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Translating around the clock: Multi-level regulation of post-transcriptional processes by the circadian clock

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Abstract

The endogenous circadian clock functions to maintain optimal physiological health through the tissue specific coordination of gene expression and synchronization between tissues of metabolic and processes throughout the 24 hour day. Individuals face numerous challenges to circadian function on a daily basis resulting in significant incidences of circadian disorders in the United States and worldwide. Dysfunction of the circadian clock has been implicated in numerous diseases including cancer, diabetes, obesity, cardiovascular and hepatic abnormalities, mood disorders and neurodegenerative diseases. The circadian clock regulates molecular, metabolic and physiological processes through rhythmic gene expression via transcriptional and post-transcriptional processes. Mounting evidence indicates that post-transcriptional regulation by the circadian clock plays a crucial role in maintaining tissue specific biological rhythms. Circadian regulation affecting RNA stability and localization through RNA processing, mRNA degradation, and RNA availability for translation can result in rhythmic protein synthesis, even when the mRNA transcripts themselves do not exhibit rhythms in abundance. The circadian clock also targets the initiation and elongation of steps of translation through multiple pathways. In this review, the influence of the circadian clock across the levels of post-transcriptional, translation, and post-translational modifications are examined using examples from humans to cyanobacteria demonstrating the phylogenetic conservation of circadian regulation. Lastly, we briefly discuss chronotherapies and pharmacological treatments that target circadian function. Understanding the complexity and levels through which the circadian clock regulates molecular and physiological processes is important for future advancement of therapeutic outcomes.

Keywords

Circadian clock; Biological Rhythms; Post-transcriptional modification; Translation; Post-translational modification

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1. Introduction

Across phylogeny, the endogenous circadian clock coordinates metabolic, physiological and molecular rhythms that oscillate with a 24 hour period across tissue and organs throughout the body to anticipate regularly occurring daily events. The circadian system evolved with the 24 hour light-dark cycles of the earth's rotation making light the predominant zeitgeber, or time giver, for circadian entrainment, although other zeitgebers including food intake, temperature and even social cues may affect circadian entrainment in many species (reviewed in [1]). Unfortunately, technological advances and the structure of round-the-clock modern societies have made it more difficult for individuals to maintain a robust circadian system, facilitating the rise of sleep and circadian disorders. For example, the vast majority of individuals in the United States and other countries worldwide spend less than 1 – 2 hours daily outside [2–6], consequently replacing entrainment via sunlight with significantly lower levels of indoor light, thus weakening entrainment of the circadian clock and causing adverse health consequences (reviewed in [7, 8]). Further exacerbating poor circadian entrainment, artificial light pollution at night has become a pervasive issue with more than 99% of individuals in the United States and Europe exposed to significant light at night with the amount of light pollution increasing yearly [9, 10]. Artificial light at night results in delayed timing of the circadian clock [11], affects sleep timing and shortens sleep duration [12, 13]. Moreover, the suppression of melatonin secretion at night increases sleep deprivation and sleep disorders (reviewed in [14]). In addition to societal challenges to circadian entrainment, the increasing use of personal electronics and smartphones at night further contributes to circadian disruption (reviewed in [14, 15]). Circadian entrainment issues are compounded in people engaged in shiftwork, and by social jetlag in which individuals remain active later at night on weekends than weekdays resulting in twice weekly phase shifts [16, 17]. Consequently, a broad swath of society face daily issues with circadian entrainment and synchronization.

Issues with circadian entrainment or desynchronization of the circadian system have been associated with increased incidence and susceptibility to numerous disease conditions including cancer, diabetes, obesity, cardiovascular abnormalities, mood disorders and neurodegenerative diseases [18–25]. The significant adverse health impacts associated with circadian dysfunction highlight necessity for understanding the circadian system from circadian gene regulation to behavioral outputs. The publication of numerous studies and reviews on the transcriptional regulation of the circadian system in various organisms (reviewed in [26, 27]) has facilitated awareness of circadian regulation of transcription and rhythmic mRNA expression; however, the impact of post-transcriptional and translational regulation by the circadian clock is less familiar. After an introduction to the circadian system, this review focuses on the mechanisms through which the circadian clock uses post-transcriptional mechanisms to modulate core oscillator function and regulate output rhythms. In addition, we briefly discuss the potential of circadian based drug and behavioral therapies that target circadian function and pathways implicated in health and disease.

2. The Circadian System

2.1. Organization of the Circadian System in Mammals

In mammals, the paired suprachiasmatic nucleus (SCN) of the hypothalamus acts as the central circadian pacemaker providing synchronization to most of the circadian oscillators in the brain, tissues and organs. Photic signals for entrainment are received through the intrinsically photosensitive melanopsin containing cells, a small subset of retinal ganglion cells that project to the SCN via the retino-hypothalamic tract [28, 29]. Synchronization of oscillatory neurons within the SCN mainly occurs via the neuropeptides, vasoactive intestinal peptide (VIP), arginine vasopressin and gastrin-releasing peptide (GRP) [30–35]. Coordination of rhythmicity in peripheral tissues is orchestrated by the SCN primarily via glucocorticoid signaling [36–38].

Recent research also has identified additional neuropeptides including angiotensin 1, neurokinin B, pro-enkaphalins and substance P that may be involved in circadian synchronization [39].

Although photic entrainment of the SCN is vital for rhythmic SCN clock gene expression, locomotor activity and rhythmic gene expression in peripheral tissues, in the absence of the SCN, photic entrainment can also occur in the liver, heart, kidney and adrenal glands as seen in SCN-ablated animals synchronized to LD cycles [40, 41]. Moreover, the liver can function as an independent circadian oscillator with the timing of food intake as the primary entrainment signal [42–44], although the mammalian liver does receive circadian information from the SCN for much of its rhythmic gene expression [45]. The olfactory bulb appears to be the only other oscillator that can entrain completely independently of the SCN in mammals [46–48].

2.2. The Core Molecular Oscillator in Mammals

Circadian rhythms are autonomously maintained by interacting transcriptional and translational feedback loops dependent upon post-translational mechanisms via kinases and protein degradation to maintain period length [49–52]. In mammals, the positive limb involves CLOCK-BMAL1 heterodimers binding to E-box cis-regulatory enhancer sequences (CACGTG) in the promoter regions of the *mPer* and *mCry* genes (as well as many clock controlled genes), thereby, initiating transcription (Fig.1)[49, 52–55]. The mRNAs of *mCry* and *mPer* are translocated to the cytoplasm and translated into the proteins where phosphorylation of unstable mPER monomers are regulated by *Casein kinase 1 delta and Casein kinase 1 Epsilon* (CK1δ and CK1ε) [56, 57]. In the cytoplasm, FBXL21 ubiquitinates unstable mCRY proteins rendering them targets for slow proteosomal degradation [50, 58, 59].

Precise timing of the circadian system is also assured through phosphorylation by another protein kinase, *Glycogen synthase kinase-3* (GSK-3), that exists in two isoforms (α and β) in mammals. Although both isoforms of GSK-3 rhythmically cycle in the SCN of wild-type mice, GSK-3β is the mammalian homologue of *Drosophila* SHAGGY shown to target many clock proteins [60–63]. Typically, when mPERs and mCRYs form PER-CRY oligomers together with CK1ε and GSK-3β, translocation to the nucleus occurs forming the negative

loop of the oscillator [51, 56, 61]. These oligomers bind to the CLOCK-BMAL1 complex thereby suppressing transcription of the *mPer* and *mCry* genes [64–66]. Once mPER and mCRY levels sufficiently drop towards the end of the night phase, CLOCK-BMAL1-mediated transcription can resume. An auxiliary feedback loop drives rhythmic changes in *Bmal1* transcription through activation by retinoic-acid-related orphan receptors (RORs) and repression by nuclear receptor subfamily 1, group D, member 1 (NR1D1) also known as REV-ERBs [67–69]. GSK-3β also controls the stability of the CLOCK-BMAL1 protein complex by phosphorylating and destabilizing BMAL1 and CLOCK making them targets for proteasomal degradation [70, 71]. Genetic and pharmacological inhibition of GSK-3β activity using siRNAs and selective inhibitors respectively, increased the amplitude and shortened the period of the molecular oscillator in SCN slices, fibroblasts and mammalian cell lines [60, 72, 73].

In the nucleus, FBXL21 counteracts the destabilizing actions of FBXL3 by ubiquitinating mCRY proteins and protecting them from FBXL3-dependent degradation [50, 58, 59, 74, 75]. Loss of FBXL21 results in significant shortening of period length [58, 59]. Comparably, FBXL3 inhibition as seen in *afterhours*- and *overtime*-mutant mice, lengthens the period by delaying the rate of mCRY protein degradation, decreasing mPER2 protein levels and repressing the transcription and translation of *mPer1* and *mPer2* [74–76]. These studies illustrate the importance of cellular compartmentalization and balance between FBXL3 and 21 for the stabilization and repressor functions of PER and CRY proteins. For more detailed descriptions on the molecular mechanism of FBXL3 and FBXL21 in the circadian oscillator, we refer the readers to [58, 77, 78]. While some of the nuances of post-translational processes in the circadian clock remain yet to be discovered, it is clear that rhythmic phosphorylation and ubiquitination function as important mechanisms to precisely time the circadian period. For more detailed descriptions on post-translational regulation within the molecular oscillator, we direct the reader to the following review articles [79–81].

2.3 Conservation of Circadian Systems

The principles that govern the function and makeup of the core oscillator appear highly conserved across eukaryotes. In *Drosophila,* CLOCK and CYCLE form the positive limb of the clock, binding to the E-box containing enhancers upstream of the *dperiod (dper)* and *dtimeless (dtim)* genes activating their transcription [82–84]. Upon reaching critical levels in the cytoplasm, dPER and dTIM physically associate and translocate to the nucleus where they repress their own transcription by inhibiting CLOCK-CYCLE function [49, 85]. Light-dependent degradation of TIM occurs in the early morning through *cryptochrome* (CRY) dependent pathway [86]. In the absence of TIM, PER is destabilized by DOUBLETIME, the fly orthologue of mammalian CK1ε, rendering it a target for ubiquitination and proteasomal degradation [87, 88]. The concomitant degradation of PER and TIM restarts the circadian cycle. In some non-mammalian vertebrates and many invertebrate species, independently entrained peripheral circadian oscillators are present throughout the organism as seen in zebrafish and *Drosophila* [89, 90]. Multi-oscillatory systems also can be found in other non-mammalian vertebrates including birds and lizards, in which the retina and pineal gland are directly entrained by environmental cues [91, 92].

3. Overview of Circadian Gene Regulation

3.1 Transcription and Translation in the Circadian Clock

Our understanding of the role of transcription and translation in the circadian oscillator began with research using invertebrate models including the marine mollusk *Aplysia californica*, the fruit fly *Drosophila melanogaster* and the bioluminescent dinoflaggelate *Gonyaulax*. The isolated *Aplysia* eye provided the first *in vitro* system to model the circadian clock using measurements of rhythmic compound action potentials as an output of the circadian clock [93]. Phase specific shifts were observed when either reversible inhibition of transcription or translation was pharmacologically induced, suggesting that the circadian oscillator mechanism was dependent upon these processes [94, 95]. Intriguingly, the effects of translation inhibitors were dependent upon the time of day, with distinct phases identified in which phase advances, phase delays or even no effect on the circadian rhythm were observed [94]. Subsequent studies of time of day effects on post-translational processes suggested that post-transcriptional regulation was key to both circadian oscillator function and the timing of circadian outputs [96, 97]. Further evidence for circadian regulation of translation was provided through studies in the bioluminescent marine alga *Gonyaulax* [98–101]. Bioluminescence is dependent upon luciferin binding protein and the abundance and activity of the enzyme luciferase [100]. The circadian clock modulates the translation of the luciferin binding protein, rather than its transcription, to regulate, at least in part, the rhythm in bioluminescence [100, 101]. Circadian rhythms in the translation and transcription of core circadian oscillator genes were first demonstrated in *Drosophila* with the analysis of mRNA and protein rhythms in the *period* gene [102, 103]. These pioneering studies using invertebrate models uncovered the fundamental principles of transcriptional regulation and negative feedback through which the core circadian oscillator is organized and demonstrated that circadian outputs were also regulated through circadian modulation of translation.

3.2 Circadian Clock Broadly Regulates Gene Expression

Advances in genome wide technologies including microarray analysis and deep RNA sequencing have revealed the surprising extent of circadian regulation of transcription both at the species level and at the individual tissue level. While previous estimates suggested that about 10% of the transcriptome was regulated by the circadian clock at the transcriptional level in individual tissues, more recent research in mice using RNA sequencing from time course experiments analyzing 12 tissues found that overall 43% of protein coding transcripts had circadian rhythms (reviewed in [104–106]). Consistent with the previous studies, circadian regulation of gene expression was found to be predominantly organ specific [106]. Mathematical analysis of peak expression, phase differences and half-lives for circadianly regulated nascent mRNA molecules, mature mRNAs and proteins estimated that rhythmic post-transcriptional regulation affects approximately 30% of rhythmic transcripts in the mammalian liver and 34% of the transcriptome in the *Drosophila* head [107]. Studies in the mammalian liver using nascent mRNA sequencing and ribosomal profiling suggest that post-transcriptional and translational mechanisms are major factors defining rhythmic gene regulation, with these processes accounting for the cycling of approximately 50–70% of rhythmically expressed genes [108–112].

For most proteins, the likelihood and timing of protein synthesis is based upon mRNA abundance in the cytosol with protein accumulation determined by the rate of transcription and mRNA export to the cytoplasm (reviewed in [113]). However, this is not the case for the hundreds of genes regulated post-transcriptionally by the circadian clock. Although rhythmic transcription accounts for a significant percentage of rhythmic protein abundance, cycling of protein levels and activity can occur regardless of the rhythmicity of mRNA transcript abundance [114–116]. Examples can be found for circadian regulation targeting almost every aspect relating to the lifespan of mRNA, from mRNA processing, mRNA capping, translation initiation, elongation, and the rate of mRNA decay (Fig. 2) (reviewed in [113, 117]). Additionally, in some cases while gene expression may be primarily regulated by non-circadian factors such as feeding cycles, the circadian clock may act as an important modulator of translation efficiency or the phase of translation as shown through research using circadian mutants [111]). Circadian regulation of post-translational modifications occurs both within the core oscillator as well as in output pathways to maintain 24-hour rhythms [115, 118]. These levels of circadian regulation are discussed in more detail in the following sections.

4. Circadian Regulation of RNA Processing

In the past two decades, advancements in molecular techniques and genome wide sequencing have revealed the extent of the complex and elegant regulation of mRNA that occurs after transcription and prior to translation, and its affect on gene regulation and cellular function. While our understanding of these processes is far from complete, it has become clear that the extent and diversity of RNA modifications represent critical mechanisms for the regulation of gene expression (reviewed in [119]). In the following sections, we discuss some of the post-transcriptional RNA processing mechanisms that are modulated by the circadian clock to affect gene regulation with general examples shown in Figures 2 and 3.

4.1 Alternative Splicing

Alternative splicing increases functional diversity and complexity by giving rise to multiple mRNA isoforms from a single gene. The interactions between the circadian clock and alternative splicing are bidirectional with alternative splicing affecting core oscillator function and the circadian clock regulating alternative splicing in mRNA transcripts. Circadian regulation of alternative splicing in both outputs and in the circadian oscillator is seen in the plant model *Arabidopsis* ([120]; reviewed in [121]). In *Drosophila*, alternative splicing in circadian oscillatory neurons has been shown important for K^+ channel kinetics, function, and neuronal firing [122]. Circadian regulation of alternative splicing permits the cycling of one transcript isoform in the absence of cycling of other isoforms or circadian differences in isoform expression [122]. Core clock genes including *period* demonstrate circadian rhythms in isoform ratios in *Drosophila* [120]. Circadian rhythms in alternative splicing are also observed in the timeless gene [123]. Additionally, regulation of RNA splicing is significantly altered in circadian mutants [124]. Alterations in splicing regulation result in decreased locomotor activity rhythms under constant conditions [120]. In mammals, circadian regulation of splicing occurs in the SCN, hippocampus and other brain

regions as well as in peripheral organs such as the liver, lung and kidney [125, 126]. Potentially, the tissue and cell specific circadian regulation of alternative splicing represents a mechanism to incorporate physiological cues into circadian regulation of gene expression as it appears to be tissue and cell type specific [125].

Alternative splicing may also affect mRNA stability and decay rates, particularly with regard to temperature changes. Temperature compensation of the circadian oscillator is, at least in part, linked to alternative splicing as seen in the fungus Neurospora [127]. In *Drosophila*, temperature dependent changes are seen in RNA splicing for *timeless* [128]. Although mammals exhibit relatively small amplitude rhythms in body temperature, these temperature changes in peripheral clocks, have also been linked to rhythmic alternative splicing for subsets of functionally related genes [129], thus indirectly linking the circadian clock to the regulation of alternative splicing and gene expression. More recent research found that body temperature regulated alternative splicing in the liver affecting mRNA stability through changes in mRNA decay, resulting in broad changes in gene expression [130]. Moreover, as with other circadian interactions with alternative splicing, this temperature and alternative splicing dependent mRNA decay is also observed across phylogeny as similar responses are seen in *Arabidopsis* [130].

4.2 Polyadenylation and Deadenylation

Polyadenylation involves the addition of adenosine monophosphates to the 3’ terminal end of RNA [114]. Poly(A) tails on mRNA increase mRNA stability and facilitate interactions leading to ribosome assembly [114, 131]. Dysfunction in adenylation has been implicated in the genetic neurological disease metachromatic leukodystropgy, immune disorders, and fatty liver disease[115, 132, 133]. Ongoing research has revealed that polyadenylation and deadenylation are influenced by the circadian clock in a gene and tissue specific manner. For example, circadian rhythms in polyadenylation of vasopressin mRNA affects its rhythmic accumulation in the SCN and release into cerebrospinal fluid where it functions as a paracrine signal [134, 135].

In astrocytes, the astrocyte fatty-acid binding protein (Fabp7) undergoes circadian rhythms in poly(A) tail length important for synaptoneurosome localization and preventing Fabp7 protein loss when transcription is reduced [134]. In the mouse liver, it is estimated that the expression for 2.3% of mRNA transcripts is modulated by rhythmic lengthening and shortening of the poly(A) tail [114]. While 80% of oscillating genes have rhythmic mRNA or pre-mRNA abundance levels, the remaining 20% only demonstrate rhythms in their poly(A) tail length with static mRNA levels [114]. Furthermore, approximately 2.9% of mouse liver mRNA rhythmically alternate the usage of adenylation sites affecting mRNA degradation, localization, and translation (Fig. 3A) [136]. Although the molecular mechanisms controlling the circadian rhythm in alternating polyadenylation sites have not been fully elucidated, cytoplasmic polyadenylation proteins have been identified as likely candidates for rhythmically controlling polyadenylation. In the case of Fapb7 and in the liver, cytoplasmic polyadenylation element-binding protein (CPEB) and CPEB1 were identified as the cytoplasmic adenylase responsible for altered protein stability and

localization (Fig. 3D) [114, 136]. However, rhythmic polyadenylation of mRNA transcripts does not provide a complete picture.

Deadenylation, the process of removing the poly(A) tail, is considered the rate limiting step for mRNA decay and can be regulated by the circadian clock [113, 137, 138]. Analysis of the liver transcriptome suggests circadian deadenylation of the poly(A) tail can explain phasic mRNA degradation of cycling mRNAs whose rhythms are not predicted by transcription [107]. The mammalian cytoplasmic deadenylase NOCTURNIN (NOC) has been well-studied for its contribution to the regulation of tissue specific circadian outputs and functions [137–141]. The gene coding for NOC is rhythmically expressed in multiple tissues including the heart, lungs, kidney, liver, and retina [142]. NOC regulates the activity of transcription factors such as sterol regulatory element binding transcription factor-1a, −1c (SREBP-1a, −1c), and peroxisome proliferator-activated receptor γ (PParg), that activate the transcription of genes involved in cholesterol and fatty acid metabolism and deposition, and adipose formation [139, 143, 144]. Though usually in the cytoplasm, NOC is also found in the mitochondria of tissues such as brown adipose fat where it mediates metabolic adaptations to temperature change, though the mechanism has not been fully defined [145]. Research in liver revealed that mitochondrial NOC acts as a phosphatase converting NADPH into NADH and $NADP^+$[141]. Though NOC has been identified as being rhythmically expressed in other tissues such as the heart, spleen, and kidneys, additional research is needed to identify specific tissue mRNA targets and the impact of NOC on tissue functions.

4.3 Circadian Regulation of mRNA Stability via microRNA-induced Degradation

MicroRNAs (miRNAs) are non-coding nucleotide sequences (21 −25 nt) that regulate the stability of mRNAs through silencing of translation and signaling mRNA degradation [118, 146]. The abundance of miRNAs as well as their targets differ between tissues [147]. Circadian regulation of miRNA activity has been demonstrated from plants to invertebrates to humans [144, 146–150]. Transgenic studies using knockout and overexpression miRNA lines in *Drosophila* have elucidated the role of multiple miRNAs in modulating protein translation to regulate circadian rhythms in locomotor activity, time-of-day immunity, feeding time, and other outputs, in addition to providing feedback and modulation of the circadian oscillator [146, 148, 151–154]. An example of miRNA mediated circadian regulation can be seen in the small ventral lateral neurons, the master pacemaker neurons, of the *Drosophila* brain in which circadian regulation of dorsal projection arborization is mediated by miRNA-210 suppression of translation for the cell adhesion *protein Fasciclin 2* (*Fas2*) [148]. Downstream of the oscillator, circadian regulation of miRNA-279 drives locomotor and rest activity [152], while rhythmic oscillations of miRNAs 959–964 affect feeding time and innate immunity [146]. miRNAs also function to modulate the circadian oscillator and output rhythms in mammals. Although many other examples exist, one example of miRNA regulation in the core oscillator is miRNA-24 that binds to the 3'UTR of *mPer2* to regulate translation and protein accumulation [155]. Downstream, miRNAs affect a broad scope of physiological and behavioral outputs from learning and memory to metabolism. In the hippocampus, the circadian clock regulates the abundance of miRNA-132 with peak expression during the night resulting in translational repression of two genes involved in neuronal plasticity, MeCP2 and Sirt1 [156]. Confirmation of the role

of miRNA-132 in circadian regulation of memory was seen using knockout and overexpression transgenic mouse lines for miRNA-132 in which circadian rhythms for hippocampal-dependent learning paradigms were abolished [156]. Despite the large number of rhythmic genes directly regulated by transcription in the liver, examples of circadian regulation via miRNAs can also be observed. Modulation of the phase or the amplitude of rhythmic mRNAs through miRNA regulation is thought to occur for up to 30% of the rhythmic transcriptome [150]. miRNA-122, regulated transcriptionally at the pre-miRNA level by the circadian clock, regulates cholesterol and lipid metabolism [110, 144]. However, it should be noted that mRNA rhythms in the liver driven solely by miRNA regulation account for a only a small fraction of rhythmic gene expression, about 20 genes [150].

Circadian regulation of miRNA activity, i.e. repression of translation, can arise through multiple mechanisms (Fig 3B). Circadian transcription of miRNA levels via core clock components can be observed in plants as seen with the transcription of miR-164B which impacts plant aging and the translation of other clock controlled genes [157, 158]. In mammalian liver, the rhythmic core clock transcription factor REVERBα regulates, at least in part, the rhythmic expression observed in the levels of miRNA precursors, primary-miRNA (pri-miRNA) and precursor-miRNA [144]. While the previously described hippocampal miRNA-132 exhibits rhythms in abundance, its expression appears to be controlled by circadian gating of CREB-mediated transcription rather than directly by CLOCK-BMAL1, consistent with the induction of miRNA-132 by other stimuli [150]. miRNA processing by endoribonucleases also can be regulated by the circadian clock with tissue specificity. Rhythmic Dicer activity results in pre-miRNA to miRNA cleavage dependent on the time of day with phase differences in peak expression observed between tissues [159]. Understanding the mechanisms through which the circadian clock regulates miRNA activity and the metabolic, physiological and behavioral outputs that are affected is important for the future development of novel disease treatments and therapeutics as miRNAs have been implicated in multiple diseases. Cycling miRNAs that have immune relevance have been implicated in several human diseases such as miRNA-146a and 125a-5p in diabetes, miRNA-132 in hepatic steatosis, and miRNA-125a-5p in cancer [159–161].

4.4 RNA Granules and Circadian Regulation of mRNA Availability

In addition to mRNA stability and abundance, the availability of mRNA transcripts for translation can be targeted by circadian regulation. mRNA binding proteins shepherd mRNA transport throughout the cytoplasm and when translation is stalled, can form RNA granules preventing additional ribosome access to the transcript or even leading to mRNA degradation (Fig. 3C). Dynamic mRNA granules, such as RNA stress granules or P-bodies, are composed of numerous proteins, rapidly forming or disassembling in response to conditions in the cell [162, 163]. Stress granules and P-bodies have been implicated in cancer and neurodegenerative diseases [164–166]. Recently, researchers found that RNA stress granule formation in the mouse liver varies by time of day [167], indicating that mRNA availability is another mechanism through which the circadian clock can regulate protein synthesis. Rapid stress granule upregulation was associated with trough BMAL1 levels and low abundance of the translation initiation factor eiF2α [167]. Stress granule formation increased in the absence of core clock gene BMAL1 expression in gene silenced

cell lines [167]. Circadian regulation of eiF2α expression appears to be the link through which the clock regulates stress granule formation as during trough phases the ratio of phosphorylated to unphosphorylated eiF2α can be rapidly changed leading to stress granule formation [167]. The abundance of other proteins associated with stress granules are also regulated by the circadian clock including FUS and TDP43 [167, 168]. In another RNA granule associated with translational regulation, the chromatoid body of germ cells, CLOCK and BMAL1 have been shown to contribute to the assembly and composition of these bodies [169].

Processing bodies (P bodies) have been commonly associated with RNA degradation, but also function in RNA sequestration potentially forming mRNA exchanges with stress granules (Fig. 3C) [170, 171]. Circadian regulation of P bodies and subsequently, circadian regulation of translation was initially shown through ribosomal profiling in a human cell line with a functional circadian clock [108]. RNA destabilization through P bodies occurs via a decapping mechanism breaking apart the cap binding complex (eIF4E and eIF4G) and it's subsequent deadenylation [172, 173]. Lsm1-Lsm7 represent a class of proteins that activate the decapping enzymes Dcp1p and Dcp2p [173]. *Lsm1* is rhythmically expressed in human U2OS cells and appears to be the mechanism underlying a two-fold rhythm in P body formation [108]. More recently, additional P body formation associated proteins, Tristetraprolin and BRF-1, were found to oscillate in abundance in phase with P body concentration [174]. These studies suggest that circadian regulation of P body formation provides an additional mechanism through which the circadian clock regulates mRNA availability and translation. Given the links between the circadian dysfunction and disease, and the growing body of evidence for the role of RNA granules in cancer and neurodegenerative diseases, more study is warranted investigating the connection between the circadian clock and RNA granule formation.

4.5 Interactions of the circadian clock with epigenetic RNA modifications

RNA methylation, particularly N6-methyladenosine (m6A), has emerged as a widespread and important modulator of gene expression affecting physiology, neuronal function and the immune system (reviewed in [175]). RNA methylation and demethylation represents a dynamic process occurring through m6A methyltransferases (writers) and demethylases (erasers) targeting approximately 30% of transcripts to modulate gene expression through mRNA splicing, mRNA nuclear export, stability and localization (reviewed in [175–177]. Although the potential interactions of the circadian clock with RNA methylation are just beginning to be explored, recent research has shown that RNA methylation can regulate the timing and speed of the circadian oscillator [178, 179]. Through *in vitro* studies in cell culture and organotypic SCN slices, researchers found that inhibition of RNA methylation lengthened the circadian period [178]. Furthermore, *in vivo* behavioral studies in mice demonstrated that transmethylation inhibition in the SCN significantly increased the free-running period in locomotor activity by approximately one hour [178], confirming the importance of RNA methylation in the circadian clock. Interestingly, many core circadian clock genes contain multiple methylation sites in their transcripts, particularly in the longest exon and near the 3' end, including *Clock*, *Per1, Per2, Per3, Dbp, Nr1d1* and *Nr1d2* [178]. Recently, inhibition of mRNA methylation was shown to increase alternative splice forms

for a key circadian kinase, *Casein kinase1 Delta* (Ck1δ), providing a link through which RNA methylation can affect the timing of the core oscillator [179]. Circadian regulation of RNA methylation also affects physiological outputs as shown through studies in the mouse liver in which rhythmic m6A methylation dependent upon the circadian clock occurs [177]. In mutant mice with *Bmal1* knocked out specifically in the liver, increases in m6A mRNA methylation are seen for the nuclear receptor peroxisome proliferator-activator alpha (*PPaRα*), resulting in reduced lipid accumulation and changes in lipid metabolism [177]. Circadian modulation of RNA methylation features in circadian systems across phylogeny. For example, in plants, daily rhythms in transcriptome wide RNA methylation and oscillations in the abundance of mRNA transcripts for writers and erasers have been recently shown in marine seagrasses [180].

RNA editing, converting adenosine to inosine through adenosine deaminases acting on RNA (ADARs), permits the incorporation of guanosine residues during translation increasing protein diversity from a single gene (reviewed in huang, 2012;[181]). The first suggestion of circadian involvement was revealed by RNA-Seq studies in *Drosophila* in which differences in RNA editing were seen in the *period* mutant, although no oscillations were seen in RNA editing [124]. However, in ADAR hypomorphs, circadian locomotor activity is altered with no morning anticipation observed ([182]). In mammals, RNA editing occurs primarily through *ADAR1* and *ADAR2* (reviewed in [181]). In the liver, *ADAR2* (also known as *Adarb1*) exhibits circadian rhythms in mRNA and protein abundance under constant conditions resulting in circadian rhythms in A to I RNA editing [183]. Moreover, in *ADAR2* knockout mice, the period length of circadian rhythms in locomotor activity is significantly shorter than in wild-type mice [183]. In subsequent studies, researchers found that ADAR2 was critical for light induced phase shifts of the circadian clock [184], demonstrating bidirectional interactions between RNA editing and the circadian system.

5. Circadian Regulation of Translation Machinery

According to recent estimates, circadian regulation of translation may contribute to the rhythmic cycling or amplitude of up to 50% of proteins synthesized [185]. Circadian regulation of translation from ribosome production to mRNA loading to translation initiation and elongation results can be seen across phylogeny. Much of the groundbreaking work identifying circadian regulation of protein translation comes from research in the fungus *Neurospora crassa,* a mainstay for circadian research, ribosomal profiling and proteomic studies of the mammalian liver, and studies of photic entrainment in the SCN.

5.1 Circadian Regulation of Ribosome Biogenesis

The complex production of the small and large subunits of the ribosomes (ribosome biogenesis) exerts a high energy demand on the cell [186]. The circadian clock regulates the transcription and translation of both ribosomal protein genes and rRNA in plants, invertebrates and mammals [187–189]. In *Drosophila*, a number of ribosomal proteins are direct targets of CLOCK-dependent transcription, including RpL38, RpL30, RpL41, RpL11, RpS8, RpS7 and PrS11, suggesting the regulation of ribosome biogenesis by the circadian clock [187]. In mammals, synchronized rhythmic transcription has been observed for pre-

mRNA accumulation for several ribosomal proteins including Rpl23, Rpl32 and Rpl34 and for the 45S rRNA [188]. Proteomic studies in the mouse liver have also shown phase specific diurnal rhythms in proteins involved in ribosome biogenesis including rRNA transcription, rRNA processing and ribosomal protein synthesis allowing a temporal pattern of ribosome biogenesis [186]. The Upstream Binding Factor 1 (UBF1) that regulates rRNA transcription also exhibits circadian rhythms in mRNA and protein abundance [188]. During rRNA maturation, small nucleolar RNAs are required for pre-ribosomal folding. Together, these studies provide examples demonstrating the broad circadian regulation of ribosome biogenesis. In *Arabidopsis*, ribosome loading onto mRNA transcripts also has been shown to be regulated, at least in part, by the circadian clock, resulting in rhythms in translation [189].

5.2 Circadian Regulation of Translation Initiation

Circadian targeting of eukaryotic initiation factors is one highly conserved mechanism from fungi to mammals through which the circadian clock regulates rhythmic protein synthesis. Initiation factors play a key role in facilitating the recruitment of mRNA to the ribosomal subunits. Circadian control of translation starts with the regulation of upstream pathways including MAPK and mTOR signaling pathways that modulate the phosphorylation state of initiation factors necessary for protein synthesis. Multiple lines of research have indicated circadian oscillations in mTOR signaling impacting behavioral, physiological and metabolic rhythms [188, 190]. Rhythmic signaling through mTOR has been shown in the SCN, hippocampus, and cortex of the brain, as well as in peripheral tissues including the liver, cardiac muscles, and skeletal muscle [191–195]. mTOR signaling regulates the translation of a subset of mRNA transcripts, cap-dependent translation, through two major downstream pathways, the mTOR-regulated eIF4E binding proteins (4E-BPs) and s6 kinase [196]. 4E-BP phosphorylation causes its dissociation from eIF4E allowing eIF4E to bind eIF4G, and subsequent 5’ cap binding for the initiation of translation (Fig. 4 A1). eIF4E also can be phosphorylated by kinase pathways under circadian control including the rhythmic activity of a MAPK-MNK pathway resulting in circadian rhythms of p-eIF4E [197] (Fig. 4 A2). In the SCN, phosphorylation of eIF4E promotes the translation of PER1 and PER2 to facilitate clock resetting [197]. Previously, circadian regulation of 4E-BP1 phosphorylation through mTOR signaling was shown to regulate the translation of VIP, an important circadian neuropeptide in the SCN [198]. In the hippocampus, rhythms have also been observed for translation initiation markers including the phosphorylation of 4E-BP1, p-eIF4E, S6 kinase and the eIF4F cap complex as well as for MAPK activity [194]. In the liver, mRNA transcripts for the initiation factors eIF4G, eIF4B, ribosomal protein S6, were found to peak in phase during the active period of mice whereas RNA cap binding protein eIF4E peaks during the rest period [188]. In peripheral tissues, entrainment to feeding cycles can regulate circadian gene expression and affect locomotor activity. Recent research has identified the acute induction of PER2 protein synthesis from existing mRNAs via an insulin dependent-mTOR pathway regulation of translation initiation as a mechanism through which restricted feeding regulates gene expression [199]. Together these studies demonstrate the pervasiveness of circadian regulation through modulation of translation initiation factors across multiple tissues.

Recently, researchers identified another mechanism involving the circadian regulation of translation that appears phylogenetically conserved. The initiation factor eIF2α is rhythmically phosphorylated by eIF2α kinase in the mouse SCN [200], the mouse brain as a whole, and in the SCN and substantia nigra of a non-human primate (presented in Suppl. Fig. 4F, 4G of [167]). In the SCN, manipulated levels of phosphorylated eIF2α alter translation of the transcription factor ATF4 and impact period length [200]. Circadian regulation of phosphorylated and total eIF2α protein has been previously shown in the liver as well as rhythms in mRNA abundance [167, 186]. Similarly, researchers using *Neurospora* found that rhythms in upstream kinase activity led to rhythmic eIF2α phosphorylation with increased eIF2α phosphorylation during the day repressing protein synthesis [185]. Importantly, the circadian regulation of translation initiation did not universally but rather specifically affected a subset of transcripts [185].

In yet another twist to circadian regulation, the core circadian clock protein BMAL1 was recently shown to function in the cytoplasm to regulate translation (Fig 4 A3). In the mouse liver, both mTOR and S6K1 activity cycle in a circadian manner with peaks during the evening phase [192]. The mTOR target S6 kinase 1 was recently shown to phosphorylate cytoplasmic BMAL1 resulting in BMAL1 association with translation initiation factors, particularly members of the cap-binding complex eIF4E, eIF4A, eIF4G and eIF2α [193]. Phosphorylation of BMAL1 by S6K1 appears necessary for stability of the translation initiation complex with peak BMAL1 phosphorylation corresponding to times of high protein synthesis in the liver [193]. In an interesting study of simulated night shift work evaluating protein synthesis markers in rats, researchers found that night shift work interfered with the circadian rhythm in protein translation in the prefrontal cortex through reduction of S6 kinase and cap-binding complex bound BMAL1 [201]. Furthermore, in control animals, no rhythm was observed for cap-dependent translation in the hippocampus [201]. Thus, the circadian clock appears to modulate the initiation of translation through multiple steps exhibiting tissue and transcript specificity.

5.3 Circadian targeting of elongation

One mechanism for regulation of protein elongation is through the phosphorylation of the eukaryotic elongation factor eEF-2, which mediates the translocation of the nascent peptide from the A site to the P site of the ribosome. When phosphorylated, eEF-2 cannot bind the ribosome. In *Neurospora*, circadian regulation of p38-like MAPK activity and subsequently its target RCK-2 lead to the rhythmic phosphorylation of the elongation factor eEF2 and rhythms in protein translation [202]. Phosphorylated eEF-2 levels peak in the subjective morning corresponding to minimum protein synthesis during the day and the observation that the majority of protein synthesis for growth in *N. crassa* occurs at night [202]. It should be noted that circadian regulation of translation via elongation is not global but rather targets a subset of mRNAs illustrating the specificity of circadian regulation of translation [202]. Translational regulation by the circadian clock mRNA transcripts that do not cycle comprises approximately 10% of the proteome in *Neurospora* [203].

In tissues, such as the liver, up to 10% of proteins that cycle in abundance do not have rhythms in mRNA suggesting, in part, direct control of rhythmicity via translation [108,

112]. Circadian targeting of elongation appears to occur through two essential elongation factors, eEF2 and eEF1A [116]. eEF2 is also a phosphorylation target of S6 kinase 1 [204]. In the SCN, although not in other brain regions, mTOR signaling through S6 kinase increases translation of eEF1A in response to light pulses [191]. In this manner, mTOR signaling and protein translation mediate light-induced phase shifts for circadian entrainment in the SCN exemplifying another way through which the circadian clock and translational regulation are linked.

6. Circadian Regulation through Post-translational Modifications

In addition to wide-ranging circadian regulation during transcription and translation, numerous examples can be found across species of circadian regulation of post-translational modifications affecting steps from protein-protein interactions to protein localization to activity (Fig. 2C). Advances in large scale proteomics and bioinformatics have facilitated broad analysis of protein modifications throughout the cell or in sub-cellular compartments. We consider a few examples below to demonstrate the breadth of post-translational circadian regulation in both regulation of the circadian clock and in regulation of output pathways. For more information on circadian regulation of post-translational modifications, we direct the reader to the following review by Louis Ptácek and colleagues discussing the role of post-translational modifications in the precision of the circadian clock [50] and a review by Daniel Mauvoisin discussing circadian rhythms and proteomics [205].

6.1 Phosphorylation

Perhaps the most well-studied post-translational modification regulated by the circadian clock is phosphorylation. Circadian regulation of kinase activity occurs both within the core circadian oscillator and as a mechanism to regulate cellular and physiological outputs. The members of the *Casein kinase 1* family are key components regulating the timing mechanism of the transcription-translation feedback loops in the circadian oscillator in eukaryotic systems as seen in fungi, invertebrates and vertebrate animals (reviewed in [206–208]). In the *Drosophila* and the mammalian circadian clock, CK1 ε and/or δ comprise a key component of the oscillator's timing mechanism modulating the degradation of protein monomers in the cytoplasm, protein translocation to the nucleus and eventually protein degradation in the nucleus to restart the circadian cycle (Fig. 1). Recent research in mammals found that multi-phosphorylation at two serine residues of PER2 by CKIδ/ε determines period length [207]. Blocking phosphorylation at Ser478 prevents subsequent polyubiquitination of substrates targeted for degradation including PER and CRY, thus controlling the stability of PER and CRY proteins [207]. Additionally, the circadian clock can regulate phosphatase activity to affect timing of the oscillator. Recent research identified circadian regulation of the phosphatase PRL-1 as an integral component of the core oscillator in *Drosophila* affecting period length and activity phase [209].

In addition to the critical function of casein kinases in the core oscillator, MAPK/ERK signaling plays a key role in clock resetting. In the SCN, the circadian clock regulates ERK/MAPK pathway activity [210]. Moreover, phase resetting and entrainment of the oscillator occur, in part, through ERK/MAPK signaling [211, 212]. Recently in the SCN, the GTPase

activating protein SynGAP, a negative regulator of Ras and consequently ERK/MAPK signaling, was shown to be regulated by the circadian clock and it modulates light-induced entrainment sensitivity [213]. These studies demonstrate the multi-level circadian regulation of kinase signaling and the feedback of these rhythmic kinase pathways to circadian oscillator entrainment and timing.

Rhythmic phosphorylation can also be seen outside of the SCN and represents a key regulatory mechanism for clock controlled protein activity. In the liver, 25% of protein phosphorylation sites exhibit rhythmic phosphorylation demonstrating the extent of circadian phosphorylation for core clock genes and clock-controlled genes [214]. For example, rhythmic protein accumulation in the nucleus is dependent upon protein phosphorylation as observed for multiple proteins including GSK-3 α/β, CKIα/δ, and the cyclin-dependent kinases CDK4 and CDK6 [186]. Rhythmic phosphorylation-dependent nuclear localization of proteins links the circadian clock to many cellular processes including the cell cycle. Previously, it has been suggested that eukaryotic clocks could be maintained by phosphorylation cycles (reviewed in [215]). Interestingly, recent research suggests that phosphorylation cycles in the mammalian liver clock continue to oscillate in the absence of the canonical CLOCK-BMAL1 positive feedback loop [216], indicating the complexity of the circadian oscillator.

Circadian regulation of learning and memory appears to be dependent, at least in part, upon rhythms in kinase activity. In *Aplysia*, rhythmic induction of MAPK signaling partially modulates circadian rhythms in intermediate and long-term memory formation [217, 218]. In the mouse hippocampus, 5.2% of the phosphoproteome undergoes circadian oscillations [219]. In contrast to *Aplysia* in which the clock does not regulate memory recall [220, 221], the circadian clock appears to regulate hippocampal memory in mammals through phosphorylation dependent memory maintenance and memory recall. Persistence of long-term memory appears to be intertwined with circadian regulation of MAPK/ERK pathways and cAMP-PKA signaling [222]. Also in the hippocampus, the circadian clock regulates memory retrieval, at least in part, through a cAMP-PKA dependent GluA1 phosphorylation [223]. Interestingly, within the hippocampus downstream of MAPK signaling, PER1 gates the nuclear shuttling of the kinase p90RSK to regulate CREB phosphorylation and affect learning and memory [224]. Although some studies have reported that a functional circadian clock in the SCN is necessary for the rhythms in hippocampal MAPK and rhythms in long-term memory [225], other researchers selectively deleted components of the hippocampal clock and found that the hippocampal clock regulates memory [226], particularly the retrieval of memory [227]. These studies highlight the multiple post-translational mechanisms through which the circadian clock affects learning and memory. The interactions of the circadian system with sleep/wake cycles have long raised the question as to whether the circadian clock or sleep/wake cycles underlie rhythms in neuronal plasticity. This question has been answered, in part, by recent large scale studies of the mammalian forebrain [228, 229]. In the mammalian forebrain, circadian rhythms appear to regulate mRNA availability in neuronal compartments (Fig. 3D), while the synaptic phosphoproteome appears primarily regulated by sleep-wake cycles [228, 229].

Circadian regulation of dephosphorylation through regulation of phosphatases occurs to modulate circadian outputs, particularly learning and memory. *In Aplysia*, phase-specific phosphatase activity acts as an important mechanism for the circadian modulation of intermediate term memory [230]. In mammals, the suprachiasmatic nucleus circadian oscillator (SCOP) protein is circadianly regulated in the SCN and it was originally reported that SCOP did not cycle in brain regions outside of the SCN [231]. However, recent research found that circadian expression of SCOP in the basolateral amygdala of mice modulated circadian rhythms in anxiety in mice [232]. Although the signaling pathways with which SCOP interact to modulated anxiety behaviors remains unknown, SCOP can dephosphorylate AKT as well as suppress MAPK signaling and CREB-mediated transcription [232–234]. Circadian regulation of kinase signaling pathways and phosphatase activity appears to be an important mechanism for the regulation of circadian behaviors as well as within the core oscillator.

The circadian clock regulates the PI3 kinase-AKT signaling pathway in many peripheral tissues, frequently affecting protein localization. For example in the retina, rhythmic AKT phosphorylation of L-type voltage-gated calcium channels affects channel subunit trafficking and thus, the rhythmic currents of these channels [235]. Similarly in the heart, CLOCK-BMAL1 mediated regulation of PI3K-AKT signaling has been shown to be important for regulating expression and function of the alpha subunit of L-type calcium channels [236]. In both skeletal muscle and the liver, AKT directly phosphorylates CLOCK, thereby negatively regulating its nuclear translocation and subsequently decreasing transcription of clock controlled genes [237]. In mice in which CLOCK cannot be phosphorylated by AKT, expression of the core clock genes *Per1*, *Per2*, *Reverbα*, *Dbp*, *Rorα* and *Npas2* have significantly reduced expression [238]. In the vascular system, deletion of the most ubiquitous form of mammalian AKT results in lower amplitude expression of positive circadian transcription factors and higher amplitude rhythms of negative circadian regulators [237]. Previously, an indirect role of PI3K-AKT signaling was shown for phospho-mediated degradation of CLOCK by GSK-3; however, in this pathway AKT activity inhibits GSK-3 phosphorylation of CLOCK thereby preventing its degradation [71]. In the liver, the PI3K-AKT signaling pathway also functions in BMAL1 protein localization affecting its transcriptional activity [239]. After feeding, insulin signaling activates the PI3K-AKT signaling pathway, providing a link for feeding as an entrainment mechanism of the liver circadian clock [239]. Thus, rhythmic AKT activity provides an important mechanism for regulating protein localization and core circadian protein function.

6.2 Ubiquitination

Ubiquitination, or the attachment of ubiquitin groups to a protein, constitutes one of the main signals for subsequent protein degradation via the proteasome [240]. Ubiquitination of target proteins is a specific and highly regulated process involving numerous ubiquitin activating proteins (E1 enzymes), ubiquitin conjugating enzymes (E2 proteins) and ubiquitin ligases (E3 proteins) [240]. Data analysis of mouse liver transcripts estimated that approximately 35% of E3 ubiquitin ligases had circadian rhythms in abundance, with the peak of most of these ligases occurring around CT 6 [107]. Analysis of targets of the E3 ubiquitin ligase FBXO6, which itself exhibits a rhythm in translation, suggests that the phase

distribution in the abundance of these target proteins depends upon rhythms in protein degradation [107]. Circadian rhythms in ubiquitination and protein degradation are important mechanism rhythms in protein abundance both for core oscillator proteins and for output pathways. Circadian rhythms in protein abundance can also be modulated through deubiquitinating enzymes. In mammals, this has been shown with the circadian regulation of USP2 that is rhythmically expressed in numerous tissues [106, 241]. USP2 mutant mice demonstrate longer free-running periods [242]. For more details on circadian regulation of ubiquitination across phylogeny, please see the recent review by Srikanta and Cermakian [243].

An elegant example of clock controlled post-translational modifications providing feedback to the circadian oscillator was shown through studies on ubiquitination in *Drosophila* and mice [244, 245]. In *Drosophila*, the F-box E3 ligase SLMB exhibits circadian rhythms and is an essential component of the circadian clock responsible for targeting phosphorylated PER and TIM proteins for degradation [246]. In *slmb* mutants, flies are arrhythmic under constant conditions [246]. Subsequent research found that CULLIN-3, another E3 ubiquitin ligase, also regulates PER and TIM protein cycling and plays a major role in the hypophosphorylation of TIM [247]. JETLAG (JET) is another E3 ubiquitin ligase that functions in the core oscillator to promote the degradation of TIM and light resetting [248]. The extent of circadian regulation of ubiquitination in oscillator cells of the *Drosophila* head was recently documented using a biotinynlated ubiquitin system to identify ubiquitinated proteins across the circadian cycle, with researchers finding a peak in ubiquitylated proteins at CT 6 [244]. Moreover, the researchers found that the proteins with rhythms in ubiquitination had little overlap with the previously identified cycling translatome [244], clearly demonstrating the circadian clock regulated protein abudance at multiple levels.

In the mammalian circadian clock, an F-box protein (FBXL3) bind to CRY proteins leading to ubiquitination by the E3 ligase SCF (Fbxl3) and subsequent degradation [74, 75]. Mutation of FBXL3 results in CRY protein stabilization and widespread transcriptional repression affecting period length [75]. As with *Drosophila*, multiple F-box proteins and E3 ubiquitin ligases have been identified as interacting with core oscillator proteins in mammals [243]. Charles Weitz and colleagues found that the CLOCK-BMAL1 complex recruit histone ubiquitination factors to *mPer*, *mCry* and other circadian genes [245]. Through this chromatin mediated mechanism, the positive loop of the oscillator provides positive feedback to the negative loop of the oscillator through histone mono-ubiquitination at E-boxes in the promoters of circadianly regulated genes [245]. The local histone mono-ubiqutination weakens CLOCK-BMAL1 binding and promotes the negative PER complexes binding at E-box sites thereby repressing circadian gene transcription. Post-translational modifications through ubiquitination form an essential mechanism in maintaining the integrity of the transcriptional-translation feedback loop.

6.3 Sumoylation

Sumoylation in which a small ubiquitin-related modifier (SUMO) approximately 10kDA is attached to a lysine residue [249] is another post-translational modification associated with the circadian clock. Early research found that BMAL1 was sumoylated on Lys259 in a

circadian manner and that this sumoylation was CLOCK protein dependent [250]. Sumoylation peaks in phase with maximum CLOCK-BMAL1 transcription and promotes the interaction of CBP to the complex [251, 252]. Inhibition of BMAL1 sumoylation decreases *Per1* transcription and reduces the response to stimuli affecting resetting of the circadian clock [252]. Interestingly, DEC1, an inhibitor of CLOCK-BMAL1 mediated transcription through recruitment of histone deacetylase1, is also sumoylated increasing its stability and activity resulting in repression of CLOCK-BMAL1 mediated transcription [253, 254]. Recently in plants, sumoylation of the circadian transcription factor CCA1 was shown to reduce its DNA binding affinity, thereby decreasing transcription [255]. Additionally, sumoylation appears to play a role in temperature compensation of the circadian clock in plants, perhaps acting as a delay mechanism to affect period length[256]. Thus, sumoylation appears to be an important post-translational modification in plants and animals that is not only regulated by the circadian clock, but also feedsback to regulate core oscillator function through sumoylation of core clock proteins.

6.4 Circadian modulation of cytoskeletal architecture

The circadian clock can also regulate protein stability, protein localization and cellular architecture through specific post-translational modifications. Actin rearrangements and changes in cellular morphology in neurons or macrophages create a dynamic cytoskeletal structure. For example, in the immune system, BMAL1 has also been linked to a protein network regulating changes in cellular architecture necessary for macrophage function with the deletion of BMAL1 inducing actin cytoskeleton rearrangements [257, 258]. In macrophages, the absence of BMAL1 induces a gain of phagocytosis through a RhoA-dependent mechanism suggesting that BMAL1 represses the immune system function of macrophages [258]. In astrocytes, BMAL1 deficiencies have also been shown to affect formation of actin fibers resulting in morphological abnormalities of astrocytic processes [259]. In peripheral tissues such the liver, signals transmitted via the blood induce the rhythmic regulation of the actin cytoskeletal dynamics linking the SCN to peripheral tissue oscillators [260]. The effect of the circadian clock on the cytoskeleton can also affect disease pathology. In tumor cells, CLOCK-BMAL1 also appears to act in a separate role distinct from their function as transcriptional activators to modulate actin skeleton dynamics [261]. CLOCK-BMAL1 leads to F actin polymerization and overexpression of CLOCK-BMAL1 regulate RHOA localization and promote cancer cell migration and proliferation [261].

6.5 Other types of post-translational modifications affected by the circadian clock

Post-translational modifications of proteins can also be used to coordinate environmental signals with circadian oscillator. For example, post-translational modifications provide a mechanism for linking the clock to metabolic needs and energy metabolism. In tissues such as the liver that are responsive to metabolic needs, BMAL1 and CLOCK can also be rhythmically modified via glycosylation, O-GlcNAcylation, increasing protein stability and subsequently leading to upregulation of BMAL1/CLOCK target genes [262]. Additionally, in the liver, the circadian clock regulates protein acetylation and deacetylation to coordinate the circadian oscillator with energy metabolism. The circadian clock regulates protein lysine acetylation of histone and non-histone proteins [263]. In the liver, mitochondrial proteins related to energy production and metabolism are rhythmically acetylated [263, 264].

CLOCK itself may also function as an acetyltransferase directly acetylating histone proteins to modulate chromatin remodeling as well as acetylating non-histone targets [265]. In the liver, CLOCK acetylates BMAL1 on Lys537 in a rhythmic manner resulting in CRY recruitment and subsequent transcriptional repression of clock controlled genes [266]. Also in the liver affecting metabolism, CLOCK can directly acetylate argininosuccinate synthase, an enzyme involved arginine biogenesis, contributing to circadian rhythms in ureagenesis [267].

The circadian clock also regulates rhythms in acetylation via deacetylation through the NAD + dependent deacetylases SIRT1 and SIRT 3 [268–270] Circadian deacetylation through SIRT1 feedsback to affect histones, core circadian clock proteins and oscillator function. The circadian clock drives rhythms in NAD+, a co-factor for SIRT1, through the circadian regulation of NAMPT [268]. SIRT1 acts as a counterbalance to CLOCK- mediated histone acetylation of BMAL1 through rhythms in deacetylation to affect the core oscillator [271]. SIRT 1 also promotes the deacetylation of other core circadian genes including mPER2 [272]. The NAD+ dependent deacetylase SIRT 3 appears to function downstream of the circadian clock to affect output pathways associated with metabolism, especially in the liver. Total and mitochondrial NAD+ exhibits rhythms in the liver [269]. The circadian clock regulates NAD+ dependent SIRT3 deacetylation in the mitochondria linking the circadian clock to mitochondrial oxidative function [264, 269].

6.6 Atypical circadian oscillators maintained by rhythmic post-translational modifications

While the above examples demonstrate the extent that post-translation regulation by the clock can affect both oscillator function and clock controlled targets, there are two more examples that clearly highlight the impact of how non-transcriptional processes and post-translational modifications can regulate the circadian system: the circadian oscillator in red blood cells and the circadian oscillator in prokaryotic photosynthetic cyanobacteria (also known as blue-green algae). Anucleated human red blood cells cannot maintain a circadian oscillator through transcriptional processes and yet, circadian rhythms under peroxiredoxins and a 24 hour redox cycle have been observed in red blood cells in constant conditions [273]. Moreover, these rhythms exhibit temperature compensation and are entrainable by external stimuli such as temperature cycles, demonstrating that nontranscriptional processes underlie the red blood cell circadian oscillator [273]. Interestingly, inhibitors of transcription and translation do not affect the rhythmic PRX oxidation suggesting that post-translational modifications are maintaining the rhythms [273]. Circadian rhythms in K+ transport also can be observed electrophysiologically in isolated human red blood cells in the absence of transcription or external signals [274]. Furthermore, experiments using pharmacological manipulation of K+ transport significantly altered the period of the red blood cell clock [274]. Recent research found that the circadian oscillator properties, period length and temperature compensation, in red blood cells were dependent upon CK1 [275]. As shown in Figure 1, CK1 functions in both the cytoplasm and nucleus of nucleated cells including the pacemaker cells of the SCN. CK1 and post-translational modifications function to affect period length and temperature compensation in a phylogenetically conserved manner from fungi to humans [276–278].

Perhaps an even more striking example of the role of post-translational processes in the circadian oscillator comes from photosynthetic cyanobacteria. In the cyanobacteria *Synechoccus*, cell division, gene expression and mRNA level are regulated by a circadian oscillator even in rapidly dividing cells [279–281]. Mutant screens identified a cluster of three genes, *kaiABC*, as the molecular components of the core oscillator in this simple organism [282]. Surprisingly, the circadian oscillator can be maintained *in vitro* in the absence of transcription or translation with robust, temperature compensated circadian oscillations of KaiC phosphorylation observed [283, 284]. Moreover, transcriptional regulation of clock gene expression occurs through the phosphorylation of KaiC, with local interactions within KaiC being between adjacent phosphorylation sites regulating KaiC activity [285, 286]. Thus, in one of the simplest systems in which circadian clocks have been observed, post-translational modifications are a key component of the oscillator mechanism.

7. Targeting the Circadian System

Throughout this review, we have highlighted the extent of circadian regulation of gene expression. Given the challenges that individuals face to maintain robust circadian entrainment and desynchronization, and that declining circadian function and misalignment are contributors to the onset and progression of many diseases, including cancer, neurodegenerative diseases, diabetes and pathologies associated with metabolic syndrome [18–23, 287, 288], it is important to consider therapies and treatments for circadian dysfunction. Many chronic conditions disrupt multiple cellular processes making them difficult to treat. As the circadian clock regulates the timing of many cellular and metabolic processes, incorporating time of day as a component of disease treatment may be beneficial for drug efficacy and to minimize drug toxicity. Research on chronotherapy and small molecule modifiers for the circadian oscillator offer insights into how regulating the rhythmicity of the core circadian clock can help manage and treat disease.

7.1 Chronotherapy as a Tool to Guide Drug Delivery

The term chronotherapy, once used to describe behavioral interventions that alter sleep-wake cycles of patients to ameliorate disease pathologies [289], now includes the use of timed drug delivery regimens to respond to circadian changes in metabolic processes or disease pathology. The circadian clock can moderate drug pharmacokinetics in the body at multiple levels (reviewed in [290, 291]). Time of day effects have been quantified for the absorption, distribution, toxicity, tolerability, efficacy, and clearance of many drugs [292–299]. The route of drug administration may also be affected by the circadian clock. For many orally administered drugs that are dependent upon the physiological parameters of the gastrointestinal tract (reviewed in [290]), absorption and distribution are greater in the morning, paralleling the increased gut motility and gastric pH and blood flow at these times [300–302]. Circadian rhythms in absorption also have been shown for lipophilic drugs, with greater absorption observed in the day compared to night [295, 296] reviewed in [298, 303]). For example, the absorption of the lipophilic beta-blocker propranolol is greater in morning than at night compared to the water-soluble beta blocker atenolol which shows no time-dependent differences in absorption [304].

Time of day differences in pharmokinetics have been observed for benzodiazepines, statins, anticoagulants, diuretics, and drugs used to treat metabolic conditions such as hypertension and diabetes [295, 305–314]. For example, a single dose of 2.5 or 5 mg of simvastatin administered in the evening significantly lowered cholesterol in hyperlipidemic patients compared patients that received the drug in the morning or the placebo controls [306]. Similarly, in human hypertensive patients, a singe dose of antihypertensive calcium blocker nifedipine prior to bedtime is more effective at lowering blood pressure while also significantly reducing adverse effects compared to morning dosing [309, 311]. Even drugs such as tricyclic antidepressants used for psychiatric disorders such as bipolar disorder and major depression have time-of-day dependent effects in their efficacy and tolerability [293, 294, 297].

Chronotherapy using temporally targeted treatments has been effectively used for multiple conditions ranging from migraine to rheumatoid arthritis, cancer and headaches [315–324]. Given that the majority of widely prescribed drugs target the products of rhythmic genes [106], chronotherapy may provide a method to improve clinical outcomes or lower adverse effects in a relatively straightforward manner to make the best use of currently available but more research is required to fully understand the scope of its applicability. However, translating circadian data from preclinical models for the treatment of human disease poses challenges. For an in depth analysis of caveats and considerations in the design of chronotherapies and timed drug treatment protocols see [325].

7.2 Small Molecule Modifiers of the Circadian Clock

High throughput screening studies have identified numerous promising synthetic compounds that influence circadian physiology by targeting protein structure and function to optimize cellular rhythms and/or reduce desynchrony between tissues. An example of a small molecule modifier that directly targets a core clock protein is KL001, a carbazole derivative, that significantly reduces BMAL1 activity at the *Per2* promoter, increases activation of CRY proteins by reducing ubiquitination and proteasomal degradation of CRYs 1 and 2, [326]. A role for CRY is suggested in fasting-induced gluconeogenesis [327, 328]. Treating mouse liver cells with KL001 for 18 h significantly reduces glucagon-induced glucose production in a dose dependent manner [326]. Given the association of the CRY gene locus with fasting blood glucose levels and the risk of diabetes in human GWAS studies [329, 330], these results demonstrate the potential of KL001 as a novel approach for developing clock based therapeutics for diabetes. KL001 is also a promising candidate to treat glioblastomas [331]. Stem cells extracted from glioblastoma patients and incubated KL001 exhibit significantly reduced proliferation and cell viability[331]. Mice in which stem cells were transplanted from GB patients and treated with KL001 also survive longer [331].

Unbiased screens have identified small molecules with therapeutic potential that influence core circadian oscillator by acting on post-translational regulators to affect clock timing and period length such as *casein kinase 1 alpha, delta and epsilon*, GSK-3β and AMPK [332]. An example of a small modifier targeting circadian post-translational regulation is the CK1 inhibitor PF-670462. Oral administration of PF-670462 induces robust rhythms in locomotor behavior in arrhythmic *Vipr2*$^{-/-}$ mice and wild-type mice housed in constant light

conditions, an environmental perturbation that disrupts locomotor behavioral rhythms [333]. Additional compounds targeting CK1s have been identified with similar effects including DH4476, CK1–7 and Compounds 1–3 [57, 72, 334, 335]. Interestingly, mutations in CK1δ and CK1ε are directly associated with familial delayed sleep phase syndrome, making these circadian modifiers a potential therapeutic target [336–338]. Another compound, longdaysin inhibits CK1α and CK1δ, thereby stabilizing mPER and lengthening the circadian period as seen *in vivo* in zebrafish studies and *in vitro* in mammalian research [339, 340]. Longdaysin administration in breast cancer grafts dose dependently suppresses Wnt/β signaling and slows tumor growth by repressing cell proliferation [341]. Altogether, these studies suggest that CK1 family members are promising targets for drug development to treat clock-mediated mechanisms in sleep disorders and cancer.

In another example, *glycogen-synthase kinase-3 Beta* (GSK-3β) interacts with many core clock moleules, including the regulation of BMAL1 protein stability, phosphorylation of CLOCK, mPER phosphorylation, and the stabilization of REV-ERB, [61, 70, 342–344], has been linked to numerous chronic diseases including Alzheimer's disease, diabetes, cancer and neuropsychiatric disorders, making it an attractive target for small molecule development [345, 346]. CHIR99021 has been identified as a potent inhibitor of GSK-3 α/β [72] and CHIR99021 is being investigated for potential use in liver cirrhosis [347], male infertility [348], retinal diseases [349] and normal cell regeneration and antitumor activity in diseases such as myocardial infarction and cancer respectively [350, 351].

The circadian nuclear receptor families, REV-ERBs and RORs, can facilitate crosstalk between the circadian clock and other cellular signaling pathways to integrate signals for multiple including development, immunity, cell proliferation and metabolism, and represent some of the most pursued targets for circadian small molecule modifiers [352–354]. Ligands under investigation targeting RORα/γ includes nobiletin (NOB) [355–359], neuroscogenin [360, 361], SR1001[362–364], SR1078 [365–367] and GSK 4112 [368]. Numerous studies have identified potential applications of NOB and its derivatives in a variety of diseases including cancer, cardiovascular diseases, diabetes, neurodegeneration and inflammatory diseases [369–378]. Given the pervasive regulation of physiology and metabolism by the circadian clock and the adverse health impacts associated with circadian dysfunction, it is likely that the next decade will see continued research identifying pharmacological compounds that modulate circadian function.

8. Conclusions

The circadian clock regulates physiological and metabolic processes across tissues. Though the core clock components are well known for their role in generating biological rhythms through transcriptional regulation such as seen in the forebrain, increasing research highlights the extent through which the circadian clock regulates outputs through post-transcriptional, translational and post-translational mechanisms [229]. In the mammalian liver only 22%−30% of cycling mRNAs are in phase with their transcription rhythm suggesting that the other oscillations in the remaining mRNA are generated by post-transcriptional modifications like those described in this review [109, 110, 116]. Circadian regulation of post-transcriptional processes exhibits immense diversity across cell types,

tissues, and species. Given the diversity of circadian regulation at multiple levels post-transcriptionally, the importance of maintaining rhythmicity cannot be overstated. When biological rhythms are comprised, there are numerous implications for human health and disease pathology including cancer, diabetes, obesity, cardiovascular abnormalities, mood disorders and neurodegenerative diseases [18–24]. Advances in proteomic technologies for the detection and quantification of proteins present new opportunities for greater understanding of the molecular signatures of diseases based on protein pathways and the complexity of circadian regulation. While chronotherapeutics may not be applicable to all treatments or conditions, consideration of the circadian clock in disease progression or treatment through timed drug delivery may enhance existing therapies for multiple conditions or diseases [325]. Continuing research is needed to fully elucidate the nuances, complexity and multiple levels of circadian regulation that affect health and physiology especially in the 21st century with all of the daily challenges to proper circadian function.

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Highlights

- Circadian dysfunction adversely impacts health
- Circadian control of post-transcriptional processes regulates mRNA stability
- Circadian clock regulates protein translation at multiple steps
- Protein localization and activity are post-translationally regulated by the clock

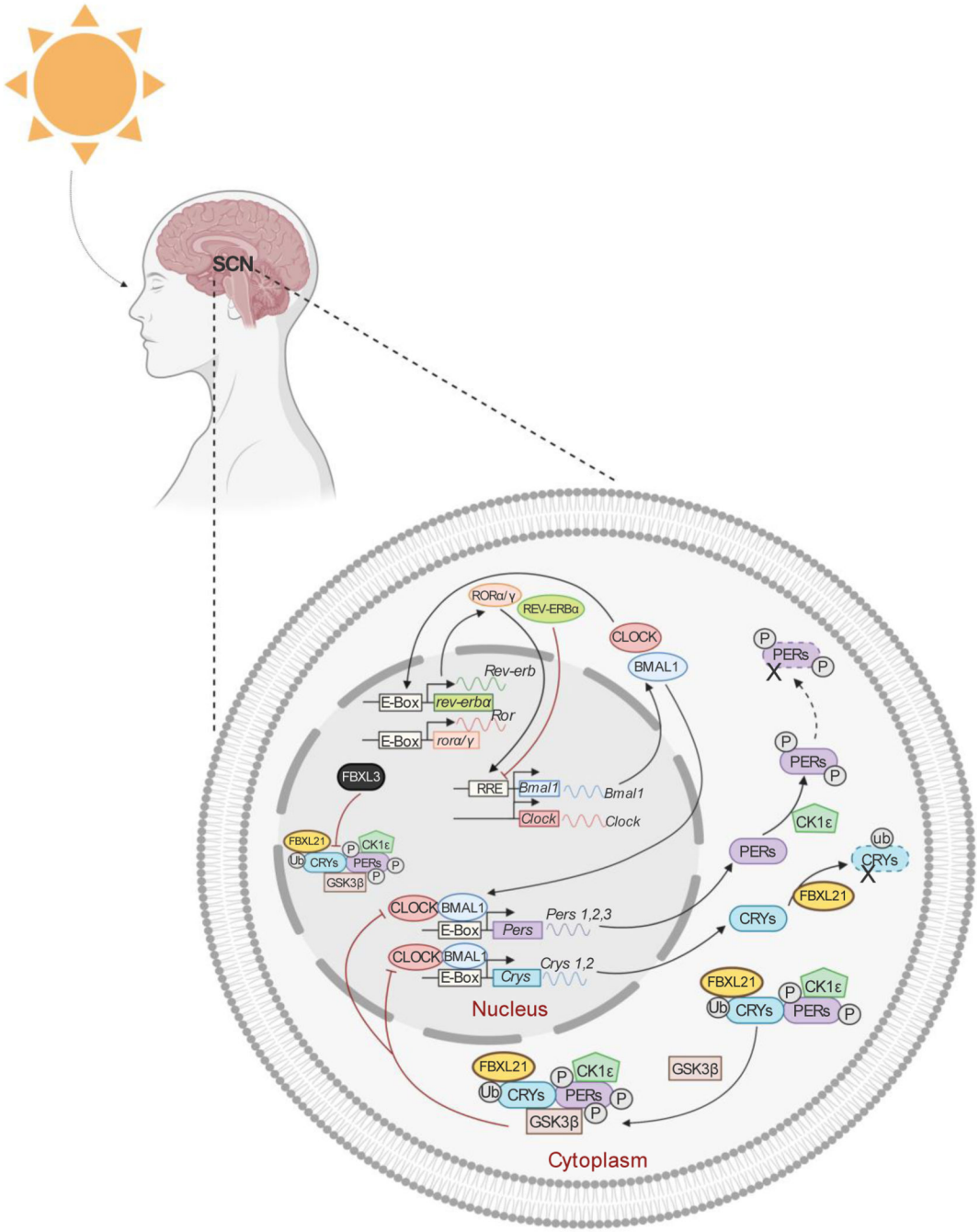

Figure 1.

Molecular transcriptional and translational feedback loops of the mammalian core circadian clock. CLOCK-BMAL1 dimers bind E-box sequences to promote transcription of *mPer, mCry, mREV-ERBα,* and other clock controlled genes. PER and CRY dimerize in the cytoplasm and translocate to the nucleus to suppress their own transcription. CK1ε and GSK-3β facilitate protein-protein interactions and PER-CRY translocation to the nucleus. Rhythmicity in *mBMAL1* expression is promoted by rhythmic RORα/γ and suppressed by REV-ERBα.

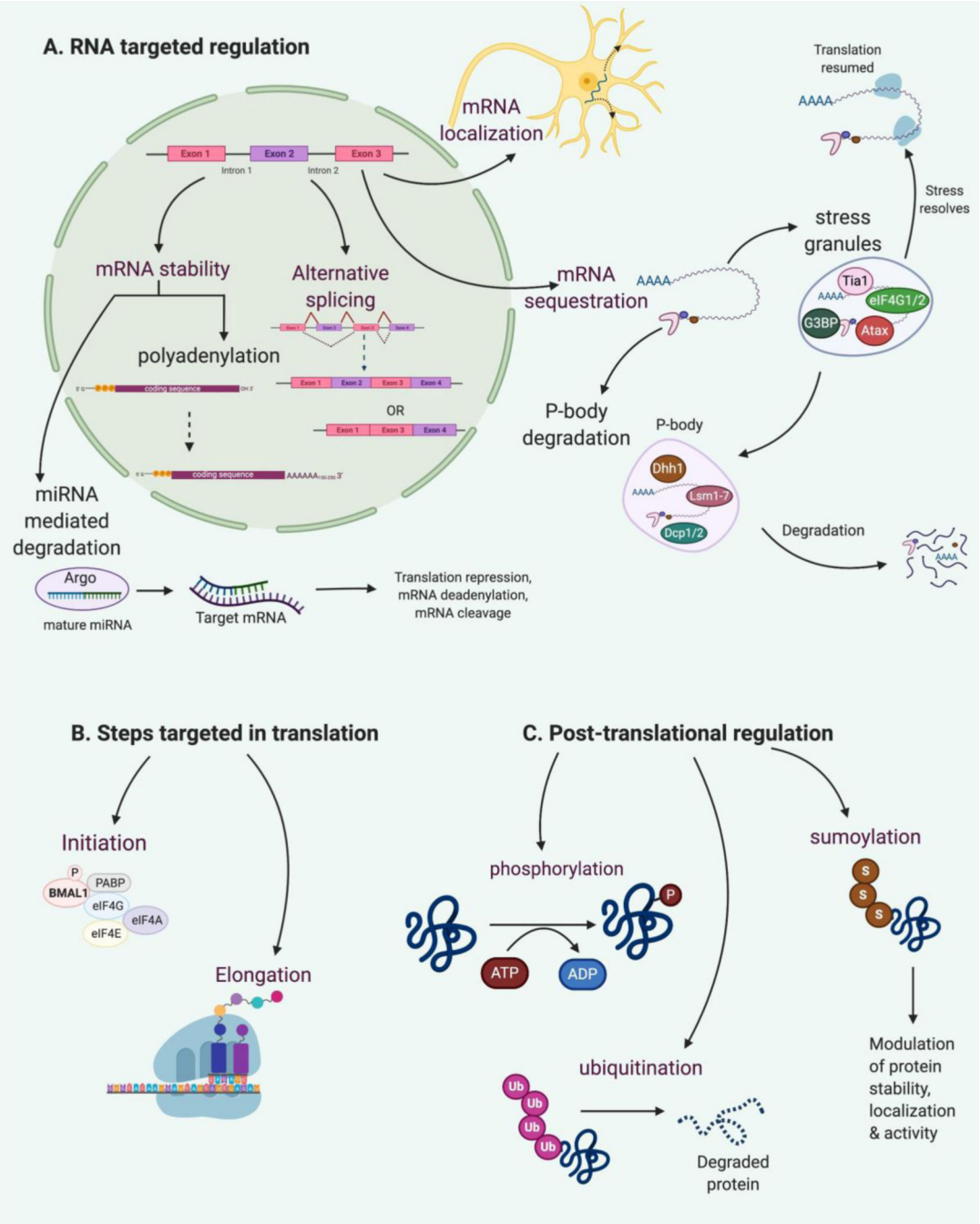

Figure 2. Steps through which post-transcriptional regulation by the circadian clock may occur.

A. The circadian clock targets RNA through alternative splicing, mRNA stability through miRNA mediated degradation, nuclear polyadenylation, cellular localization of mRNA, and availability for translation. B. Circadian clock can influence the initiation and elongation steps in translation. C. Examples of post-translational modifications rhythmically regulated by the circadian clock.

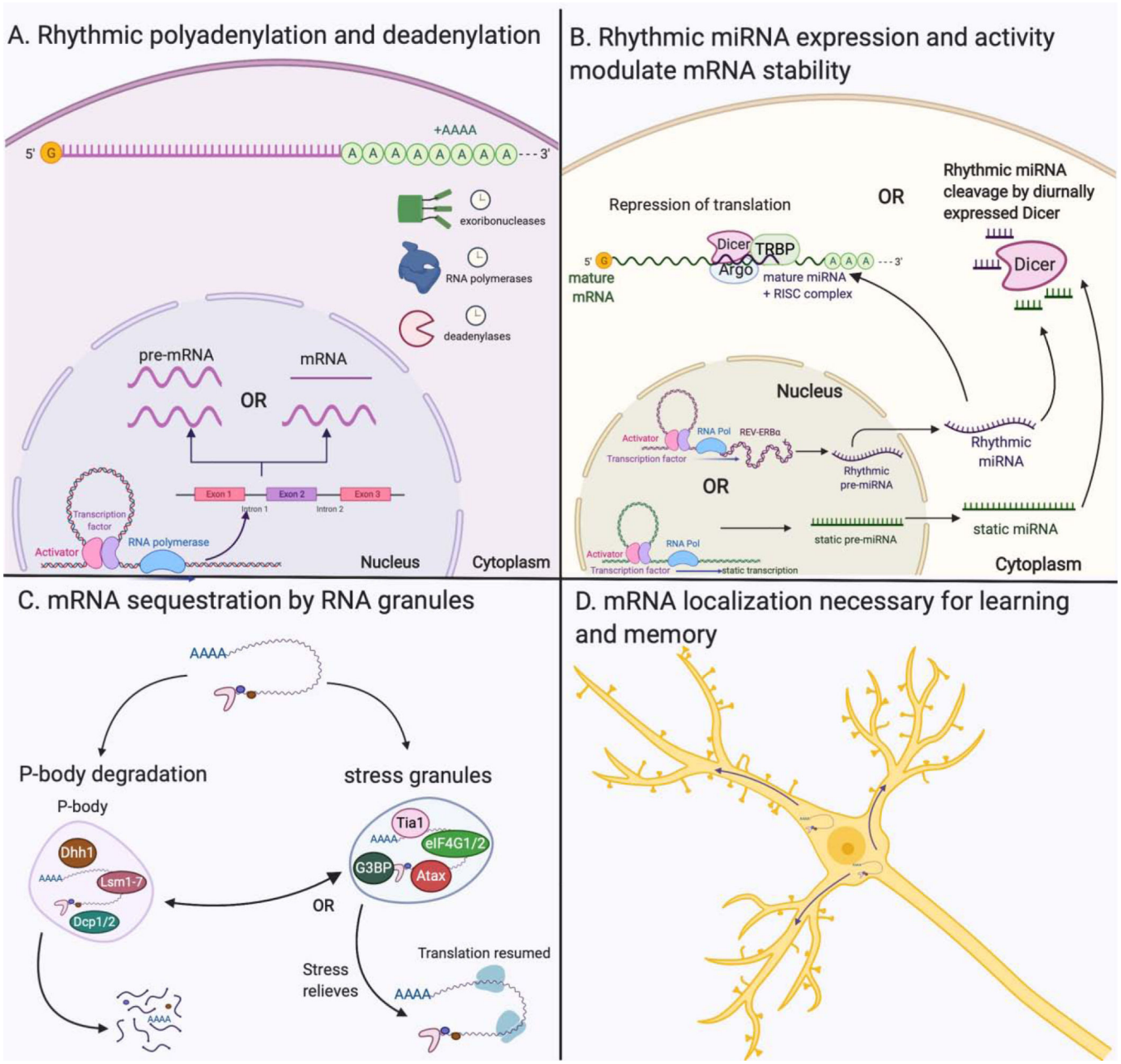

Figure 3. The circadian clock regulates mRNA lifespan, availability and localization.

A. The circadian clock regulates mRNA stability and localization through polyadenylation in the nucleus. For some genes mRNA polyadenylation sites are alternated in a circadian fashion. Cytoplasmic circadian regulation of deadenylation produces rhythmic mRNA degradation rates. B. miRNAs are regulated by the circadian clock at the level of transcription or during processing the rhythmically expressed Dicer. C. The circadian clock can regulate P body and stress granule formation and rhythmically sequester or degrade specific transcripts D. Circadian rhythms have been observed in mRNA localization.

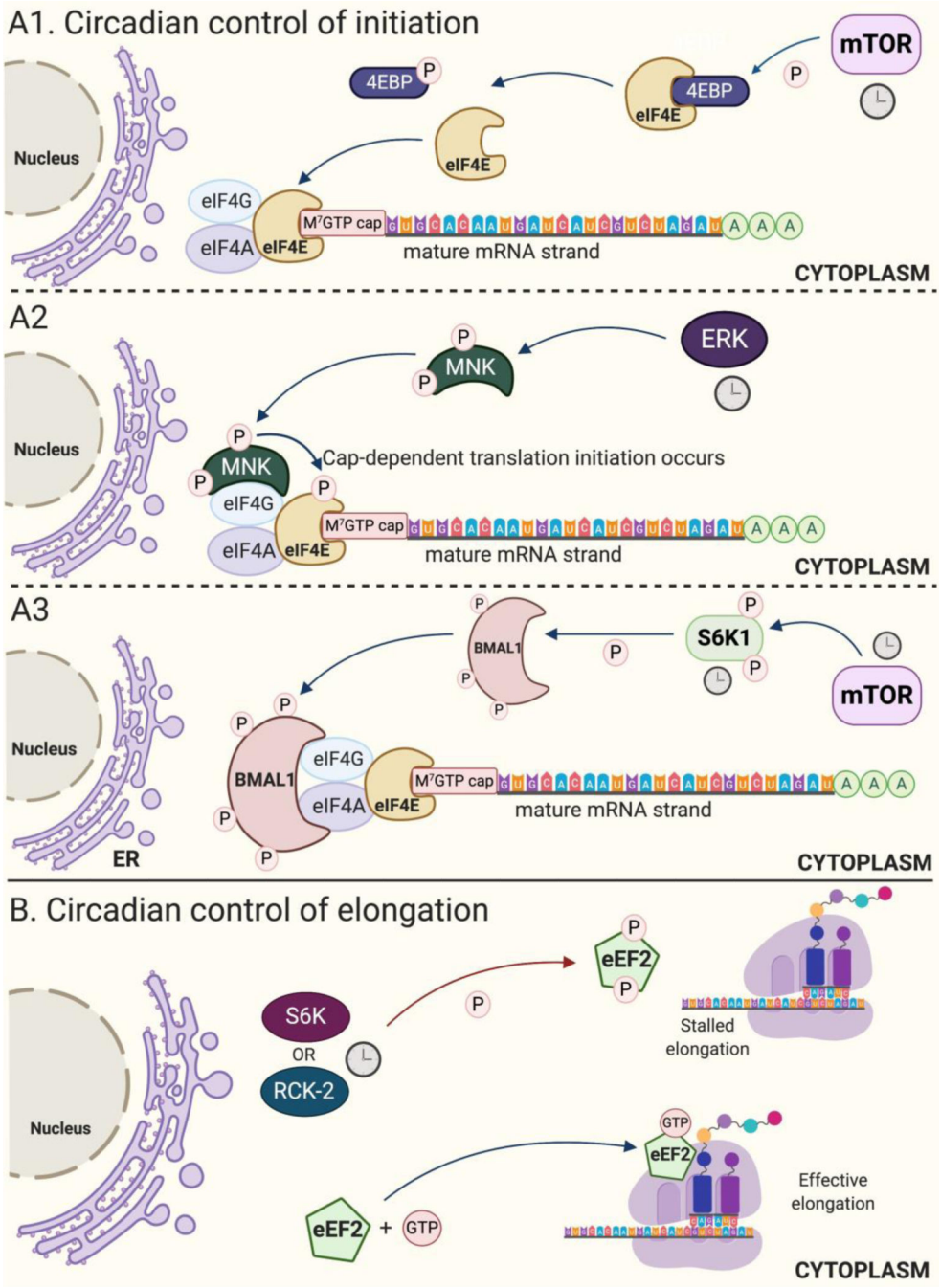

Figure 4. Mechanisms by the circadian clock to regulate translation initiation and elongations.

The circadian clock produces rhythms in multiple initiation pathways including (A1) the phosphorylation of 4E-BP by mTOR, (A2) the phosphorylation of MNK by ERK followed by MNKs phosphorylation of translation machinery and (A3) rhythmic activity of S6K1 that phosphorylates BMAL1 and causes its association with the cap binding complex. B. The circadian clock influences elongation through rhythmic phosphorylation of eEF2.