BMAL1 in cardiovascular diseases: Molecular mechanisms, circadian regulation and translational perspectives (Review)

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Abstract. Brain and muscle ARNT-like 1 (BMAL1) is a core transcription factor of the molecular circadian clock and links daily timing with cardiovascular electrophysiology, metabolism, vascular function and inflammation. Altered BMAL1 expression or rhythmicity has been reported in arrhythmias, atherosclerosis, myocardial ischemia/reperfusion injury and heart failure. However, its specific role has remained elusive, as local effects in cardiovascular cells are often mixed with the broader effects of whole-body circadian disruption. The present review addressed this gap by separating evidence from central and peripheral clocks, cell-specific and systemic models, and experimental and human studies. Cardiomyocyte-specific models provide relatively direct evidence that the local clock supports electrical stability, substrate use, mitochondrial homeostasis and contractile function. However, in endothelial cells, vascular smooth muscle cells and immune cells, the effects of BMAL1 are more variable and depend on cell type, metabolic conditions, disease stage and circadian phase. Human evidence remains mainly associative, whereas most mechanistic findings come from cell and animal studies. The present review also assessed small-molecule clock modulators, chronotherapy and non-pharmacological interventions, as well as time-resolved multi-omics and machine-learning approaches. Current evidence does not support viewing BMAL1 as simply protective or harmful. A selective BMAL1-binding small molecule has recently been identified, but its cardiovascular efficacy and safety have not been established. In addition, the clinical benefits of chronotherapy vary across treatments and patients. Further translation will require tissue-specific human models, repeated sampling across biological time and prospective studies of treatment guided by individual circadian phases.

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1. Introduction

The circadian system is an endogenous timekeeping network that coordinates physiological processes over a ~24-h cycle. Cardiovascular parameters, including heart rate, blood pressure, heart rate variability, vascular tone and endothelial function, vary during the day (1). This temporal organization is clinically relevant as acute myocardial infarction, ventricular arrhythmias and sudden cardiac death do not occur randomly, but demonstrate characteristic time-of-day patterns (2-4). Shift work, sleep disruption, transmeridian travel and irregular light exposure may disturb this organization and have been associated with a higher risk of cardiovascular disease (5,6). These observations have prompted growing interest in the mechanisms by which the molecular clock contributes to cardiovascular adaptation and disease.

Brain and muscle ARNT-like 1 (BMAL1), encoded by aryl hydrocarbon receptor nuclear translocator-like gene (*ARNTL*), is a central component of the positive transcriptional limb of the molecular clock. After heterodimerizing with circadian

locomotor output cycles kaput (CLOCK), it binds to E-box elements and drives the expression of clock-controlled genes, including members of the period circadian regulator (PER) and cryptochrome circadian regulator (CRY) families, whose protein products subsequently repress CLOCK-BMAL1 activity (7,8). In cardiovascular tissues, BMAL1 influences electrical, metabolic, vascular and inflammatory programs, although the direction and magnitude of these effects vary across cell types and disease contexts (4,9-11). These effects are not uniformly protective or detrimental, and their direction depends on the cell type, disease stage, metabolic environment and circadian phase in which BMAL1 is examined (4,9-11). BMAL1 was selected as the focus of the present review, as it is an essential component of the positive transcriptional limb of the clock and has been examined in multiple cell-specific cardiovascular models (7-11). These models help to distinguish the local effects of the molecular clock from the broader consequences of systemic circadian disruption. In addition, other clock components, such as CLOCK, PER, CRY, nuclear receptor subfamily 1 group D (REV-ERB) and retinoic acid receptor-related orphan receptor (ROR), and their regulation of BMAL1 or contribution to related cardiovascular pathways, are discussed.

Cardiovascular timing is governed by interactions between the central clock and peripheral clocks within the heart, vasculature and immune system. The central clock coordinates autonomic activity, hormonal secretion, sleep-wake behavior, feeding and body temperature, whereas local clocks regulate tissue-specific transcriptional and metabolic programs (1,8). This distinction affects the interpretation of BMAL1 studies. Cell-specific genetic models can provide evidence for a direct, cell-autonomous function, while whole-body knockout, altered light-dark cycles, sleep deprivation or feeding interventions simultaneously affect several systemic pathways (1,9-11). Similarly, changes in BMAL1 expression in human blood or diseased tissue may indicate circadian misalignment without demonstrating that BMAL1 is the primary cause of cardiovascular injury (1,5,6). Clinical studies of timed antihypertensive therapy further suggest that treatment timing may influence cardiovascular outcomes, although the benefits are not consistent across trials or patient populations (12,13).

Previous reviews have mainly addressed the broader relationship between the circadian clock and cardiovascular disease (1,14). The present narrative review focuses specifically on BMAL1 and evaluates the available evidence using three related distinctions: i) Central vs. peripheral clocks; ii) cell-autonomous vs. systemic regulation; and iii) adaptive vs. maladaptive circadian remodeling. Mechanistic findings from cell-specific manipulation and rescue experiments are considered separately from evidence derived from whole-animal circadian disruption and observational human studies. Within this framework, the involvement of BMAL1 in cardiac electrophysiology, vascular inflammation and remodeling, myocardial ischemia/reperfusion injury and heart failure was examined, before assessing the current evidence for chronotherapy, pharmacological modulation and other time-based interventions. Particular attention is given to conflicting findings, methodological limitations and the barriers that currently restrict clinical translation.

Relevant English language studies were identified through searches in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and Scopus (https://www.scopus.com/) from database inception to February 2026. Search terms included combinations of 'BMAL1', '*ARNTL*', 'circadian clock', 'cardiovascular disease', 'arrhythmia', 'atherosclerosis', 'myocardial ischemia/reperfusion', 'heart failure', 'vascular function', 'inflammation' and 'chronotherapy'. The reference lists of relevant original articles and reviews were also screened. Priority was given to mechanistic studies, cell-specific genetic models, human cardiovascular studies and clinical studies with clearly defined temporal information. No formal risk-of-bias assessment or quantitative synthesis was performed. A schematic overview of the cell-specific cardiovascular roles and translational implications of BMAL1 is presented in Fig. 1, while its principal post-translational, protein-stability and metabolic regulatory mechanisms are summarized in Table I.

2. Conceptual and molecular framework of BMAL1

Central and peripheral circadian regulation. Cardiovascular circadian regulation operates at both central and peripheral levels. The suprachiasmatic nucleus coordinates daily cardiovascular rhythms through autonomic, endocrine, behavioral and temperature-related signals (1,8). In parallel, cardiomyocytes, endothelial cells, vascular smooth muscle cells, fibroblasts and immune cells contain local clocks that generate cell-specific oscillations (1,8). A change in cardiac or vascular BMAL1 expression may therefore arise from intrinsic disruption of a peripheral clock, altered systemic entrainment or a combination of the two (15).

Although the core feedback loop is shared across tissues, the regulation and transcriptional output of BMAL1 differ between central and peripheral clocks. In the suprachiasmatic nucleus, circadian rhythmicity is maintained through light entrainment and coupling among neuronal oscillators, whereas cardiac and vascular clocks are also influenced by autonomic, hormonal, feeding-related and local metabolic signals (1,8). Studies of mouse heart, liver and kidney tissues further showed that most BMAL1-binding sites were tissue-specific, reflecting differences in chromatin accessibility and cooperating transcription factors (16). Thus, similar BMAL1 expression across tissues does not necessarily indicate the same downstream transcriptional program. These tissue-specific binding data were obtained from mouse organs and comparable genome-wide evidence from human cardiovascular tissues remains limited.

This distinction also affects the manner in which experimental evidence should be interpreted. Cell-specific experimental models provide stronger evidence that local BMAL1 activity contributes directly to cardiovascular homeostasis (9). By contrast, whole-body gene deletion, altered light-dark cycles, sleep deprivation and feeding interventions produce broader physiological changes and cannot isolate the contribution of BMAL1 within a single cardiovascular cell type (1,15,17). Cell-specific deletion and rescue experiments therefore provide stronger evidence of causality, whereas peripheral blood measurements and observational human studies more often demonstrate circadian association.

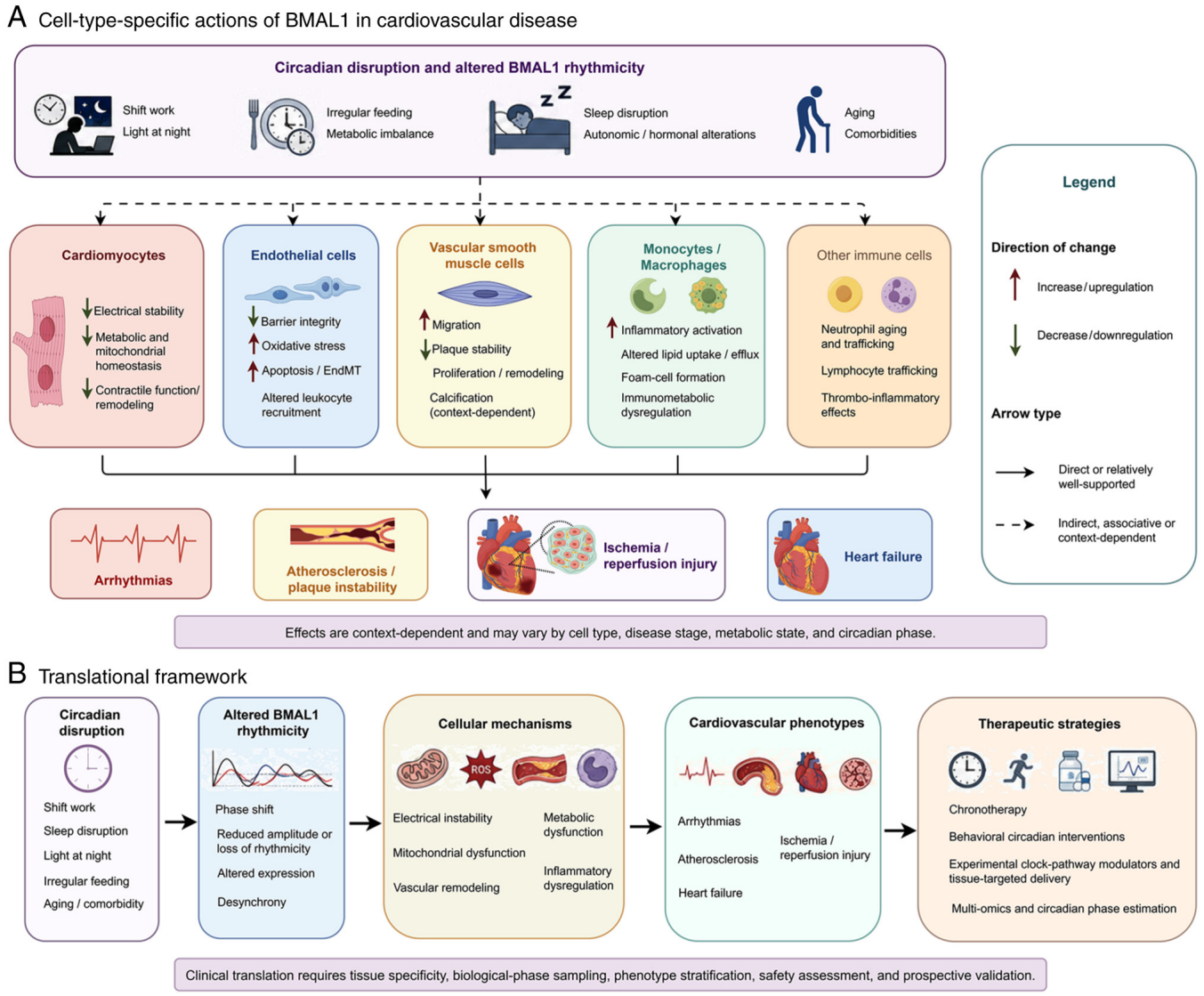

Figure 1. Cell-type-specific actions and translational framework of BMAL1 in cardiovascular disease. (A) Circadian disruption and altered BMAL1 rhythmicity affect cardiomyocytes, endothelial cells, vascular smooth muscle cells, monocytes/macrophages and other immune cells, contributing to arrhythmias, atherosclerosis, ischemia/reperfusion injury and heart failure. (B) Translational framework linking circadian disruption, altered BMAL1 rhythmicity, cellular mechanisms, cardiovascular phenotypes and potential therapeutic strategies. Solid arrows indicate direct or relatively well-supported relationships, whereas dashed arrows indicate indirect, associative or context-dependent relationships. Upward and downward arrows indicate relative increases and decreases, respectively, rather than pooled quantitative effect sizes. The effects of BMAL1 may vary by cell type, disease stage, metabolic state and circadian phase. FigDraw (https://www.figdraw.com) was used to generate the figure. BMAL1, brain and muscle ARNT-like 1; EndMT, endothelial-to-mesenchymal transition; ROS, reactive oxygen species.

Circadian remodeling is not uniformly adaptive or maladaptive. Altered BMAL1 activity may be adaptive or maladaptive depending on its anatomical location, circadian phase, amplitude, duration and disease stage (1,9,14). These distinctions are used throughout the following sections to assess the strength and biological relevance of the available evidence.

Transcriptional, post-translational and metabolic regulation of BMAL1. BMAL1, encoded by the human *ARNTL* locus on chromosome 11p15.3, is a basic helix-loop-helix PER-ARNT-SIM (PAS) transcription factor and a core component of the mammalian circadian clock (7,8). The locus generates alternatively spliced transcripts with alternative translation-initiation-site usage (18). The canonical BMAL1 protein contains an N-terminal basic helix-loop-helix domain, tandem PAS-A and PAS-B domains, and a C-terminal transactivation domain (18-21). The basic helix-loop-helix domain mediates binding to E-box sequences, whereas the PAS domains support heterodimerization with CLOCK or neuronal PAS domain protein 2 (19,20). The C-terminal transactivation domain recruits transcriptional coactivators and interacts with CRY1, thereby contributing to the transition between transcriptional activation and repression (21).

Among these transcripts, human *ARNTL* encodes the canonical BMAL1b isoform and a shorter isoform termed BMAL1a (18,22). BMAL1a lacks part of the N-terminal region containing the nuclear localization signal and showed reduced nuclear localization and inhibitory effects on CLOCK-BMAL1-dependent transcription in cultured human

Table I. Post-translational, protein-stability and metabolic mechanisms regulating BMAL1 and their cardiovascular relevance.

Regulatory mechanism	Enzyme or regulator	Effect on BMAL1 or the circadian clock	Main experimental evidence	Cardiovascular relevance and limitations	(Refs.)
Phosphorylation	CDK5	Alters BMAL1 phosphorylation, nuclear binding and rhythmic transcription	General cellular and peripheral-clock models	Direct evidence in defined cardiovascular cells remains limited	(29)
Phosphorylation and stability regulation	GSK3β	Influences BMAL1 phosphorylation, ubiquitination and protein stability	General cellular models	May link metabolic signaling with circadian regulation, but direct cardiovascular evidence is insufficient	(30)
Dephosphorylation	PPP4	Reduces BMAL1 phosphorylation, delays negative feedback and contributes to circadian timing	General cellular models	Direct cardiovascular relevance has not been established	(32)
Ser42 phosphorylation	PKA	Promotes BMAL1 cytoplasmic accumulation and reduces *Per2* and *Nr1d1* transcription	Mouse myocardial tissue and rat H9c2 cardiac myoblasts	Relatively direct cardiac evidence in a β1-adrenoceptor autoantibody model; relevance to human myocardium and other cardiovascular diseases remains elusive	(48)
Ubiquitination	UBR5	Promotes BMAL1 ubiquitination and degradation, reducing its stability and transcriptional activity	General cellular models	No direct evidence in defined cardiovascular cell types	(33)
K48-linked ubiquitination	HRD1	Promotes proteasome-dependent degradation of BMAL1	General cellular models	Cardiovascular relevance has not been directly examined	(34)
Deubiquitination	USP1	Removes ubiquitin from BMAL1 and extends its half-life	Genome-wide screening and cellular models	No direct cardiovascular evidence	(35)
Ubiquitin-independent degradation	p62/SQSTM1	Facilitates proteasomal degradation of nuclear BMAL1	General cellular models	Direct relevance to cardiac, vascular or immune cells remains elusive	(36)
Acetylation	CLOCK	Acetylates BMAL1, promotes CRY1 recruitment and contributes to transcriptional repression	General molecular-clock and cellular models	Direct BMAL1-specific evidence in cardiovascular cells remains limited	(37,38)
SUMOylation	SUMO2/3 conjugation machinery	Coordinates BMAL1 transcriptional activation with subsequent ubiquitination and turnover	General cellular models	No direct evidence in cardiovascular cells	(39)
O-GlcNAcylation	O-GlcNAc transferase	Stabilizes BMAL1 and CLOCK by limiting their ubiquitination	Nutrient-sensitive cellular models	Potentially relevant under metabolic stress, but cardiovascular evidence remains indirect	(40)

Table I. Continued.

Regulatory mechanism	Enzyme or regulator	Effect on BMAL1 or the circadian clock	Main experimental evidence	Cardiovascular relevance and limitations	(Refs.)
Chaperone-dependent stabilization	Necdin-SGT1-HSP90	Supports the folding and stability of BMAL1; loss of Necdin promotes its degradation	General cellular models	Roles in cardiac and vascular BMAL1 regulation remain uncertain	(41)
Indirect stabilization	DISC1-GSK3β pathway	Reduces BMAL1 ubiquitination and increases protein stability	General cellular models	Cardiovascular relevance has not been established	(42)
Chromatin remodeling and deacetylation	SIRT1	Rhythmically modulates BMAL1 and histone acetylation within the CLOCK-BMAL1 complex	General cellular and metabolic models	Relevant to metabolic regulation, but direct BMAL1-specific cardiovascular evidence is limited	(43)
NAD^+ metabolic feedback	CLOCK-BMAL1-NAMPT-NAD^+-SIRT1 pathway	Links BMAL1-dependent transcription with cellular NAD^+ availability and SIRT1 activity	General metabolic and circadian models	May connect circadian timing with cardiovascular redox and metabolic states; direct cell-specific evidence remains limited	(44)
Energy sensing	AMPK-CRY1 pathway	Alters circadian phase by promoting CRY1 phosphorylation and degradation rather than directly modifying BMAL1	General metabolic models	Indirectly relevant to BMAL1-dependent clock function; cardiovascular-specific evidence remains insufficient	(45)
Nutrient-sensitive phosphorylation	mTORC1-S6K1	Phosphorylates cytoplasmic BMAL1 and links nutrient availability with rhythmic protein synthesis	General cellular and metabolic models	Potential relevance to myocardial metabolism and growth, but direct cardiac evidence remains limited	(46)

Cardiovascular relevance was assessed according to whether the regulatory mechanism had been directly examined in defined cardiovascular cells or tissues. 'General cellular models' refers to non-cardiovascular or unspecified cellular systems. BMAL1, brain and muscle ARNT-like 1; PTM, post-translational modification; CDK5, cyclin-dependent kinase 5; GSK3β, glycogen synthase kinase 3β; PPP4, protein phosphatase 4; PKA, protein kinase A; UBR5, ubiquitin protein ligase E3 component N-recognin 5; HRD1, HMG-CoA reductase degradation protein 1; USP1, ubiquitin-specific peptidase 1; p62/SQSTM1, sequestosome 1; CLOCK, circadian locomotor output cycles kaput; CRY1, cryptochrome circadian regulator 1; *Per2*, period circadian regulator 2; *Nr1d1*, nuclear receptor subfamily 1 group D member 1; SUMO2/3, small ubiquitin-like modifier 2/3; O-GlcNAc, O-linked β-N-acetylglucosamine; SGT1, suppressor of G2 allele of SKP1 homolog; HSP90, heat shock protein 90; DISC1, disrupted-in-schizophrenia 1; SIRT1, sirtuin 1; NAMPT, nicotinamide phosphoribosyltransferase; NAD^+, nicotinamide adenine dinucleotide; AMPK, AMP-activated protein kinase; mTORC1, mechanistic target of rapamycin complex 1; S6K1, ribosomal protein S6 kinase 1.

cells (22). However, its expression and function have not been established in human cardiovascular tissues. Mouse *Bmal1* also generates several splice variants, but their transcript organization is not identical to that reported in humans (23). These differences should be considered when isoform-level findings are extrapolated across species.

BMAL1 expression and activity are controlled by the canonical CLOCK-BMAL1/PER-CRY feedback loop and by REV-ERB/ROR regulation of *ARNTL* transcription (24-26). Protein turnover, post-translational modification, chromatin state and metabolic sensing further shape the phase and amplitude of BMAL1-dependent transcription (27,28).

Phosphorylation is a major post-translational modification regulating BMAL1 activity, intracellular localization and stability (28). Cyclin-dependent kinase 5 interacts with BMAL1 in a time-dependent manner and alters its phosphorylation, nuclear binding and rhythmic transcription (29). Glycogen synthase kinase 3β (GSK3β) also influences BMAL1 phosphorylation and stability, linking metabolic signaling with circadian-clock function (30). Phosphorylation of CLOCK can further modify the transcriptional activity of the CLOCK-BMAL1 complex (31), whereas protein phosphatase 4-mediated dephosphorylation delays negative feedback and contributes to the maintenance of circadian timing (32). The majority of these mechanisms were established in general cellular or non-cardiovascular experimental systems.

Ubiquitination-mediated degradation represents another core mechanism regulating the half-life and circadian stability of BMAL1 (33-36). Ubiquitin protein ligase E3 component N-recognin 5 promotes BMAL1 ubiquitination, thereby reducing its stability and transcriptional activity and altering the amplitude of cellular circadian rhythms (33). HMG-CoA reductase degradation protein 1 facilitates proteasome-dependent degradation via K48-linked polyubiquitination, modulating the amplitude of rhythmic gene expression (34). The deubiquitinating enzyme ubiquitin-specific peptidase 1 removes ubiquitin tags from BMAL1, extending its half-life to maintain stability (35). The ubiquitin-independent proteasomal degradation pathway mediated by sequestosome 1 provides an alternative mechanism for regulating nuclear BMAL1 levels (36).

Acetylation, small ubiquitin-like modifier (SUMO) conjugation and O-linked β-N-acetylglucosamine (O-GlcNAc) modification provide additional layers of BMAL1 regulation. CLOCK possesses intrinsic histone acetyltransferase activity and acetylates both histones and BMAL1 (37,38). Acetylation of BMAL1 facilitates CRY1 recruitment and contributes to the repression of CLOCK-BMAL1-dependent transcription (38). In addition, BMAL1 can undergo SUMO2/3 modification, which coordinates its transcriptional activation with subsequent ubiquitination and protein turnover (39). In addition, rhythmic O-GlcNAcylation stabilizes BMAL1 and CLOCK by inhibiting their ubiquitination, thereby linking glucose availability and nutrient sensing to clock-protein stability (40). These modifications interact dynamically to influence the amplitude, phase and duration of circadian transcription.

Protein stability is also influenced by chaperone-related pathways. Necdin interacts with a chaperone complex comprising suppressor of G2 allele of SKP1 homolog and heat shock protein 90, which supports the proper folding and stability of BMAL1 (41). Loss of Necdin promotes ubiquitin-dependent BMAL1 degradation and disrupts circadian rhythmicity (41). Disrupted-in-schizophrenia 1 indirectly stabilizes BMAL1 by suppressing GSK3β activity and reducing BMAL1 ubiquitination (42). These mechanisms were identified outside the cardiovascular system, and their roles in cardiac or vascular BMAL1 regulation remain uncertain.

BMAL1-dependent transcription is also shaped by rhythmic chromatin remodeling. CLOCK-mediated histone acetylation increases chromatin accessibility at circadian promoters, whereas the nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase sirtuin 1 (SIRT1) associates with the CLOCK-BMAL1 complex and rhythmically modulates the acetylation of BMAL1 and histones (37,43). Conversely, CLOCK-BMAL1 promotes the transcription of nicotinamide phosphoribosyltransferase, generating daily oscillations in NAD^+ availability and SIRT1 activity (44). This reciprocal feedback loop links cellular redox and metabolic states with the epigenetic regulation of circadian transcription.

Other metabolic-sensing pathways also influence circadian timing. AMP-activated protein kinase (AMPK) responds to energetic stress and can alter the clock phase by promoting CRY1 phosphorylation and degradation (45). By contrast, signaling through mechanistic target of rapamycin complex 1 (mTORC1) and ribosomal protein S6 kinase 1 (S6K1) phosphorylates cytoplasmic BMAL1 and links nutrient availability to rhythmic protein synthesis (46). Together with SIRT1 and NAD^+ metabolism, these pathways provide potential connections between circadian regulation, mitochondrial function, autophagy, and protein synthesis (43-47). However, much of the direct mechanistic evidence has been obtained from non-cardiovascular tissues, and its relevance to individual cardiovascular cell types remains to be established.

Direct evidence linking a defined BMAL1 post-translational modification to a cardiovascular phenotype remains limited and is currently strongest in cardiac experimental models. In mouse myocardial tissue and rat H9c2 cardiac myoblasts, β1-adrenoceptor autoantibody-induced protein kinase A activation increased BMAL1 phosphorylation at Ser42, promoted its cytoplasmic accumulation, reduced transcription of the period circadian regulator 2 and nuclear receptor subfamily 1 group D member 1 genes, and was associated with increased cardiac cell death (48). This study provides relatively direct evidence for a phosphorylation-dependent mechanism, but it was conducted in a specific experimental setting and does not establish that Ser42 phosphorylation has the same role across other cardiovascular diseases or in human myocardium.

Cardiomyocyte-specific *Bmal1* models show abnormalities in myocardial metabolism, mitochondrial quality control, autophagy and contractile function (9,47,49), but these phenotypes do not identify a specific modification of the BMAL1 protein. Similarly, smooth-muscle-specific *Bmal1* deletion alters vascular contractile signaling and remodeling (10,50), whereas evidence linking these effects to a defined BMAL1 modification is lacking. Evidence for specific post-translational modifications in endothelial and immune cells is even more limited. Among the aforementioned mechanisms, Ser42 phosphorylation has relatively direct support from a specific cardiac experimental model (48), whereas ubiquitination, deubiquitination (33-36), acetylation (37,38), SUMOylation (39),

O-GlcNAcylation (40) and chaperone-dependent stabilization (41,42) have been characterized mainly in general cellular or non-cardiovascular systems. Therefore, they should be regarded as mechanisms with potential cardiovascular relevance rather than established therapeutic targets. Their principal regulators and current level of cardiovascular evidence are summarized in Table I.

3. Mechanistic roles of BMAL1 in cardiovascular disease

Cardiac electrophysiology and arrhythmias. The most direct evidence for a cardiovascular role of BMAL1 comes from studies of the cardiomyocyte molecular clock. BMAL1 contributes to the rhythmic transcription of cardiac ion-channel genes, including potassium voltage-gated channel subfamily H member 2, which encodes the ether-a-go-go-related gene potassium channel, and sodium voltage-gated channel α subunit 5, which encodes the Nav1.5 sodium channel (51,52). Disruption of the cardiomyocyte clock alters ventricular repolarization, action-potential duration and conduction properties, supporting a cell-autonomous contribution to electrical stability (4,51,52).

Regional and cell-type differences in cardiac BMAL1 expression remain incompletely defined. Most mechanistic evidence has been obtained from ventricular cardiomyocytes and has focused on ventricular repolarization, conduction and ion-channel regulation (4,51,52). Direct comparisons of BMAL1 rhythmicity between atrial and ventricular myocardium are limited, and evidence from the sinoatrial node, atrioventricular node and Purkinje system is even rarer (51-54). Human single-cell and spatial atlases have revealed marked transcriptional heterogeneity among atrial and ventricular cardiomyocytes, fibroblasts, endothelial cells, mural cells, immune cells and specialized conduction-system regions (53,54). However, these datasets were not generated through repeated sampling across defined circadian phases. They therefore describe regional and cellular heterogeneity of the human heart but cannot establish whether the phase or amplitude of BMAL1 expression differs among cardiac chambers, conduction tissues or individual cell populations. Addressing this question will require region-specific and cell-resolved sampling across the circadian cycle.

Human myocardial studies provide complementary, although less direct, evidence. Rhythmic expression of clock-related and ion-channel genes has been detected in failing human myocardial tissue (55). However, advanced cardiac disease is accompanied by fibrosis, neurohumoral activation, medication exposure and changes in tissue composition, all of which can influence the observed transcriptional profile (53-55). The temporal clustering of ventricular arrhythmias and sudden cardiac death confirms that arrhythmic risk varies during the day (3,4), but it does not establish BMAL1 as the principal causal determinant.

Evidence linking BMAL1 to atrial fibrillation is more limited and remains mainly observational. In a clinical study, patients with persistent atrial fibrillation showed lower peripheral leukocyte expression of several clock genes, including BMAL1. Decreased clock-gene expression was associated with a greater burden of atrial high-rate episodes, while lower BMAL1 expression correlated with left atrial enlargement (56). However, BMAL1 was not experimentally manipulated, and the measurements were not obtained as a circadian time series. Without experimental manipulation or repeated circadian sampling, this study does not establish that BMAL1 dysregulation causes atrial fibrillation.

Systemic circadian disruption and autonomic BMAL1 signaling should be distinguished from disruption of the local myocardial clock. Altered light-dark cycles can simultaneously affect sympathetic activity, heart-rate variability, blood pressure, metabolism, renal function and cardiac structure (17). Therefore, electrophysiological abnormalities in these models cannot be attributed solely to BMAL1 within cardiomyocytes. In a canine myocardial ischemia model, targeted *Bmal1* knockdown in the left stellate ganglion reduced sympathetic neural activity and ventricular arrhythmias (57). This finding supports a role for neural BMAL1 in arrhythmia susceptibility, but does not demonstrate a cardiomyocyte-autonomous mechanism.

The time-of-day variation in ventricular arrhythmias and sudden cardiac death provides a rationale for studying the timing of antiarrhythmic treatment. However, current evidence is insufficient to recommend universal or BMAL1-guided dosing schedules. Drug half-life, formulation, arrhythmia type, autonomic state and individual biological phase should be considered, and timed administration should not currently be regarded as a BMAL1-specific intervention (58).

Overall, cardiomyocyte-specific studies support a direct role for the local molecular clock in ventricular repolarization and conduction. Evidence for atrial arrhythmias, neural BMAL1 signaling and BMAL1-directed antiarrhythmic treatment is considerably less developed. As systemic manipulation may affect myocardial and neural clocks differently, its net electrophysiological effect remains difficult to predict. These cardiomyocyte-specific effects are summarized in Fig. 1A.

Myocardial metabolism, ischemic stress and heart failure. The cardiomyocyte clock coordinates daily changes in substrate utilization, mitochondrial activity and contractile demand (9,49,59,60). The cardiomyocyte clock, including BMAL1-dependent regulation, contributes to fatty-acid uptake and oxidation, triglyceride metabolism and metabolic flexibility (9,59,60). Disruption of the local clock impairs the myocardial response to fatty acids and alters pathways involved in energy production, signaling and contractile performance (9,49,59).

Persistent disruption of cardiomyocyte BMAL1 is associated with progressive structural and functional abnormalities. Genetic disruption of *Bmal1* or the cardiomyocyte clock produces metabolic dysfunction, mitochondrial abnormalities, impaired contractility and a dilated cardiomyopathy-like phenotype in experimental models (47,49,61). These observations support a direct contribution of the local cardiomyocyte clock to myocardial homeostasis, although deletion of a core clock component perturbs a broad transcriptional network and does not identify a single downstream mechanism.

Circadian phase may influence myocardial susceptibility to ischemia/reperfusion injury. In a closed-chest mouse model, infarct size, fibrosis, adverse remodeling and contractile dysfunction varied according to the time of ischemia, and disruption of the cardiomyocyte clock abolished this temporal

difference (62). However, subsequent comparisons showed that both the presence and phase of this rhythm differed between ischemia/reperfusion and permanent-ligation models, indicating that the effect is sensitive to the experimental protocol (63). More recently, inducible cardiomyocyte-specific *Bmal1* deletion abolished the difference in myocardial injury between zeitgeber time 8 (ZT8; 8 h after lights on) and ZT20 (20 h after lights on), and attenuated the relative protection observed at ZT8. This study identified a BMAL1-hypoxia-inducible factor 2α-amphiregulin pathway and also reported time-dependent transcriptional differences relevant to ischemic responses in human left-ventricular biopsy samples obtained during morning and afternoon aortic-valve replacement surgery (64). As mice are nocturnal and experimental protocols vary, zeitgeber time in rodents should not be directly equated with human clock time (14,64).

Human studies also suggest that the time of ischemic onset may affect infarct severity. Certain studies of ST-segment elevation myocardial infarction reported larger infarcts during the morning or the transition from darkness to light, whereas others identified different peak periods (65,66). The reported associations remain observational and may be influenced by the accuracy of symptom-onset reporting, reperfusion delay, infarct location, medication use, sleep timing and metabolic disease. They support time of day as a relevant clinical variable but do not establish BMAL1 as the principal determinant of myocardial injury.

Several mechanisms may contribute to this temporal variation. Ischemic stress involves metabolic failure, mitochondrial dysfunction, oxidative injury, impaired autophagy and regulated cell death (67). Experimental studies have linked cardiac-clock disruption to impaired mitophagy, altered mitochondrial dynamics and reduced cardiomyocyte survival (47,68). Circadian antioxidant and inflammatory pathways may also modify ischemic injury, but much of the BMAL1-specific evidence for nuclear factor erythroid 2-related factor 2 (NRF2) and related signaling comes from macrophages or non-cardiovascular tissues (11,69). Their direct role in cardiomyocytes remains uncertain.

Metabolic-sensing pathways involving SIRT1-NAD^+ signaling, AMPK and mTORC1-S6K1 may link circadian timing with substrate selection, mitochondrial quality control and autophagy during myocardial energetic stress (43-46). However, their direct contribution to human myocardial ischemia/reperfusion injury remains uncertain. Therefore, BMAL1 should not be regarded as a universal protective factor during myocardial injury. Its effects may vary across acute ischemia, reperfusion, repair and remodeling, as well as with circadian phase, metabolic context, age and comorbidities. Direct BMAL1-specific evidence in aged or diabetic human myocardium remains limited.

Heart failure phenotypes should not be considered interchangeable. Most direct evidence for BMAL1 comes from cardiomyocyte-specific *Bmal1* disruption and dilated cardiomyopathy-like models characterized by impaired systolic function, and may therefore more closely resemble heart failure with reduced ejection fraction (HFrEF) (47,49,61). By contrast, heart failure with preserved ejection fraction (HFpEF) is a heterogeneous syndrome involving diastolic dysfunction, hypertrophy, fibrosis and variable metabolic and inflammatory abnormalities (70,71). Human transcriptomic, metabolomic and biomarker studies have identified overlapping but distinct molecular profiles in HFpEF and HFrEF (70-72). However, these studies did not establish that BMAL1 has a different causal role in the two phenotypes.

Preclinical evidence linking circadian disruption specifically to HFpEF remains limited. In a chronic jetlag mouse model, circadian disruption produced cardiac hypertrophy, fibrosis and diastolic dysfunction with preserved ejection fraction through altered signaling involving CLOCK, soluble guanylate cyclase, cyclic guanosine monophosphate and protein kinase G1 (73). This finding supports a possible connection between circadian misalignment and an HFpEF-like phenotype, but does not demonstrate a BMAL1-specific mechanism. Comorbidities and circadian or sleep dysregulation may further influence heart-failure phenotypes through changes in metabolism, inflammation, vascular function and myocardial remodeling (14,70,71,73,74). Human studies combining repeated circadian sampling with ejection-fraction phenotype and detailed comorbidity assessment remain scarce.

One human study suggested that peripheral circadian organization may persist in HFrEF despite dampened central hormonal output (74). Altered BMAL1 expression in advanced disease may represent a pathogenic mechanism, a compensatory response or a consequence of myocardial remodeling. Available human studies have not adequately integrated ejection-fraction phenotype, comorbidity profile and biological phase (70-72,74). Therefore, whether BMAL1 dysregulation differs between HFrEF and HFpEF, and the manner in which it should be modulated in individual patients remains unclear.

The evidence supports a cell-autonomous role for cardiomyocyte BMAL1 in metabolic homeostasis and long-term systolic remodeling. Its contribution to ischemic injury is more dependent on circadian phase and experimental context, while a distinct causal role in HFrEF and HFpEF has not been established. BMAL1 should consequently not be interpreted as a uniform marker or therapeutic target across myocardial disease states.

Vascular homeostasis, inflammation and atherosclerosis. Vascular circadian regulation involves coordinated clocks in endothelial cells, vascular smooth muscle cells, circulating immune cells and metabolic organs. BMAL1 has been linked to endothelial barrier function, vascular remodeling, leukocyte recruitment and lipid handling, although the direction of these effects varies across cell types, experimental conditions and disease stages (1,75).

Evidence from endothelial models is derived from several distinct experimental settings. In cultured endothelial cells and a mouse corneal injury model, BMAL1 was reported to reduce endothelial apoptosis through repression of signal transducer and activator of transcription 6 (76). In human aortic endothelial cells exposed to oxidized low-density lipoprotein, loss- and gain-of-function experiments linked BMAL1 to reduced reactive oxygen species (ROS) accumulation and suppression of endothelial-to-mesenchymal transition (77). By contrast, the association between clock disruption and endothelial toxicity induced by polychlorinated biphenyls was demonstrated in cultured brain endothelial cells under environmental toxicant exposure (78). Endothelial-specific disruption of *Bmal1* also

impaired endothelial proliferation in neonatal vascular tissues and tumor angiogenesis models in mice (79). These models support roles for BMAL1 in endothelial survival, integrity and proliferation, but they represent different vascular beds and disease settings and should not be interpreted as equivalent evidence for human atherosclerosis.

The effects of BMAL1 in vascular smooth muscle cells are similarly context-dependent. In mice with smooth-muscle-specific *Bmal1* deletion and experimentally induced carotid atherosclerosis, loss of BMAL1 increased vascular smooth muscle cell (VSMC) migration, oxidative stress, monocyte infiltration and plaque instability (10). Mechanistic experiments linked these effects to reduced Rho GDP dissociation inhibitor α expression and increased Ras-related C3 botulinum toxin substrate 1 activity (10). This model supports a context-specific protective role for VSMC BMAL1 in limiting migration and plaque destabilization.

By contrast, BMAL1 may participate in proliferative or pro-remodeling responses under other conditions. BMAL1 expression was increased in injured mouse carotid arteries and in platelet-derived growth factor-BB-stimulated cultured VSMCs, while BMAL1 knockdown reduced extracellular signal-regulated kinase activation and cell proliferation (80). These findings suggest that BMAL1 can support growth-factor-driven vascular proliferation, which may contribute to repair in one setting, but pathological remodeling in another. Other vascular models also indicate potentially maladaptive effects. In human valvular interstitial cells cultured under osteogenic conditions and in calcified human aortic-valve tissue, increased BMAL1 was associated with osteogenic differentiation involving runt-related transcription factor 2 through nuclear factor-κB (NF-κB), protein kinase B and mitogen-activated protein kinase signaling (81). In mouse pulmonary artery smooth muscle cells exposed to acute hypoxia, BMAL1 promoted voltage-dependent anion channel 1-mediated mitochondrial DNA leakage and NLR family pyrin domain-containing 3 (NLRP3) inflammasome activation (82). These findings concern calcific valve disease and acute high-altitude hypoxia, respectively, and cannot be generalized directly to systemic atherosclerosis or endothelial dysfunction.

Circadian regulation also intersects with lipid metabolism and macrophage function. Hepatic BMAL1 influences pathways involved in lipoprotein production (83), whereas macrophage BMAL1 has been implicated in cholesterol uptake and efflux through cluster of differentiation 36, ATP-binding cassette subfamily A member 1 and ATP-binding cassette subfamily G member 1 (84). As these pathways involve several clock and metabolic regulators, the resulting vascular phenotype cannot always be attributed specifically to BMAL1. At the lesion level, these cell-specific effects may influence successive stages of atherosclerosis, from endothelial injury and leukocyte recruitment to foam cell formation and plaque instability. However, direct evidence supporting that BMAL1 controls plaque rupture or arterial thrombosis remains limited.

Taken together, BMAL1 cannot be regarded as uniformly protective or harmful in the vascular system. Preserved BMAL1 activity may limit endothelial apoptosis, oxidative injury, smooth muscle migration and plaque instability in selected models. In other settings, it may support angiogenesis or growth-factor-driven proliferation, which may be adaptive or maladaptive depending on the disease context, and may also contribute to osteogenic differentiation or hypoxia-related inflammasome activation. These divergent findings likely reflect differences in vascular cell type, arterial bed, metabolic and inflammatory environment, disease stage and circadian phase. This context dependence remains a major obstacle to systemic BMAL1 activation or inhibition as a cardiovascular treatment. The principal endothelial- and smooth-muscle-cell effects of BMAL1 are summarized in Fig. 1A.

Immune regulation and sterile inflammation. BMAL1 displays circadian oscillation in immune cells and contributes to the temporal organization of inflammatory responses (85,86). The most direct evidence concerns monocytes and macrophages. In experimental macrophage models, BMAL1 has been linked to inflammatory transcription, cellular redox balance, necrotic signaling and lipid handling (11,84,87). One study reported that the rhythmically expressed long non-coding RNA AK023617 promoted BMAL1 nuclear translocation and its binding to the *immunity-related GTPase family M member 1* promoter, thereby altering macrophage necrotic signaling and plaque-related processes (87). Although this pathway provides a plausible connection between the molecular clock and atherosclerotic inflammation, its relevance to human lesions has not been established.

Myeloid BMAL1 integrates redox, inflammatory and metabolic signals. Loss or suppression of BMAL1 can enhance NF-κB-related signaling and weaken NRF2-dependent antioxidant responses in experimental systems (11,88). In myeloid *Bmal1*-deficient models, impaired mitochondrial function, succinate dehydrogenase-derived ROS, hypoxia-inducible factor 1α-dependent metabolic reprogramming and increased interleukin-1β (IL-1β) production have also been reported (89,90). Conversely, endotoxin can disrupt macrophage circadian oscillations through ROS-dependent mechanisms (91), indicating that the interaction between the clock and inflammation is bidirectional. These findings support a cell-autonomous immunometabolic role for BMAL1, but they arise mainly from cultured cells, infection models and genetically modified rodents. Their direction and magnitude may vary with the stimulus, metabolic environment and sampling time. The conventional binary classification of macrophage polarization also does not fully capture the macrophage states present in atherosclerotic plaques or injured myocardium (92).

Circadian timing may also influence trained immunity, in which previous stimulation induces persistent metabolic and epigenetic changes in innate immune cells. A human study showed that the magnitude of trained immune responses following Bacillus Calmette-Guérin vaccination varied according to the time of vaccination (93). However, BMAL1 was not directly manipulated in the study, and its involvement remains inferred from the broader circadian regulation of innate immune function. These observations link the timing of immune stimulation with trained innate responses, but they do not yet establish a BMAL1-dependent mechanism in cardiovascular disease.

Immune cells within cardiovascular tissues should not be considered a uniform population. Circulating monocytes undergo marked diurnal changes in abundance and tissue

recruitment (85,94). After entering injured myocardium or atherosclerotic plaques, they may differentiate into macrophage states that differ from resident macrophages in inflammatory, lipid-handling, reparative and profibrotic functions (95-97). Neutrophils have a distinct circadian aging program that influences their migration and vascular effects (98), whereas BMAL1-related effects in lymphocytes appear to be more evident in trafficking than in all aspects of differentiation or effector function (94,99). However, direct comparisons of BMAL1 function between resident macrophages and recruited monocyte-derived macrophages remain limited.

Single-cell and multimodal profiling have substantially refined the immune landscape of cardiovascular lesions. In human atherosclerotic plaques, combined single-cell transcriptomic and proteomic analyses identified distinct macrophage and T-cell states and revealed differences between symptomatic and asymptomatic carotid plaques (95). An integrated atlas subsequently harmonized single-cell datasets from carotid, coronary and femoral lesions, and resolved recurrent immune and vascular cell states across different arterial beds (97). In experimental myocardial infarction, serial single-cell RNA sequencing demonstrated marked changes in immune composition after injury, including early inflammatory macrophage populations, later apoptotic neutrophils and profibrotic macrophage subsets (96). These studies demonstrate cell-state and post-injury temporal heterogeneity, but most were not designed with repeated circadian-phase sampling. Therefore, they do not establish that the identified immune states oscillate across the day or are directly controlled by BMAL1.

BMAL1 also contributes to the temporal regulation of leukocyte trafficking through both immune-cell-intrinsic and vascular mechanisms. Conditional disruption of *Bmal1* in endothelial cells or specific leukocyte populations abolished time-of-day-dependent expression of pro-migratory factors and rhythmic leukocyte recruitment, indicating that immune-cell homing depends on coordinated clocks in circulating cells and the vascular microenvironment (94). Neutrophils additionally undergo circadian aging characterized by changes in their migratory and vascular properties. Experimental disruption of this timer caused the persistence of aged neutrophils within the circulation and increased vascular injury and thrombo-inflammatory complications (98). Rhythmic vascular inflammation is also shaped by tissue-specific endothelial signals and sympathetic innervation (100). Together, these studies suggest that circadian control of leukocyte trafficking may influence vascular inflammation and thrombo-inflammatory injury. However, evidence from human atherothrombosis and myocardial infarction is still sparse.

Inflammasome activation represents another link between circadian timing and sterile cardiovascular inflammation. NLRP3 inflammasome activation and IL-1β production exhibit time-of-day dependence in synchronized macrophages, while myeloid-specific *Bmal1* deletion enhances this response through altered mitochondrial function (101). Whether this mechanism operates similarly within human plaques or infarcted myocardium remains to be determined. Adaptive immune responses are also heterogeneous. A single-cell study identified distinct activated, cytotoxic, exhausted and regulatory T-cell states within atherosclerotic plaques (95). BMAL1-dependent mechanisms can influence lymphocyte trafficking (94), whereas a genetic study suggests that the lymphocyte-intrinsic clock is not essential for all aspects of T- and B-cell differentiation or effector function (99). Therefore, the contribution of BMAL1 to adaptive immunity is likely to vary across lymphocyte subsets and experimental contexts.

BMAL1 appears to organize the timing of myeloid redox metabolism, inflammatory signaling and leukocyte trafficking, rather than acting as a uniform suppressor of inflammation. Evidence is strongest in monocytes and macrophages, whereas direct data for neutrophils, lymphocytes and tissue-resident immune populations remain limited. Current single-cell cardiovascular datasets generally lack repeated sampling across defined circadian phases, making it difficult to distinguish circadian variation from disease stage, cell recruitment and changes in cellular composition. In addition, low transcript abundance and single-cell RNA-sequencing dropout may limit the reliable detection of clock-gene oscillation. Future studies should combine repeated circadian sampling with single-cell transcriptomics, chromatin-accessibility profiling, spatial analysis and lineage-specific BMAL1 perturbation. This approach would help distinguish immune states driven by local clock activity from those arising from tissue injury, cell recruitment or systemic circadian signals (95-101). The principal immune-cell effects of BMAL1 are summarized in Fig. 1A.

4. Human evidence for circadian disruption and BMAL1 dysregulation

Direct human evidence linking BMAL1 dysregulation to cardiovascular risk remains limited. Available data are largely observational and are derived mainly from studies of shift work and circadian misalignment (5,6,102,103). In night-shift nurses, the 24-h rhythm of BMAL1 expression in peripheral blood mononuclear cells was disrupted, alongside internal misalignment among peripheral clock-gene, cortisol and melatonin rhythms (102). Shift work has also been associated with endocrine, metabolic, inflammatory and cardiovascular changes (6,102,103). These findings indicate systemic circadian misalignment, but they do not establish a BMAL1-specific cardiovascular mechanism.

Interpretation is difficult without detailed temporal and clinical information. BMAL1 expression in circulating cells varies with sampling time and may also be influenced by sleep duration, food intake, medication exposure, systemic inflammation and leukocyte composition (86,102,104). Therefore, a lower value in a single blood sample may reflect a phase shift or a change in cell populations rather than reduced clock activity (102,104). Thus, peripheral BMAL1 should be regarded as an indicator of circadian state, unless repeated sampling, cell-specific analysis or functional validation supports a causal interpretation. The gap between relatively strong experimental evidence and limited human causal evidence remains a major barrier to clinical translation.

5. Translational and therapeutic strategies

Potential BMAL1-related translational approaches include small-molecule clock modulators, cardiovascular chronotherapy and non-pharmacological circadian interventions. The

translational framework linking circadian disruption to these strategies is shown in Fig. 1B.

Small-molecule clock modulators. Small molecules can alter circadian-clock function through several targets, including REV-ERBs, RORs, cryptochromes and clock-regulatory kinases (105-107). Compounds identified through cellular or biochemical screening can modify circadian period, phase or amplitude, but most remain experimental tools without demonstrated cardiovascular efficacy (105-107). They may also indirectly alter BMAL1 expression or CLOCK-BMAL1-dependent transcription and should not be regarded as direct BMAL1 modulators unless specific target engagement has been established (105-108).

An exception is the recently identified small molecule core circadian modulator, which selectively binds a cavity in the PAS-B domain of BMAL1, alters CLOCK-BMAL1-dependent transcription, and modulates circadian oscillations and macrophage inflammatory pathways (108). This study provides proof of principle that BMAL1 is pharmacologically accessible. However, the evidence remains limited to biochemical, structural and cellular studies, and its cardiovascular efficacy, pharmacokinetics, tissue selectivity and long-term safety have not been established.

Among the most studied synthetic compounds, the putative REV-ERB agonist SR9009 reduced inflammatory activity and atherosclerotic plaque burden in mouse models (109). However, a subsequent study showed that SR9009 altered metabolism and cell viability even in cells lacking both REV-ERBα and REV-ERBβ (110). Its beneficial effects in a mouse pressure-overload model also persisted after cardiomyocyte-specific deletion of both REV-ERBs (111). These findings raise important concerns regarding target specificity and indicate that the cardiovascular effects of SR9009 cannot be attributed solely to REV-ERB activation or indirect repression of BMAL1.

Nobiletin, a natural polymethoxylated flavone, enhanced circadian amplitude and improved metabolic phenotypes in cultured cells and mouse models (112). However, nobiletin influences ROR-related clock regulation as well as several metabolic, inflammatory and stress-response pathways (112). Therefore, its beneficial effects cannot be interpreted as evidence of selective BMAL1 modulation. The evidence discussed for synthetic REV-ERB ligands and nobiletin remains preclinical and their clinical cardiovascular efficacy has not been established.

Demonstrating that these compounds alter circadian period or amplitude in reporter systems is not sufficient to progress them toward clinical testing. Safety is a particular concern, as REV-ERB signaling is closely involved in hepatic lipid and glucose metabolism, and a metabolic change that appears beneficial in one experimental setting may be undesirable in another (105). SR9009 can alter cell viability and metabolism even in the absence of REV-ERBα and REV-ERBβ (110), making it difficult to separate intended clock modulation from off-target effects. Therefore, chronic studies should assess lipid and glucose homeostasis, liver injury, and disruption of sleep-wake and endocrine rhythms alongside cardiovascular efficacy, particularly in aged or metabolically diseased models. Phase-resolved pharmacokinetic and pharmacodynamic studies, tissue-selective exposure and a defined therapeutic window will be required before these compounds can be considered clinically viable clock-targeted cardiovascular therapies (105,110,111).

Cardiovascular chronotherapy. Chronotherapy aims to align drug administration with daily variation in disease activity, pharmacokinetics and pharmacodynamic responses (113). Blood pressure, autonomic activity, platelet reactivity, lipid synthesis and vascular function vary across the 24-h cycle, providing a rationale for timed cardiovascular treatment (1,113). However, these rhythms reflect the combined effects of the central clock, peripheral clocks, sleep, posture, meals and activity (104). Therefore, BMAL1 expression alone is insufficient to determine the optimal dosing time for an individual patient.

Antihypertensive treatment provides the clearest clinical test of cardiovascular chronotherapy. However, the Hygia and Treatment in Morning vs. Evening (TIME) trials examined this question under substantially different conditions. The Hygia Chronotherapy Trial enrolled hypertensive patients from Spanish primary-care centers using ambulatory blood-pressure criteria and repeated 48-h ambulatory monitoring at least annually (12). By contrast, TIME recruited a broader United Kingdom population receiving typical antihypertensive treatment through a decentralized, pragmatic design and did not include routine ambulatory blood-pressure monitoring (13). Therefore, the trials differed in geographical and clinical settings, blood-pressure phenotyping, follow-up procedures and the extent to which treatment adjustment was linked to nocturnal blood pressure. In addition, their primary endpoints were not identical. The Hygia Chronotherapy Trial used a broader composite of cardiovascular death, myocardial infarction, coronary revascularization, heart failure and stroke, whereas TIME assessed vascular death or hospitalization for non-fatal myocardial infarction or non-fatal stroke (12,13). These differences may have contributed to the discrepant findings, but they do not fully explain the markedly larger treatment effect reported in the Hygia Chronotherapy Trial. TIME provides strong evidence against recommending a universal evening schedule for an unselected hypertensive population (13). However, the Hygia Chronotherapy Trial raises the possibility that treatment timing may be more relevant in patients with nocturnal hypertension or a non-dipping pattern identified by ambulatory monitoring (12). This possibility remains unproven and should be tested prospectively by randomizing patients according to a predefined ambulatory blood-pressure phenotype rather than clock time alone.

Drug-specific properties also influence the clinical value of timed administration. For short-acting statins, such as simvastatin, evening administration may produce slightly greater reductions in low-density lipoprotein cholesterol, as hepatic cholesterol synthesis is higher overnight (114). By contrast, differences between morning and evening administration are small for long-acting statins such as atorvastatin and rosuvastatin, making adherence more important than clock time (114). Evidence that statin timing alters cardiovascular events is lacking.

Bedtime aspirin has reduced morning platelet reactivity in a randomized crossover trial, but it did not improve 24-h blood pressure, and whether this laboratory effect reduces

thrombotic events remains uncertain (115). For beta-blockers, antiarrhythmic drugs and other cardiovascular agents, evidence remains insufficient to recommend routine morning or evening administration (58,113). Drug half-life, formulation, target rhythm, symptoms, adverse effects and concomitant medications may be more relevant than a fixed dosing time.

Safety also depends on the drug class and the baseline physiology of the patient. TIME, BedMed and BedMed-Frail did not indicate an overall safety disadvantage with evening antihypertensive dosing, and BedMed and BedMed-Frail found no excess in falls or fractures (13,116,117). However, these population-level findings do not exclude harm in susceptible individuals. Moving the peak effect of antihypertensive or heart-rate-lowering therapy into the sleep period may aggravate nocturnal hypotension or bradycardia in patients with low nighttime blood pressure, conduction disease, autonomic dysfunction, frailty or polypharmacy (13,113,116,117). Future studies should therefore assess ambulatory blood pressure and heart rate, orthostatic symptoms, syncope, falls, renal events and treatment discontinuation alongside cardiovascular efficacy.

The chronotype substudy of TIME provides preliminary support for a more individualized approach, as its findings suggested that alignment between dosing time and chronotype may be associated with cardiovascular outcomes (118). However, this was an exploratory analysis, and participants were not randomized according to chronotype-dosing alignment. A definitive test would require prospective treatment assignment based on the biological phase or ambulatory phenotype rather than morning or evening clock time alone.

Therefore, chronotherapy should be evaluated as a drug- and phenotype-specific strategy rather than a universal schedule. Its clinical value will depend on pharmacokinetics, the rhythm of the therapeutic target, adherence, safety and whether biological phase can be measured reliably. At present, timed administration may optimize selected treatments but cannot be regarded as a validated BMAL1-directed intervention.

Non-pharmacological circadian interventions. Time-restricted eating (TRE) limits food intake to a defined daily interval and can strengthen the alignment between feeding rhythms and peripheral metabolic clocks (119,120). In animal models, time-restricted feeding improves glucose and lipid metabolism even under conditions of circadian-clock disruption (119). Early clinical studies have also reported improvements in insulin sensitivity, blood pressure and oxidative stress, although the populations studied have generally been small and metabolically selected (121,122). These benefits may reflect varying contributions from energy intake, fasting duration, body weight, insulin signaling and sleep-wake behavior, and they cannot be attributed specifically to restoration of BMAL1 activity.

Safety is particularly relevant when TRE is used in patients with diabetes. A 6-month randomized trial in adults with type 2 diabetes reported no increase in hypoglycemia or serious adverse events, but insulin and sulfonylurea doses were adjusted according to baseline glycemic control, and glucose levels were monitored throughout the intervention (123). By contrast, a randomized trial of intermittent fasting in patients receiving glucose-lowering medication found an increased rate of hypoglycemia despite medication reduction (124). Although intermittent fasting and daily TRE are not identical interventions, these findings indicate that safety depends strongly on medication use and clinical monitoring (123,124). Therefore, TRE should be accompanied by medication review and glucose monitoring in patients using insulin or sulfonylureas. Additional consideration should be given to renal function, frailty, nutritional adequacy and a history of disordered eating.

Exercise is another timing cue for peripheral clocks. Scheduled physical activity can shift molecular rhythms in skeletal muscle and alter human circadian phase (125,126). Its physiological effects may vary with exercise intensity, duration, baseline fitness and time of day (126). Evidence that exercise improves cardiovascular outcomes specifically through BMAL1 remains indirect, as most studies assess broader metabolic or physiological responses rather than BMAL1-dependent mechanisms (125,126).

Light exposure primarily affects the central clock and may improve circadian alignment when sleep and activity schedules are irregular (127). Appropriately timed light exposure, exercise and regular sleep schedules may be useful for shift workers or individuals with circadian misalignment (127-129). However, improvements in metabolic or cardiovascular risk factors do not demonstrate that BMAL1 is the direct mediator. Light also influences melatonin, cortisol and sleep duration, all of which may independently affect cardiovascular physiology (127-129).

Therefore, TRE, exercise, light exposure and sleep regularization should be viewed as broad circadian and behavioral interventions, rather than as BMAL1-specific treatments. Most BMAL1-specific mechanistic evidence comes from animal studies, while human trials have usually focused on intermediate metabolic or hemodynamic outcomes rather than major cardiovascular events (121-124,126-129).

Clinical trials also need to distinguish circadian alignment from the broader behavioral changes produced by these interventions. In studies of TRE, the effects of meal timing should be separated from changes in energy intake and body weight; exercise trials should distinguish time-of-day effects from differences in training volume and fitness; and light or sleep interventions should measure changes in sleep duration and quality alongside circadian phase. Objective measures of adherence, activity, light exposure, ambulatory blood pressure and biological phase would improve mechanistic interpretation (104). Longer studies assessing cardiovascular events, functional outcomes and adverse effects are needed before changes in intermediate metabolic or hemodynamic markers can support clinical recommendations.

The clinical use of non-pharmacological circadian interventions also requires individualized assessment. Regular exercise, stable sleep timing and consistent meal schedules may be feasible for numerous patients, but fixed morning or evening prescriptions may be unsuitable for shift workers, frail older adults or patients with heart failure, orthostatic symptoms, diabetes or complex medication schedules. Exercise safety, nutritional requirements, sleep disorders and adherence should take priority over theoretical circadian optimization. Chronotype-guided exercise, light exposure or meal timing remains promising, but evidence for

improved major cardiovascular outcomes is currently insufficient (122,123,126,128,129).

These approaches occupy different positions along the translational pathway. Chronotherapy has the strongest human outcome evidence but little BMAL1 specificity; behavioral interventions are generally more feasible, but their mechanisms are difficult to isolate; and small-molecule modulators allow more direct pharmacological manipulation of clock pathways but face the greatest challenges in target selectivity, tissue delivery and long-term safety. None currently supports routine BMAL1-directed cardiovascular treatment. The most informative future studies will be those that link demonstrable target or phase engagement to clinically meaningful cardiovascular outcomes while evaluating improvements in surrogate metabolic or hemodynamic markers against prespecified safety outcomes. A favorable clinical risk-benefit profile should not be inferred from efficacy signals alone.

6. Translational challenges and future directions

Tissue specificity and cross-species translation. The aforementioned differences have direct consequences for translation. Findings from cardiomyocyte-, endothelial-, smooth-muscle- and myeloid-specific models cannot be assumed to apply across cardiovascular tissues, whereas whole-body manipulation introduces systemic effects that make local mechanisms difficult to isolate (9-11,61,75,79). Even cell-specific knockout models with sustained genetic disruption may not fully reproduce circadian disruption that develops later in adult cardiovascular disease, whereas inducible models may be more suitable for examining adult-onset effects (64). Therefore, translational models need to preserve tissue specificity, while still accounting for systemic entrainment, metabolism, behavior and comorbidity.

As BMAL1 is widely expressed across central and peripheral clocks, molecular selectivity for BMAL1 would not by itself confer tissue selectivity (1,8,16). Therefore, spatial restriction would depend largely on the delivery strategy. Cardiomyocyte-directed gene or RNA modulation could combine cardiotropic vectors with cardiomyocyte-specific regulatory elements (130), whereas ligand-functionalized lipid or polymeric nanoparticles could deliver small-molecule or nucleic-acid payloads preferentially to activated endothelium or lesional macrophages (131,132). Regional intracoronary or intramyocardial administration may provide an additional degree of localization for selected myocardial indications. Given the risk of disturbing systemic circadian organization, early therapeutic designs should prioritize partial, reversible and phase-limited modulation, rather than sustained activation or suppression. Development should include quantitative biodistribution, cell-specific target engagement, assessment of BMAL1 phase and amplitude in non-target tissues and monitoring of systemic circadian outputs, including sleep-wake, endocrine, metabolic and immune rhythms. At present, these approaches remain design principles derived from cardiovascular delivery research rather than validated BMAL1-targeted therapies.

Cross-species differences go beyond the fact that mice are nocturnal and humans are diurnal. The core clock retains a ~24-h rhythm in both rodents and primates, and a consistent species-wide difference in intrinsic period has not been established (8,133,134). More relevant differences concern phase, amplitude and downstream transcriptional output. In human myocardium, BMAL1 and PER rhythms have been reported in antiphase to those observed in rodents (133), while a multi-tissue baboon atlas showed marked tissue-dependent variation in the abundance, phase and rhythmicity of clock-controlled transcripts (134). Therefore, comparable changes in BMAL1 abundance or phase may engage different metabolic, inflammatory or vascular programs across species. Differences in heart rate, lipid metabolism, immune composition, aging and comorbidity further limit direct extrapolation of temporal susceptibility to ischemia, remodeling and heart failure from mice to humans (14,134).

Human-derived models can help to determine which of these effects are conserved. Human pluripotent-stem-cell-derived cardiomyocytes develop BMAL1 and period circadian regulator 2 oscillations and contain a rhythmic network of stress-related transcripts (135). Cardiac organoids and engineered tissues could extend this work by incorporating vascular, stromal and immune components, although their suitability for circadian studies remains to be established and they cannot reproduce systemic entrainment (136). Non-human primates may be useful when diurnal behavior, endocrine timing, autonomic activity and cardiovascular physiology need to be studied together. However, BMAL1-deficient macaques showed broad disturbances in sleep, endocrine function and behavior, as well as inflammatory and stress-related transcriptional programs (137), making tissue-specific cardiovascular effects difficult to isolate. Primate studies should therefore be reserved for questions that cannot be addressed adequately in human cellular models and should favor longitudinal monitoring, repeated phase-resolved sampling and reversible or tissue-restricted perturbation.

Two cross-disciplinary settings further illustrate the potential translational relevance of BMAL1. In perioperative medicine, experimental studies have shown time-of-day-dependent differences in myocardial ischemia/reperfusion injury (62-64), while human left-ventricular biopsy samples obtained during morning and afternoon aortic-valve replacement surgery exhibited temporal differences in ischemia-related transcriptional responses (64). These findings suggest that circadian phase may influence perioperative myocardial susceptibility, although BMAL1 has not been validated as a perioperative biomarker or as a basis for determining surgical timing. Ocular vascular disease provides another relevant connection. Conditional *Bmal1* deletion in endothelial and hematopoietic cells aggravated both retinal microvascular injury and femoral-artery neointimal hyperplasia in mice (138), suggesting that BMAL1-dependent endothelial and inflammatory mechanisms may be shared across retinal and systemic vascular beds. However, direct evidence from human ocular and cardiovascular diseases remains limited.

Temporally resolved multi-omics and computational approaches. Multi-omics studies can clarify the manner in which BMAL1-related regulation varies across cardiovascular cell types, disease stages and circadian phases. However,

their interpretation requires time to be treated as a primary experimental variable. A single measurement cannot distinguish a phase shift from reduced amplitude, altered baseline expression or changes in cellular composition. Therefore, time-series sampling across multiple circadian phases is needed to estimate rhythmicity, phase and amplitude using methods such as cosinor analysis or non-parametric rhythmicity algorithms (139,140). Sampling should preferably be indexed to biological phase, with sleep, feeding, activity, medication exposure and disease severity considered as potential confounders (104,139).

Molecular layers should be integrated, as rhythmic transcription does not necessarily predict rhythmic protein abundance or activity (139,141). In the murine heart, day-night proteomic profiling identified temporal variation in ~7.8% of detected protein spots, together with changes in myofilament phosphorylation (141). Therefore, combining transcriptomics with proteomics, phosphoproteomics, metabolomics, epigenomic profiling and chromatin-accessibility data may reveal regulatory changes that are not apparent from RNA expression alone. These molecular profiles could also be integrated with longitudinal clinical information, sleep and physical-activity records, ambulatory blood-pressure monitoring, and continuous electrocardiography to relate molecular rhythms to cardiovascular physiology. However, differences in sampling frequency, temporal resolution, data quality and patterns of missing data across these sources complicate their integration. Day-night differences under ordinary light-dark conditions should not automatically be interpreted as endogenous circadian rhythms without constant-condition or clock-perturbation experiments (139).

Single-cell and spatial approaches may help separate cell-intrinsic regulation from changes in cell composition and tissue architecture. Studies of atherosclerotic plaques and infarcted myocardium have identified heterogeneous immune, endothelial and stromal states (95-97), while spatial transcriptomics has revealed region-specific programs associated with stable and unstable coronary plaques (142). As these datasets were not generated as circadian time series, they do not establish that the identified states oscillate across the day or are directly controlled by BMAL1. More informative studies would combine repeated circadian sampling with single-cell or spatial profiling and lineage-specific BMAL1 perturbation.

Machine-learning approaches such as ZeitZeiger, TimeSignature, BodyTime and TimeMachine can estimate the internal or systemic circadian phase from high-dimensional molecular data (143-146). The human applications discussed in the present review rely mainly on blood-based gene-expression profiles and do not directly measure BMAL1 activity within the myocardium, vascular wall or atherosclerotic plaque. Numerous current models have been developed in relatively small or narrowly selected cohorts and may be vulnerable to batch effects, missing data, overfitting, data leakage, and population- or platform-specific bias. Therefore, their reproducibility across populations, clinical centers and assay platforms remains uncertain. Clinical translation will require participant-level separation of training and test data, validation against an independent phase marker, external testing in diverse clinical cohorts and prospective evaluation of whether molecular-phase-guided treatment improves cardiovascular outcomes (104,143-146). At present, these approaches are best viewed as tools for phase estimation, temporal data integration and mechanistic investigation, rather than validated guides to BMAL1-directed precision therapy.

7. Conclusion

BMAL1 contributes to cardiovascular timing, but its role is neither uniformly protective nor interchangeable across tissues and disease stages. The most consistent mechanistic evidence comes from cardiomyocyte-specific experimental models, in which disruption of BMAL1 impairs substrate utilization, mitochondrial homeostasis, electrical stability, contractile function and long-term structural integrity. These findings provide relatively strong support for a role in arrhythmogenic susceptibility and dilated cardiomyopathy-like remodeling. However, direct causal evidence in human arrhythmias and heart failure remains limited.

In vascular and immune systems, BMAL1 influences endothelial function, smooth-muscle-cell phenotype, leukocyte trafficking and inflammatory metabolism, but the direction of these effects depends on cell type, disease stage and experimental context. Evidence in atherosclerosis is strongest for endothelial, smooth-muscle and macrophage mechanisms in animal models, whereas its contribution to human plaque instability, rupture and thrombosis remains preliminary. Similarly, circadian phase modifies ischemia/reperfusion injury in experimental studies, but the timing and magnitude of protection vary among models, and human evidence remains largely observational. In heart failure, cardiomyocyte-clock disruption more closely resembles systolic dysfunction, while BMAL1-specific mechanisms in HFpEF and in elderly patients or patients with obesity, diabetes, hypertension or sleep disruption remain poorly defined.

Therefore, clinical translation will require more than global activation or inhibition of BMAL1. The available evidence raises the possibility that cardiovascular injury is driven less by the absolute amount of BMAL1 than by a mismatch between systemic timing cues and tissue-specific BMAL1 activity. Testing this idea will require tissue- and cell-specific human models, repeated sampling aligned to biological phase and prospective studies that distinguish disease phenotype, comorbidity and treatment timing. Therapeutic development must also define the appropriate target tissue, circadian phase, disease stage and safety window. BMAL1 is best viewed as a context-dependent regulatory node that may support selected cardiovascular interventions, rather than as a universal therapeutic target.

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Authors' contributions

YL, DL, XMW, ZJZ and WQL participated in the conceptualization of the study. YL, DL, XMW and WQL provided supervision. WQL and TJC designed and prepared Fig. 1. YL, DL, XMW and HDZ contributed to writing the original draft. YL, TJC and HDZ were involved in reviewing and editing. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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