMAL1* disorders and the onset of immune-related diseases. The impact of *BMAL1* on immune function underscores its pivotal role in these conditions. Insight into the connection between *BMAL1* and immune-related diseases is crucial for gaining a deeper understanding of how maintaining *BMAL1* levels can aid in the prevention and treatment of such conditions. Based on these findings, we elucidated the specific functions of *BMAL1* in immune cells, including their development, differentiation, migration, homing, metabolism, and effector capabilities. *BMAL1* significantly influences immune function. Dysregulated expression of *BMAL1* is a key factor in autoimmune diseases, infectious diseases, and cancer. Therefore, comprehending the dysregulation of *BMAL1* in immune-related diseases is essential for the development and optimization of chronotherapeutic strategies that can offer maximal benefits to patients.

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Conflict of interest

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