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REVIEW ARTICLE

Post-translational Modifications are Required for Circadian Clock Regulation in Vertebrates

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Abstract: Circadian clocks are intrinsic, time-tracking systems that bestow upon organisms a survival advantage. Under natural conditions, organisms are trained to follow a 24-h cycle under environmental time cues such as light to maximize their physiological efficiency. The exact timing of this rhythm is established *via* cell-autonomous oscillators called cellular clocks, which are controlled by transcription/translation-based negative feedback loops. Studies using cell-based systems and genetic techniques have identified the molecular mechanisms that establish and maintain cellular clocks. One such mechanism, known as post-translational modification, regulates several aspects of these cellular clock components, including their stability, subcellular localization, transcriptional activity, and interaction with other proteins and signaling pathways. In addition, these mechanisms contribute to the integration of external signals into the cellular clock machinery. Here, we describe the post-translational modifications of cellular clock regulators that regulate circadian clocks in vertebrates.

Keywords: Circadian clock, cellular clock, clock protein, post-translational modification, transcription, clock gene.

1. INTRODUCTION

Circadian clocks regulate a number of physiological functions, such as sleep and metabolism, in a broad spectrum of organisms ranging from bacteria to humans [1]. They generate daily changes (circadian rhythms) in various biochemical, physiological and behavioral processes. Under natural conditions, circadian clocks are trained according to the 24-h cycle based on environmental time cues, such as light, to maximize an organism's physiological efficiency [2]. Thus, disrupting circadian clocks can have a profound effect on organisms' health and is linked to various diseases, including sleep disorders and metabolic syndromes [3, 4].

At the molecular level, circadian clocks can be divided into three conceptual components [1, 5]. The first is the pacemaker that is dedicated to generating and sustaining circadian rhythms by receiving and integrating signals from external time cues [6]. The second component is the input, which refers to the pathway through which external time cues are perceived and act upon the central pacemaker. The third element relates to how the circadian clock affects physiology and is achieved through the output pathways.

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The pacemaker in the members of *Neurospora* and *Drosophila* and in vertebrates are transcription/translation-based negative feedback loops that rely on positive and negative oscillator elements [7]. In vertebrates, three basic helix-loop-helix Per-ARNT-Sim (PAS) domain-containing transcription factors, known as CLOCK, neuronal PAS domain protein 2 (NPAS2), and brain-muscle-ARNT-like protein (BMAL), constitute the positive elements [1, 5, 8]. CLOCK or NPAS2 heterodimerizes with BMAL to form a transcriptionally active complex that binds to E-box elements (CACGTG) present in the promoters of the members of the *period* (*per*) and *cryptochrome* (*cry*) families. Once PER and CRY proteins are translated, they form heterodimers that can then translocate into the nucleus to repress CLOCK(NPAS2)–BMAL-mediated transcription through direct protein−protein interaction. Importantly, when active, the CLOCK(NPAS2)–BMAL complex stimulates the transcription of various other clock-controlled genes. The protein products of these genes, in turn, influence functions external to the oscillatory mechanism itself and mediate the "output" function of the clock. This partly accounts for the presence of circadian rhythms in a variety of physiological processes [3, 4].

Although the relatively straightforward mechanisms of positive and negative feedback loops are necessary to establish and maintain cellular clocks, these clocks are complex and involve processes such as the post-transcriptional regulation of cellular clock components (clock proteins) [4, 9, 10].

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These modifications have essential roles in appropriately regulating clock protein stability, cellular localization, transcriptional activity, and interaction with other proteins. In addition, a variety of studies revealed that the post-transcriptional modifications of clock proteins are involved in the regulation of the input and output processes of circadian clocks [11-13]. Here, we describe the roles of the post-translational modifications of clock proteins involved in controlling circadian clocks in vertebrates.

2. IMPORTANCE OF THE PHOSPHORYLATION OF CELLULAR CLOCK PROTEINS FOR REGULATING THE CLOCK'S PERIODICITY AND LIGHT RESPONSE

The functions of various mammalian cellular clock proteins, including CLOCK, BMAL1, PER1, PER2, PER3, CRY1, and CRY2, are regulated *via* phosphorylation by various kinases [4, 9, 10]. The first major step towards understanding the importance of phosphorylation in vertebrate circadian clock regulation was taken when the *tau* mutation, which causes a short-period phenotype in the Syrian hamster, was identified [14]. The *tau* locus encodes casein kinase I epsilon (CKIε) that phosphorylates PERs. The short-period phenotype observed in the mutant hamster was generated because of a low rate of CKI-dependent phosphorylation of PER2. Defects in the phosphorylation of cellular clock proteins have been implicated in human disorders [15, 16]. A missense mutation in the circadian clock gene *Per2* is associated with familial advanced sleep phase syndrome. The corresponding mutated PER2 protein is less effectively phosphorylated than the wild-type PER2; moreover, the phosphorylation-dependent stability control of the mutated PER2 was demonstrated to have been eliminated *in vitro*. Additionally, polymorphism in a region of human *Per3*, the presumed CKIε-binding domain, may be associated with delayed sleep phase syndrome [17]. CKIε specifically interacts with and phosphorylates PER1, 2 and 3 proteins, and thus regulates each of them differently [4, 9, 10, 18, 19].

A number of pharmacological studies have used luciferase-based clock reporter cells to identify the molecules that regulate cellular clocks. These studies identified various kinases that are important for establishing or regulating cellular clocks. For example, using mammalian clock reporter cells, a small-scale screening of kinase inhibitors identified candidate molecules affecting the period-length of the mammalian cellular clock [20]. As a result, casein kinase II (CKII), PI3-kinase (PI3K), and c-Jun N-terminal kinases (JNKs) were identified as candidate regulators for the cellular clock. Another research group examined the effect of various kinase inhibitors on the periodicity of cellular clocks and found that the period-length of the clocks of mammalian cultured cells increased following treatment with p38 (SB203580), JNK (SP600125), CKI (IC261) and CDK (roscovitine) kinase inhibitor and decreased following treatment with GSK-3 (SB216763) or CaMKII (KN93) inhibitors [21]. It is important to stress that several of the already-mentioned inhibitors have off-target effects. Therefore, confirming these findings by using pharmacological approaches in other experimental settings is warranted. In fact, a number of genetic and biochemical analyses reported the involvement of these kinases in the functional regulation of clock proteins and the maintenance of circadian clocks at the molecular, cellular, and organismic levels [11, 22-27]. Below, we describe the role of JNKs in circadian clock regulation.

3. ROLES OF THE JNK-MEDIATED SIGNALING PATHWAY IN CIRCADIAN CLOCK REGULATION

JNK activity is regulated *via* the phosphorylation of particular tyrosine and threonine residues located in the kinase domain [28]. JNK phosphorylation is catalyzed by two dual-specificity kinases, MKK4 and MKK7, which act in a synergistic manner [29, 30]. Although it is primarily activated in response to external stress (osmolarity changes, heat shock and UV irradiation), phosphorylated JNK has been detected in unstressed cultured cells and in isolated mouse tissues, such as the brain [30-32]. Notably, previous studies have shown that JNK phosphorylation levels, and thus its kinase activity, fluctuate in a circadian manner in both the suprachiasmatic nucleus (SCN), the location of the central clock in mammals, and in cultured mammalian cells [33, 34]. These studies indicate the importance of JNK signaling in physiological processes other than cellular stress responses, including circadian clocks.

In this context, it was previously reported that the MKK7–JNK signaling pathway is an essential regulator of periodicity in the cellular clocks of mammals. The MKK7–JNK signaling pathway induces PER2 phosphorylation and stabilizes PER2 by inhibiting its ubiquitination, which has an effect opposite to that of CKIε-induced PER2 destabilization [24] (Fig. **1A**). Because genetically inhibiting MKK7's function results in the extension of the cellular clock's periodicity in cultured cells, this phosphorylation-mediated PER2 stability control may be necessary to maintain the normal periodicity of cellular clocks. In addition, a recent study generated neuron-specific *Mkk7*-deleted mice, in which MKK7 was genetically inactivated in the central clocks of the SCN [32]. A behavioral analysis of these mice revealed that the neuron-specific disruption of *Mkk7* resulted in longer periods of circadian behavioral rhythms and also reduced the amplitude of rhythmicity compared with wild-type mice. These findings provide evidence that the MKK7–JNK signaling pathway is involved in the regulation of the circadian pacemaker at an organismic level.

In addition to PER2, JNK phosphorylates BMAL1 and CLOCK in mammals. In particular, Yoshitane *et al*. reported that neuron-specific isoform JNK3-deficient mice have longer free-running periods of behavioral rhythms and compromised phase shifts to light [11]. In nocturnal animals, the higher the light intensity in constant light conditions, the longer the circadian period becomes (and vice versa in diurnal species). This phenomenon is known as Aschoff's rule [35, 36]. In JNK3-deficient mice, behavioral rhythms are insensitive to intensity changes in constant light, thus deviating from Aschoff's rule [11]. These findings provide solid evidence that JNK-mediated BMAL1 phosphorylation is an important regulatory mechanism underlying the circadian pacemaker, as well as the light input pathway of the circadian clock *in vivo*.

4. REGULATION OF CELLULAR CLOCKS *VIA* BMAL1 AND DIFFERENTIATED EMBRYO-CHONDROCYTE EXPRESSED GENE 1 (DEC1) SUMOylation

SUMOylation is the covalent linking of small ubiquitin-related modifier proteins to lysine residues [37, 38]. This modification is a reversible post-translational modification that has been implicated in transcriptional regulation by a number of mechanisms. Previous studies found that BMAL1 is Sumoylated on a highly conserved lysine residue (Lys259) in cultured cells and that BMAL1 SUMOylation shows a circadian pattern in mouse liver tissue [39]. In addition, BMAL SUMOylation has been demonstrated to control BMAL protein stability and to play a critical role in the regulation of the pacemaker in the circadian clock.

Reportedly, BMAL1 SUMOylation promotes the interaction of CREB-binding protein to the CLOCK–BMAL1 complex, which resets the cellular clock in response to serum stimuli [40]. The formation of this ternary complex induces the acute activation of the CLOCK–BMAL1-mediated transcription of *Per1*, resetting the phase of the cellular clock. These findings clearly demonstrate that BMAL1 SUMOylation is a regulatory element for the input pathway of the circadian clock.

Differentiated embryo-chondrocyte expressed gene 1 (DEC1) is a basic mammalian helix-loop-helix protein that acts as a transcription factor [41, 42]. DEC1 inhibits CLOCK–BMAL1-mediated transcription through direct interaction with BMAL1 and/or competition for E-box elements in the promoters of cellular clock-controlled genes [43]. Moreover, DEC1 is Sumoylated on highly conserved lysine residues (Lys159 and Lys279) at its C-terminal domain [44]. SUMOylation stabilizes DEC1 by inhibiting its ubiquitination and promoting the inhibition of CLOCK–BMAL1-mediated transcription. These findings suggest that SUMOylation serves as a key regulatory element of cellular clocks by controlling multiple transcriptional factors.

5. IMPORTANCE OF THE ACETYLATION OF CELLULAR CLOCK PROTEINS FOR THE MAINTENANCE OF CLOCK PERIODICITY

Chromatin, the nucleoprotein structure into which the eukaryotic genome is organized, enables the functioning of essential biological processes, such as the regulation of transcription, DNA repair, apoptosis, and cell division [45-47]. Histone acetylation plays a pivotal role in the modulation of the chromatin structure associated with transcriptional activation [48, 49]. The activation of clock-controlled genes by the CLOCK–BMAL1 complex has been shown to be coupled to circadian changes in histone acetylation at their promoters, evidence that transcription-permissive chromatin states are dynamically established in a circadian-time-specific manner [50-52].

In mammals, the core circadian regulator, CLOCK, has intrinsic histone acetyltransferase (HAT) activity [53]. Moreover, CLOCK regulates the circadian pattern of gene expression by the virtue of its HAT activity. This finding modifies the common view of the CLOCK protein, demonstrating that it operates not only as a transcription factor but also as an enzyme. The finding of CLOCK's HAT activity suggests that the HAT enzymatic activity also targets other non-histone proteins, which is a characteristic of other HATs. In fact, CLOCK acetylates its heterodimeric partner, BMAL1 [54, 55] (Fig. **1B**). This CLOCK-mediated acetylation increases the interaction of the CLOCK–BMAL1 complex with CRY1. One study reported that BMAL1 is deacetylated by SIRT1, a nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylase (HDAC) [56, 57], in a time-dependent manner [58] (Fig. **1B**). Accordingly, BMAL1 acetylation is significantly rhythmic in mice liver as well as in cultured cells and SCNs. Another study demonstrated that SIRT1 also deacetylates PER2, giving SIRT1 an additional function in the transcriptional regulation of the cellular clock [59].

Notably, several pharmacological studies have confirmed the importance of the acetylation of cellular clock proteins in clock regulation. For example, it has been reported that the inhibition of SIRT1 activity by its inhibitors, such as nicotinamide and the drug splitomicin, disturbs the circadian expression of clock-controlled genes and histone H3 and BMAL1 acetylations [58]. In addition, the study using several specific SIRT1 activators demonstrated that SIRT1 activation led to the suppression of clock-controlled gene expressions and H3 acetylation at corresponding promoters *in vitro* and *in vivo* [60].

6. THE POSSIBLE ROLE OF *O*-LINKED*N*-ACETYLGLUCOSAMINYLATION (*O*-GLCNACYLATION) OF CLOCK PROTEINS IN TRANSDUCING NUTRITIONAL SIGNALS TO THE CIRCADIAN CLOCK MACHINERY

O-GlcNAcylation is one of the most common post-translational protein modification with the high-energy compound, UDP-GlcNAc, as the direct donor [61]. Two enzymes regulate *O*-GlcNAcylation: *O*-GlcNAc transferase (OGT), which attaches UDP-GlcNAc to the serine and threonine residues of proteins through a β-glycosidic *O*-linkage, and *O*-GlcNAcase (OGA), which hydrolyzes *O*-GlcNAc in proteins [61, 62]. Analyses with *O*-GlcNAcylation inhibitors (the OGT inhibitor Alloxan) and activators (the OGA inhibitor PUGNAc) have revealed that the suppression of *O*-GlcNAcylation shortened the periodicity of cellular clocks, whereas its activation lengthened the periodicity of cellular clocks in mammalian cultured cells [13]. These findings provide evidence that *O*-GlcNAcylation is involved in cellular clock regulation.

Both CLOCK and BMAL1 are rhythmically *O*-GlcNAcylated, and this modification stabilizes both the proteins by inhibiting their ubiquitination [12, 63] (Fig. **1C**). Consistent with these findings, OGT facilitates CLOCK–BMAL1-mediated transcription. Another study reported that PER2 is also *O*-GlcNAcylated at the region that regulates the human sleep phase in humans, competing with phosphorylation in this region [13].

Glucose flux *via* the hexosamine biosynthesis pathway leads to intracellular glycosylation by increasing the *O*-GlcNAcylation of proteins [61]. It is well established that *O*-GlcNAcylation regulates fundamental cellular processes in response to diverse nutritional cues. Because circadian

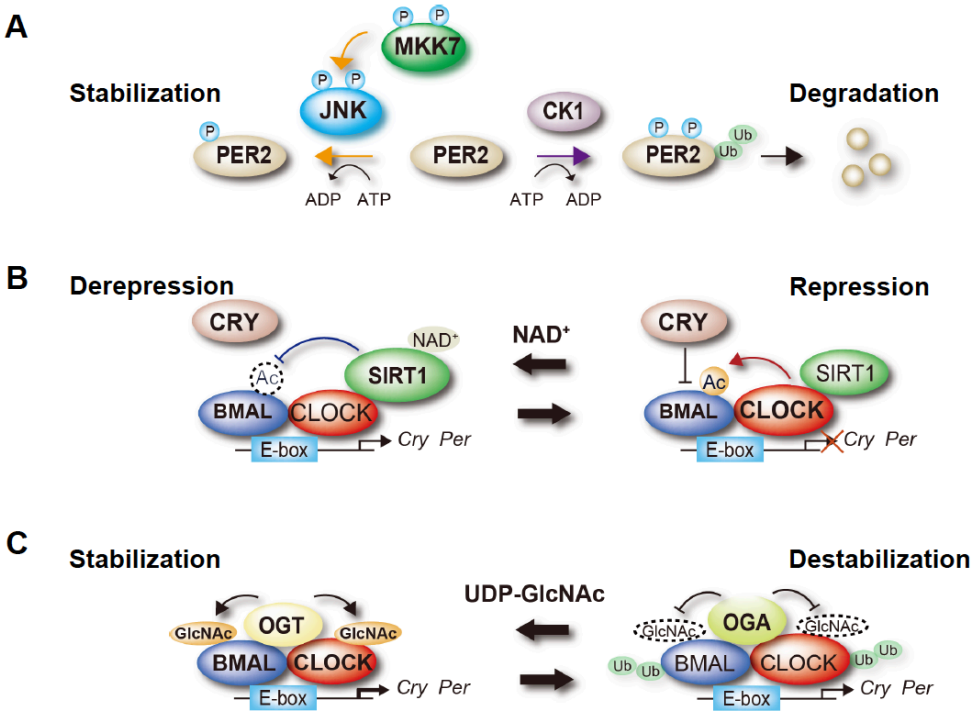

Fig. (1). Functional regulation of clock proteins through post-translational modifications. (**A**) Phosphorylation-dependent control of PER2 stability. The activity of JNK is regulated *via* the phosphorylation of the tyrosine and threonine residues located in the kinase domain, which is catalyzed by MKK7. MKK7-mediated JNK activation induces phosphorylation of PER2 and increases its protein half-life by competing with the CKI-induced ubiquitination and the subsequent degradation of PER2. (**B**) Regulation of CLOCK:BMAL-mediated transcription by BMAL acetylation. CLOCK acetylates its heterodimeric partner BMAL. This CLOCK-mediated acetylation increases the interaction of the CLOCK:BMAL complex with CRY, facilitating repression of the CLOCK:BMAL complex's activity. SIRT1 deacetylates BMAL, which cancels the CRY-dependent repression of CLOCK:BMAL-mediated transcription. (**C**) *O*-GlcNAcylation-dependent regulation of CLOCK:BMAL complex's stability. Both CLOCK and BMAL1 are *O*-GlcNAcylated, which is catalyzed by OGT and reversed by OGA. This modification stabilizes both proteins by inhibiting their ubiquitination. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

clocks are coupled with metabolic oscillations through nutrient-sensing pathways [3, 6], these facts indicate that the *O*-GlcNAcylation of clock proteins plays a crucial role in transducing nutritional signals to the cellular clock machinery.

7. ROLE OF POLY(ADP-ribosyl)ATION OF CLOCK IN FEEDING-DEPENDENT CIRCADIAN CLOCK REGULATION

Mammals have no photoreception in peripheral tissues; therefore, the effect of light on peripheral clocks is indirect [6]. SCN, the site of the master clock in mammals, integrates photic cues from the retina and transmits this information to peripheral clocks, synchronizing them through humoral signals [2, 4]. In addition to the input of the central clock (SCN), peripheral cellular clocks respond to cellular metabolism [3, 6]. When feeding in nocturnal animals is restricted to daytime, the phase of peripheral cellular clocks differs from that of SCN. Feeding cue affects peripheral cellular clocks *via* the poly(ADP-ribosyl)ation of CLOCK [64]. PARP-1, an NAD(+)-dependent ADP-ribosyltransferase, has been shown to interact with and poly(ADP-ribosyl)ate CLOCK. The poly(ADP-ribosyl)ation of CLOCK leads to reduced DNA binding ability in the CLOCK–BMAL1 complex, and modulates the interaction of this complex with PER and CRY. These poly(ADP-ribosyl)ation-dependent functional regulations of the CLOCK–BMAL1 complex, in turn, influence the expression patterns of cellular clock-controlled genes. Notably, PARP-1-deficient mice show altered expression profiles in CLOCK–BMAL1-dependent gene expression, particularly in response to changes in feeding times [64]. In addition, PARP-1-deficient mice exhibit impaired food entrainment of peripheral cellular clocks. These findings support the idea that the PARP-1-mediated poly(ADP-ribosyl)ation of CLOCK plays a role in connecting feeding with the circadian clock system in mammals.

8. POSSIBLE CROSSTALK BETWEEN THE CIRCADIAN CLOCK AND CELLULAR PROCESSES THROUGH SHARED POST-TRANSLATIONAL MODIFICATIONS

Reportedly, clock proteins have important physiological roles that are not restricted to their functions as cellular clock regulators. Previous studies in mice and zebrafish reported that PER2 physically interacts with nuclear receptors such as PPARα, REV-ERBα, RORα, and PPARγ to regulate their transcriptional activities [65-67]. Particularly, the PER2-mediated regulation of PPARγ's transcriptional activity contributes to the control of metabolism in mice [66]. It is tempting to speculate that post-translational modifications of

PER2 would regulate the interactions between PER2 and nuclear receptors, contributing to metabolic controls.

Recent studies found that BMAL1 interacts with HIF-1α to regulate the expression of HIF-1α target genes [68, 69]. The BMAL1–HIF-1α complex targets glycolysis genes, suggesting its control over cellular ATP levels. Furthermore, *Bmal1*$^{-/-}$ mice show reduced life spans with the symptoms of premature aging, implicating BMAL1 in control of aging [70]. Notably, a recent study reported that cellular clocks are not involved in the process of *in vitro* cellular senescence, suggesting that the BMAL1-mediated control of aging is not dependent on BMAL1's function in cellular clock control [71]. Particularly, as various studies have reported SIRT1's roles in aging [72], it is tempting to speculate that BMAL1 acetylation, which is regulated by SIRT1 [58], is involved in the BMAL1-mediated control of aging.

Cellular responses to the UV component of solar light and/or photo-oxidative stress have been proposed to be the evolutionary origin of circadian clocks [4, 73]. In support of this idea, the alteration of a cell's reduction–oxidation state triggers the transduction of photic signals that regulate circadian clock gene transcription [74-76]. In addition, various studies have implicated the role of core cellular clock components in the regulation of both, the cell cycle and DNA damage responses (DDRs) [4, 73]. Indeed, cellular clocks control the timing of cell proliferation by regulating the expression of key cell cycle genes in mammals and zebrafish [77, 78]. Moreover, post-translational modifications are vital for the regulation of the cell cycle and DDR. SIRT1 and casein kinase 2, already identified as being responsible for the post-translational modifications of clock proteins [22, 23, 58, 79] (Fig. **1**), have also been implicated in the post-translational modifications of proteins such as p53 and E-cadherin, which are involved in the cell cycle and DDR [80, 81]. These findings support the hypothesis that circadian clock regulators may be linked to non-circadian physiologies through shared post-translational modifications.

CONCLUSION

It is now clear that the circadian-time dependent regulation of clock proteins' phosphorylation is important for fine-tuning the period of the circadian clock. A number of kinases, such as CKIε, CK2, GSK3β and JNK, contribute to the circadian oscillation of phosphorylated clock proteins, regulating the clock proteins' functions. Besides phosphorylation, other posttranslational modifications, such as SUMOylation, acetylation, *O*-GlcNAcylation and ADP-ribosylation, are essential modulators of clock proteins, regulating their transcriptional activity, subcellular localization, and protein stability. These modifications play a role in controlling the core mechanism of the circadian clock itself as well as the light signaling pathway to the circadian clock. In addition, it has been implicated that the post-translational modifications of clock proteins are import regulators of cellular physiology, apart from circadian timekeeping. The findings of new clock proteins' post-translational modifications will reveal a yet unappreciated level of regulation within the core mechanism of the circadian clock and cellular physiology.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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