

# The circadian coordination of cell biology

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Circadian clocks are cell-autonomous timing mechanisms that organize cell functions in a 24-h periodicity. In mammals, the main circadian oscillator consists of transcription–translation feedback loops composed of transcriptional regulators, enzymes, and scaffolds that generate and sustain daily oscillations of their own transcript and protein levels. The clock components and their targets impart rhythmic functions to many gene products through transcriptional, posttranscriptional, translational, and posttranslational mechanisms. This, in turn, temporally coordinates many signaling pathways, metabolic activity, organelles' structure and functions, as well as the cell cycle and the tissue-specific functions of differentiated cells. When the functions of these circadian oscillators are disrupted by age, environment, or genetic mutation, the temporal coordination of cellular functions is lost, reducing organismal health and fitness.

## Introduction

Life evolved with daily predictable changes in light, temperature, and food availability. With sunlight being the primary source of energy for photosynthetic organisms, there was a strong evolutionary pressure to produce carbohydrates during the day and store them for use during “nighttime fasting.” This might have given rise to daily rhythms in metabolism, with anabolic and catabolic pathways operating at different times of the day. Such intense pressure for the temporal regulation of cellular processes in an ~24-h time scale is likely to have contributed to the evolution of circadian oscillators in diverse organisms, ranging from unicellular photosynthetic cyanobacteria to multicellular heterotrophic mammals.

A better understanding of the interactions between the circadian clock and cellular biology in physiological conditions is required to apprehend how their disturbance can lead to pathological development. Disruption of the clock has been associated with human cancers (Fu and Kettner, 2013; Haus and Smolensky, 2013), metabolic diseases (Dupuis et al., 2010; Paschos, 2015),

and aging in mice (Libert et al., 2012; Chen et al., 2014; Fonseca Costa and Ripperger, 2015). Targeting the circadian clock could lead to new therapeutic approaches to treat these diseases. The focus of this review is to provide a broad overview of our current knowledge of the circadian biology of the cell, as defined by cellular activities that show diurnal oscillations that are controlled by the cell's circadian clock. Although we focus on circadian rhythms in mammalian cells, examples from other organisms are discussed to illustrate the variety of mechanisms used to generate circadian oscillations and demonstrate the universality of the control of cell biology by circadian clocks.

## The molecular clockwork of circadian rhythms: Different mechanisms to create 24-h oscillations

**Common properties of different clock systems.** Circadian oscillators are self-sustained, with an ~24-h rhythm under constant conditions, yet possess plasticity to integrate intracellular and environmental changes to temporally regulate a diverse set of cellular functions and optimize adaptation (see text box). Entrainment by external cues (called zeitgebers) such as light, food, or temperature allow clock-controlled processes to be tuned to actual environmental conditions. Circadian oscillators are also temperature compensated, allowing them to function with ~24-h periodicity within a wide range of temperatures. Despite their common properties, clock mechanisms across the phylogenetic kingdoms use different modalities to generate ~24-h oscillations (Fig. 1).

**Cyanobacteria: A protein-based posttranslational oscillator.** In cyanobacteria, the core oscillator consists of three proteins: KaiA, KaiB, and KaiC. KaiC bears three different enzymatic activities: kinase, phosphatase, and ATPase. Even when reconstituted *in vitro* by mixing KaiABC and ATP, the phosphorylation status of KaiC oscillates within a period of 24 h. The rate at which KaiC autophosphorylates and dephosphorylates is modulated by KaiA and KaiB (Fig. 1 A; Ishiura et al., 1998). Although mammalian clocks cannot be reconstituted *in vitro*, such cellular energy (ATP)–dependent modulation of oscillator components is conserved.

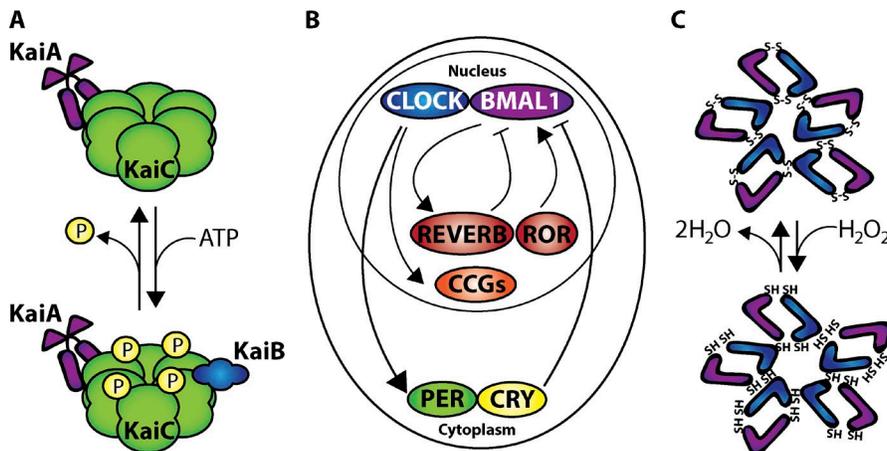
**Eukaryotes: The transcriptional-translational feedback loop.** The circadian oscillator in eukaryotic cells works through interlocked transcription–translation negative-feedback loops in which clock genes activate the transcription of their own repressors. In the mammalian transcriptional-translational feedback loop (TTFL), two

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Abbreviations used: AMPK, AMP-dependent protein kinase; GSK, glycogen synthase kinase; FAO, fatty acid oxidation; HSC, hematopoietic stem cell; NE, nuclear envelope; NER, nucleotide excision repair; PRX, peroxiredoxin protein; RBP, RNA-binding protein; ROR, retinoic acid–related orphan receptor; ROS, reactive oxygen species; SCN, suprachiasmatic nucleus; TTFL, transcriptional-translational feedback loop; UPR, unfolded protein response.

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**Figure 1. Molecular oscillators that generate circadian rhythms in multiple organisms.** Circadian rhythms are generated by autonomous molecular oscillators that cycle between different activation states within a period of ~24 h. (A) In cyanobacteria, the KaiABC complex, made of KaiA, KaiB, and a hexamer of KaiC (green), constitute the molecular oscillator. The complex transitions between a phosphorylated and unphosphorylated state within a period of 24 h. (B) In fungi, plants, and animals, the circadian oscillator is based on a TTFL. In mammals, the TTFL involves the activation of *Per*, *Cry*, *Rev-Erb*, and *Ror* transcription by the CLOCK/BMAL1 heterodimer. Upon translation, PER and CRY proteins form a complex that is imported in the nucleus and suppresses CLOCK/BMAL1 transcriptional activity. ROR and REV-ERB proteins can activate or repress the transcription of BMAL1, respectively. ROR/REV-ERB also act on the transcription

of other clock components and refine their phase of expression. The alternating waves of activation and repression, coupled with the short  $t_{1/2}$  of their respective mRNA and proteins, generate circadian oscillations of clock components. These circadian transcriptional regulators also act on other genes to produce transcriptional oscillation. (C) In bacteria, archaea, and eukaryotes, antioxidant enzymes called PRX cycle between the oxidized (S-S disulfide bond) and reduced (SH thiol bond) state; this cycle can function as a circadian oscillator (see main text for details). CCG, clock-controlled gene.

transcription factors, CLOCK and BMAL1, dimerize and drive the expression of CRY (CRY1 and CRY2) and PER proteins (PER1, PER2, and PER3), which in turn repress the activity of the CLOCK/BMAL1 complex. CLOCK/BMAL1 also activate the nuclear hormone receptors retinoic acid–related orphan receptor (ROR; ROR $\alpha$ , ROR $\beta$ , and ROR $\gamma$ ) and REV-ERB (REV-ERB $\alpha$  and REV-ERB $\beta$ ), which, in turn, regulate *Bmal1* gene expression (Lowrey and Takahashi, 2011; Fig. 1 B). Both TTFL oscillators and KAI protein oscillators drive transcription of a large number of transcripts (clock-controlled genes) and thereby connect the core oscillator to circadian regulation of cellular function.

#### Diurnal and circadian rhythms

Events and processes that repeat themselves within a period of ~24 h are called diurnal rhythms. If they persist in constant condition (i.e., without a signal from the environment), they are called circadian rhythms. Circadian rhythms are born from the activity of an internal biological clock, or “body clock.” The signals that provide environmental cues that can be integrated by the circadian clock are called zeitgebers.

#### Clock and oscillator

A circadian oscillator is a biochemical entity (a protein or a network of proteins) that oscillates between different states within a period of 24 h. In a cell, these oscillations are self-sustained and cell autonomous, which constitute fundamental properties that characterize circadian rhythms. The activity of the cellular oscillators is orchestrated by the master clock, a pacemaker located in the SCN in the hypothalamus.

#### Period, amplitude, and phase

When looking at the circadian oscillation of a given process, the mathematical parameters that characterize a cosine wave can be defined. Hence, the period of the oscillator is the exact length of time from one peak of activity to the next, the amplitude is half the height from the lowest to the highest point of activity, and the phase is the time of the peak using the time at which the light turns on as the reference time (circadian time 0).

#### Gating and phase-locking

When multiple oscillators are present in a cell (e.g., the circadian oscillator and cell cycle), they can interact in various ways. When the activity of one oscillator is gated by another oscillator, certain outputs from the first oscillator can only happen at specific phases (or gates) of the activity of the second. Two phase-locked oscillators oscillate at the same frequency with a constant relationship between their phases.

**Additional clock systems.** Challenging the concept of transcription-based clocks, circadian rhythms in oxidation-reduction of peroxiredoxin proteins (PRX) persist in nucleus-free human RBCs (O’Neill and Reddy, 2011) and in the absence of transcription in the algae *Ostreococcus tauri* (O’Neill et al., 2011; Fig. 1 C). Although the mechanism of PRX oscillation and whether it is ancestral to transcriptional oscillator are still unknown, their discovery has highlighted the daily oscillation in cellular redox state and its relation to TTFL. For example, reduced forms of NAD(H) and NADP(H) promote, whereas the oxidized forms inhibit, CLOCK/BMAL1 DNA-binding activity (Rutter et al., 2001). Similarly, the redox sensor heme regulates the affinity of REV-ERB proteins to the histone deacetylase–nuclear receptor corepressor complex (Yin et al., 2007). Reciprocally, the production of NAD and heme are transcriptionally regulated by the circadian clock (Kaasik and Lee, 2004; Nakahata et al., 2009; Ramsey et al., 2009). This illustrates the reciprocal regulation between the circadian clock and the cellular redox state.

Regardless of the mechanisms of their generation, circadian rhythms in the activity of the clock machinery can affect gene expression. In mammals, clock transcription factors directly control gene transcription, but the circadian timing system also influences additional layers of regulation of gene expression.

#### Circadian regulation of gene expression and protein homeostasis

The circadian clock controls the rhythmic expression of many genes. Additionally, some posttranslational modifications depend on the availability of substrates and moieties for which abundance varies with the time of day. Altogether, the transcription, translation, and posttranslational modification of numerous gene products show daily oscillation, and this is believed to impart metabolic efficiency (Wang et al., 2015).

**Transcriptional regulation: The proximal output of the circadian clock.** In cyanobacteria, the KaiABC oscillator regulates global changes in chromosomes topology, which in turn drives the rhythmic expression of most genes (Woelfle and Johnson, 2006). Similarly, in mammals, up to 50% of the genome shows circadian modulation (Panda et al., 2002;

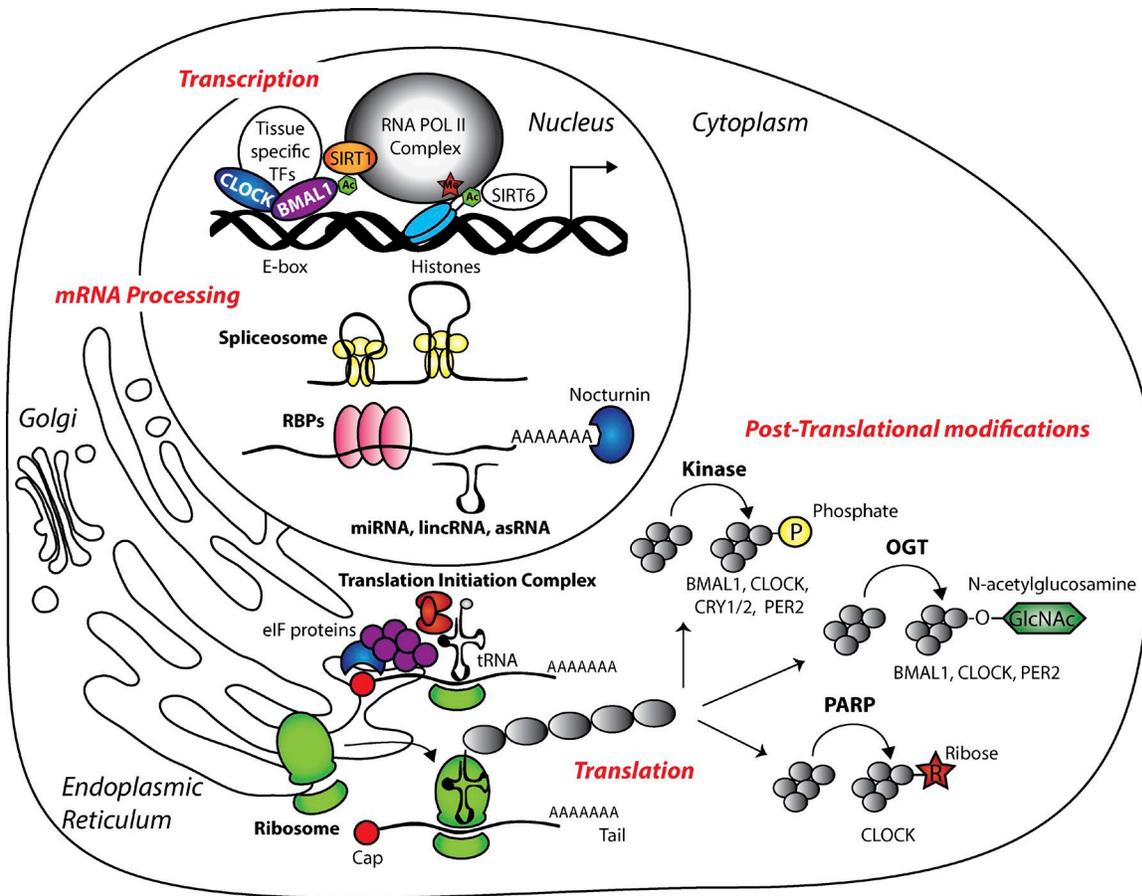


Figure 2. **Many steps of gene expression have a circadian rhythm of activity.** “Omics” technologies, primarily in mouse hepatocytes, show that circadian rhythms are involved in almost all of the steps of gene expression, from transcription to posttranslational modifications of proteins. Between 3 and 16% of the transcriptome displays circadian rhythms. Several mechanisms have been involved in this regulation. The recruitment of clock transcription factors (TFs) associated with tissue-specific transcription factors is circadian. As a result, the activity of the RNA polymerase II (RNA Pol II) is circadian. The architecture of the chromatin as well as histone modifications also show circadian rhythms. The sirtuin family of deacetylases is involved in this regulation. Even in absence of rhythmic transcription, some mRNA oscillate daily owing to general circadian rhythms in mRNA processing. Splicing factor expression and splicing activity varies with the time of day. PolyA tail editing (as by nocturnin) or binding to RBPs affecting mRNA stability as well as modifications by noncoding RNAs also are circadian. Translation also peaks at a certain time of the day. In hepatocytes, this happens in sync with feeding, when the cellular energy level is high. Cyclical changes in both the activation of the translation initiation complex and biogenesis of ribosome contributes to circadian translation. Finally, at the proteome level, posttranslational modifications like phosphorylation (P), poly-ADP-ribosylation (R), and glucose-N-acetylation (O-GlcNAc) oscillate daily. In hepatocytes, they are tuned to cellular energetics because the donors for these posttranslational modifications are directly affected by metabolic activity. asRNA, antisense RNA; lincRNA, long intergenic noncoding RNA.

Storch et al., 2002; Fig. 2), at least in one organ, even though the percentage of oscillating RNA transcripts varies between tissues (from 16% in the liver to 3% in the hypothalamus; Zhang et al., 2014). But only 10 mouse genes, encoding the oscillator components or their direct targets, oscillate in all organs, thus suggesting circadian clock components interact with tissue specific factors to drive locus-specific circadian gene expression (Zhang et al., 2014).

Owing to its ease of access and relevance in metabolism, the mouse liver is used extensively to study circadian gene expression at the cistrome (the cis-acting DNA elements bound by transcription factors), DNA methylome, chromatin modifications (via chromatin immunoprecipitation sequencing), and transcriptome levels. Several studies (DiTacchio et al., 2011; Koike et al., 2012; Le Martelot et al., 2012) revealed daily chromatin level rhythms, along with rhythms in promoter occupancy of circadian transcription factors RNA polymerase II, CREB-binding protein, and P300. This suggests that circadian clock components closely interact with histone modification

enzymes and with the transcription machinery and that these interactions drive daily rhythms in transcription of their target genes. In addition, these studies provide insight into the complexity of circadian regulation, some of which are discussed in the next paragraph.

The cistromes of each oscillator components are overlapping, but not identical. In addition to shared targets, individual clock components, by their interaction with other transcription factors, can exert circadian regulation of different sets of targets to cater to tissue-specific or metabolic needs. For example, CRY proteins repress CLOCK/BMAL1 activity at E-boxes, and they also repress the transcriptional activity of glucocorticoid receptors at promoters harboring glucocorticoid response elements (Lamia et al., 2011). Similarly, REV-ERB proteins compete for binding to ROR response elements to drive rhythmic expression of clock components while they are tethered to the promoters of metabolic genes through interaction with the histone deacetylase–nuclear receptor corepressor complex (Yin and Lazar, 2005). Even the core clock activators CLOCK/BMAL1

interact with SIRT1 and SIRT6 in a locus-specific manner to regulate the expression of different sets of metabolically relevant genes (Masri et al., 2014).

Circadian rhythms in chromatin modification suggest interactions between the clock components and enzymes that write, read, or erase chromatin modification marks. Accordingly, histone lysine methylases and demethylases and histone acetyltransferases and deacetylases interact with the circadian clock components (Yin and Lazar, 2005; DiTacchio et al., 2011; Masri et al., 2014) and participate in circadian chromatin modifications. These chromatin-modifying enzymes use cofactors or substrates including *S*-adenosyl methionine,  $\alpha$ -ketoglutarate, acetyl coenzyme A, and NAD<sup>+</sup>, whose concentration in the liver shows daily fluctuations and is also affected by feeding or fasting (Eckel-Mahan et al., 2012; Hatori et al., 2012; Peek et al., 2013).

**mRNA processing and its relationship with the circadian clock.** A comparison of chromatin marks of transcription, nascent RNA, and processed mRNA has revealed that numerous transcripts are not transcribed in a circadian manner; instead, their mature mRNAs show circadian rhythmicity (Koike et al., 2012; Atger et al., 2015). This is because the circadian clock in mammals rhythmically regulates RNA processing and degradation (Kojima et al., 2011). This renewed interest in posttranscriptional mRNA regulation has led to an examination of the roles of antisense RNAs, miRNA, RNA splicing factors, RNA-binding proteins (RBP), and cis-acting elements in modulating the circadian transcriptome (Kojima et al., 2011; Lim and Allada, 2013; Fig. 2).

In the mouse liver, splicing displays a diurnal rhythm and, in some cases, can be responsible for the cycling of mature mRNA (McGlincy et al., 2012). In fact, many, splicing factors themselves display a circadian rhythm (McGlincy et al., 2012). One of the well-characterized RBPs, nocturnin, is a Poly(A) tail shortening deadenylase, which is under circadian control in mice (Wang et al., 2001). Conversely, the transcript levels of some of the clock genes are modulated by RBPs. Circadian clock and feeding/fasting rhythms drive the daily cycle of core body temperature. Simulated body temperature rhythm can drive daily rhythms in cold-inducible RBP, which confers robustness to CLOCK expression by binding and stabilizing CLOCK RNA (Morf et al., 2012). Several dozen miRNAs in the mouse liver show circadian rhythms in abundance (Vollmers et al., 2012). These oscillating miRNAs can potentially drive rhythms in degradation of target RNAs. Accordingly, in liver-specific DICER knockout mice, miRNAs are largely undetectable (Chen et al., 2013). In the absence of their potential action on RNA degradation, the time of peak level of several mRNAs and the peak or trough levels (amplitude) of some rhythmic transcripts are affected, thus indicating a role of miRNA in fine-tuning circadian rhythms (Du et al., 2014). Similarly, recently discovered antisense RNAs of clock components *Per2*, *Bmal1*, and *Rev-ErbA*, or antisense RNAs of several other rhythmic mRNAs (Vollmers et al., 2012; Zhang et al., 2014) likely impose additional layers of regulation of rhythmic gene expression.

**Translation: Another layer of circadian control.**

Does the circadian transcriptome give rise to circadian proteome? Unbiased qualitative as well as quantitative analyses of mouse liver proteome have revealed that up to 20% of soluble proteins have diurnal patterns of abundance (Reddy et al., 2006; Mauvoisin et al., 2014; Robles et al., 2014). Although initial comparison of circadian transcriptome and proteome from the whole liver found limited overlap, recent studies using

subcellular fractionation of the mouse liver and quantitative proteomics of the purified mitochondria has revealed much higher correlation between cycling transcripts and proteins that encode mitochondria components (Neufeld-Cohen et al., 2016). However, this study also reconfirmed earlier observations that many cycling proteins do not have a concomitant oscillation of their mRNA. Diurnal rhythm in overall ribosome biogenesis (Jouffe et al., 2013) and activation of the translation initiation complex (Jouffe et al., 2013) or in preferential recruitment of certain mRNAs to ribosomes and translation (Atger et al., 2015; Jang et al., 2015; Janich et al., 2015) have been observed in the mouse liver and may explain cycling protein level in the absence of cycling mRNAs (Fig. 2).

**Circadian regulation and posttranslation modification.** Changes in the functional state of proteins often involve posttranslational modifications, including phosphorylation, glycosylation, acetylation, poly-ADP ribosylation, and ubiquitination.

Posttranslational modifications of mammalian clock components is integral to the regulation of the phase and amplitude of the circadian clock (Reischl and Kramer, 2011) as well as represent a mechanism to integrate the metabolic state. Indeed, the activity of many enzymes involved in posttranslational modifications as well as the availability of the modification donors depend on the metabolic state of the cell. For example, in the mouse liver, the fasting/fed state is integrated to the circadian clock through phosphorylation from either cell-autonomous or exogenous/endocrine signals. Both cell-autonomous and endocrine signals act through phosphorylation to integrate fasting or fed state with the circadian clock. Fasting-induced reduction in ATP/AMP activates the cell-autonomous energy sensor AMP-dependent protein kinase (AMPK) and phosphorylation of its target proteins including the circadian repressor CRY1, which primes it for degradation (Lamia et al., 2009). During fasting, glucagon induces CREB activation that drives the transcription of downstream gluconeogenic targets and also controls *Per1* gene expression (Tischkau et al., 2003). In both of these examples, the overall protein levels of AMPK or CREB lack circadian variation, whereas their phosphorylation or activation fluctuates with the metabolic state. Similarly, phosphorylation of glycogen synthase kinase (GSK) 3 $\beta$  oscillates with a peak level coinciding with the fed state, though its protein level remains constant (Iitaka et al., 2005). GSK3 phosphorylation of CRY2 may underlie another mechanism in which fed or fasting state is integrated with the circadian clock.

It is very likely that AMPK, GSK3, and other kinases have daily fluctuation in their activation state and phosphorylation of downstream targets. An unbiased assessment of circadian phosphoproteome still needs to be completed. However, a recent proteomics study revealed that glycosylated proteins are enriched among mouse liver proteins that show robust daily oscillation (Robles et al., 2014), whereas acetylated and ubiquitinated proteins oscillate with low amplitude (peak to trough changes). An example of protein glycosylation is the attachment of *N*-acetylglucosamine (GlcNAc) to serine and threonine amino acids. Because of this residue's specificity, the glucose-sensitive *O*-GlcNAcylation often competes with other modifications. For instance, BMAL1 and CLOCK are stabilized by *O*-GlcNAcylation via the inhibition of ubiquitin-mediated degradation and this maintains the normal periodicity of circadian rhythms in mice and *Drosophila melanogaster* (Kaasik et al., 2013; Li et al., 2013). PER2 also undergoes

O-GlcNAcylation, which competes with its phosphorylation by casein kinase 1 (Kaasik et al., 2013).

Another metabolite that reflects cellular energy state is NAD<sup>+</sup>. Cellular NAD<sup>+</sup> level shows circadian rhythm (Peek et al., 2013) and can affect the activity of posttranslational protein modification enzymes that use it as a cosubstrate. For example, the sirtuin class of deacetylases and poly-ADP-ribosylation polymerases that catalyze the covalent attachment of multiple ribose moieties to arginine residues. Thus, NAD<sup>+</sup> can influence the acetylation and poly-ADP-ribosylation state of nonhistone proteins including some clock components (Asher et al., 2010; Masri et al., 2014). This activity ensures that the circadian clock is recalcitrant to small changes in daily feeding time. In summary, several posttranslational modifications in the liver occur in response to cell-autonomous or extracellular signals that convey the feeding/fasting state. Many of these feeding-fasting-induced posttranslational changes also target clock components and thereby integrate the energy state with the molecular clock.

Although daily variations in transcription, translation, and posttranslational modifications explain molecular underpinning of diurnal rhythms, cellular processes are spatially organized in different organelles. Next, we will discuss circadian rhythms in organelle functions.

### Circadian regulation of intracellular organelle biology

Cellular organelles, including the nucleus, ER, lysosomes, and mitochondria, display diurnal rhythmicity in their structural properties (Chedid and Nair, 1972), functions, and their ability to mount specific stress responses (Fig. 3).

**Circadian rhythmicity in the nucleus.** Primary functions of the nucleus, including transcription and DNA repair, show circadian rhythms (Fig. 3, blue panels). In concert with thousands of loci undergoing circadian transcription in the liver (Zhang et al., 2014), the spatial organization of the chromosomes show a circadian rhythm (Aguilar-Arnal et al., 2013). Additionally, the nuclear envelope (NE) regulates the spatial organization of the genome and transcription by interacting with transcription factors and chromatin-modifying enzymes (Stancheva and Schirmer, 2014). The disruption of nuclear lamina proteins LMNB1, LBR, and MAN1 affects the period of CLOCK protein oscillations in both *Drosophila* cells and human U2OS cells, and MAN1 binds to Bmal1 promoter. This suggests that NE proteins play a role in the circadian control of transcription (Lin et al., 2014).

The nucleus hosts various DNA repair mechanisms. Nucleotide excision repair (NER) responds to single-strand DNA damage and UV-induced DNA adducts. Both the activity and efficiency of this repair pathway exhibits circadian rhythmicity (Kang et al., 2009), as do the protein levels of a key coordinator of NER, xeroderma pigmentosum A (Kang et al., 2010; Bee et al., 2015). Three different repair pathways target DNA double-stranded breaks. All three initially recognize such breaks via the kinase ataxia telangiectasia mutated, which coimmunoprecipitates with the clock protein PER1 (Gery et al., 2006). *Per1* expression levels also affect cell sensitivity to DNA-damaging agents (Gery et al., 2006). Thus, the circadian clock influences transcription, the DNA damage response, and the general architecture of the nucleus.

**Circadian rhythmicity in the ER.** The ER is the first organelle in the secretory pathway that properly sorts and folds ~40% of the proteome that transits through this pathway

(Fig. 3, red panels; Uhlén et al., 2015). The liver has various secretory functions, and hepatic protein secretion has diurnal oscillations (Reddy et al., 2006; Mauvoisin et al., 2014; Robles et al., 2014). The protein components of the secretory pathway, including ribosome docking, ER chaperones, and key components of both ER and Golgi vesicle formation and trafficking, display circadian oscillations that are in sync with liver secretion (Robles et al., 2014). In addition, proper protein folding requires the maintenance of an appropriate redox state in the ER, especially for disulfide bond formation. Circadianly expressed PRX4 plays a central role in hydrogen peroxides detoxification and oxidative protein folding (Zhu et al., 2014).

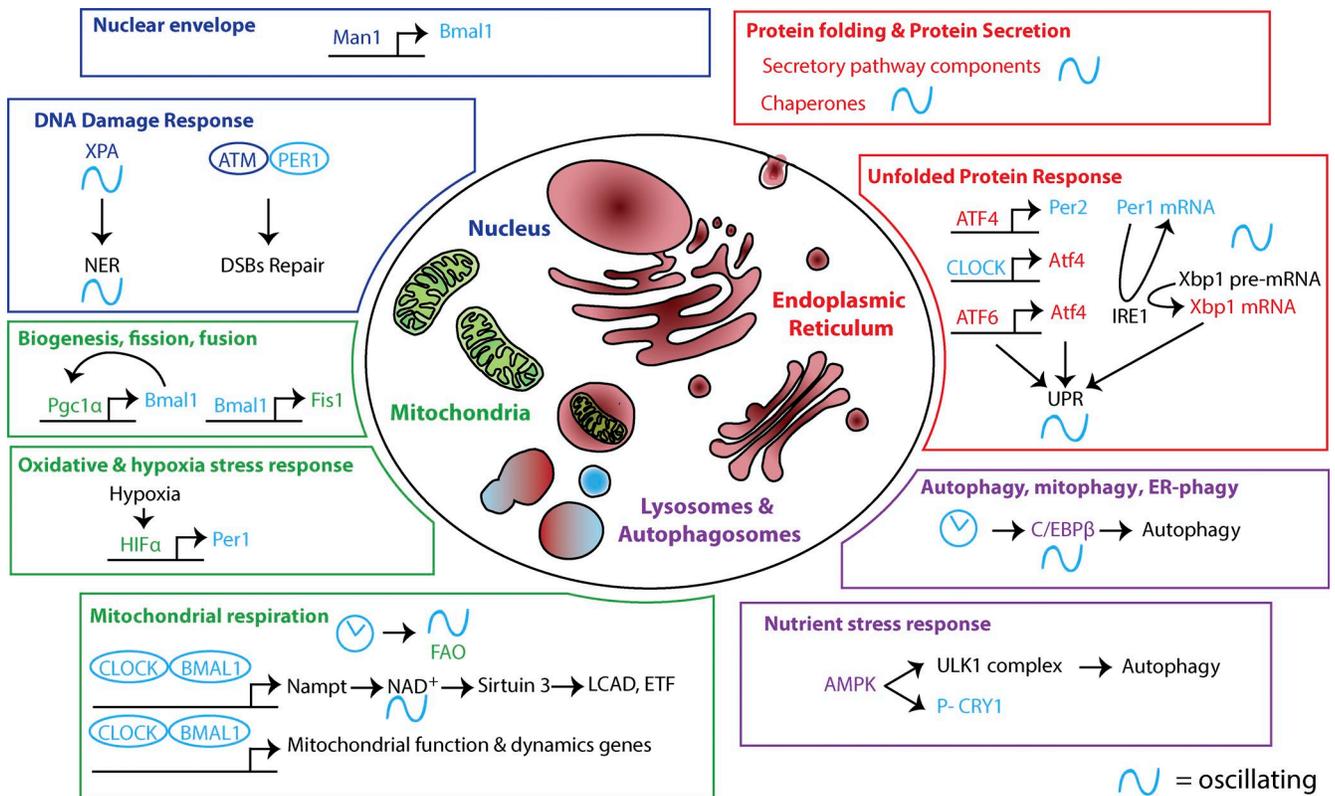
When protein-folding demand exceeds folding capacity, the unfolded protein response (UPR) is activated in the ER to prevent proteotoxicity. Proteins involved in the ER stress response include sensors (ATF6 and the endoribonuclease IRE1a) and effectors (XBP1, ATF4, and ATF6; Oakes and Papa, 2015). ATF4 is a transcriptional target of CLOCK (Koyanagi et al., 2011), and XBP1 splicing by IRE1a follows a 12-h rhythm that is coordinated by the clock machinery (Cretenet et al., 2010). The UPR itself is linked to the circadian clock. For instance, in vitro, *Per1* mRNA is a target of the endoribonuclease IRE1a (Pluquet et al., 2013), and ATF4 is required for the circadian transcription of the *Per2* gene in mouse embryonic fibroblasts (Koyanagi et al., 2011). Temporal coordination of protein folding, unfolding response, and secretion by the circadian clock likely reduces proteotoxicity.

### Circadian rhythmicity in the mitochondria.

Several nutrient and energy metabolic pathways are under circadian regulation, and the redox state impacts the circadian clock (Fig. 3, green panels). Mitochondria, being the hubs for both energy metabolism and redox regulation, show reciprocal regulation with the circadian clock. Mitochondria oxidative capacities display a diurnal oscillation (Bray et al., 2008; Peek et al., 2013). This diurnal rhythm of mitochondria function likely results from direct transcriptional regulation of a large number of nuclear-encoded mitochondrial genes by the core oscillator components (Koike et al., 2012; Jacobi et al., 2015). The expression of these mitochondrial genes is well correlated with daily rhythms in the respective mitochondria proteins (Neufeld-Cohen et al., 2016). Even at metabolite level, the rhythmic production of NAD<sup>+</sup>, which results from the rhythmic transcription of the rate-limiting enzyme through the salvage pathway (nicotinamide phosphoribosyltransferase), couples the circadian clock to mitochondrial oxidative capacity. The activity of key fatty acid oxidation (FAO) enzymes is controlled by acetylation. The deacetylase SIRT3 can modulate the activity of these enzymes, thus driving a circadian rhythm in their activity (Peek et al., 2013).

Mitochondria are also dynamic organelles that undergo fusion, fission, mitophagy, and biogenesis (Chan, 2012) to maintain their functional homeostasis. Diurnal changes in mitochondrial architecture, observed by EM and fluorescent markers, are abolished in Bmal1-deficient mouse hepatocytes (Jacobi et al., 2015). Some of these structural changes may be directly driven by transcriptional regulation of genes involved in mitochondrial fission and mitophagy, with higher expression occurring in the fed state (Jacobi et al., 2015). In the absence of Bmal1, mitochondria are defective and abnormally swollen (Jacobi et al., 2015).

The mitochondrial responses to oxidative stress and hypoxia are also connected to the circadian clock. Indeed, hypox-



**Figure 3. Circadian oscillations in intracellular organelle's structure and function.** Intracellular organelles play critical cellular functions. Recently, their structure and function have been shown to be time-of-day dependent. In the nucleus (blue), the NE protein Man1 binds to Bmal1 promoter, and disruption of NE proteins affects CLOCK oscillations. DNA damage responses (NER and double-strand breaks [DSBs]) also show circadian rhythms because of the circadian oscillations in the level of xeroderma pigmentosum A (XPA) and the interaction of ataxia telangiectasia mutated (ATM) with PER1. In the mitochondria (green), mitochondria biogenesis is circadian owing to the reciprocal interaction between Pgc1 $\alpha$  and Bmal1. Furthermore, Bmal1 controls the expression of Fis1, which plays a major role in mitochondrial dynamics (fission and fusion). Oxidative and hypoxia stress responses have a circadian component. Reciprocally, hypoxia affects the clock via hypoxia-inducible factor 1 $\alpha$  (HIF1 $\alpha$ )-mediated transcriptional control of Per1. The circadian clock is required for oscillation of mitochondrial metabolic activity, in particular FAO. CLOCK/BMAL1 entrains cyclical mitochondrial function and gene expression. Furthermore, they control the expression of nicotinamide phosphoribosyltransferase (Nampt), which drives a circadian rhythm in the level of NAD<sup>+</sup>. Sirt3 activity depends on the level of the cofactor NAD<sup>+</sup>. Because they are targets of Sirt3, the activity of the FAO enzymes long-chain acyl coenzyme A dehydrogenase (LCAD) and electron-transferring flavoprotein (ETF) oscillates. Additional mechanisms likely contribute as well. In the lysosomes (purple), upon nutrient deprivation, the kinase AMPK activates the ULK1 complex, which induces autophagy to recycle cellular energy. AMPK also controls the circadian clock by phosphorylating CRY1. The clock also drives rhythmic expression of CCAAT enhancer-binding protein  $\beta$  (C/EBP $\beta$ ), a master regulator of transcriptional activation of autophagy. In the ER (red), the expression of components of the secretory pathway is circadian. In hepatocytes, this happens in sync with feeding, when liver exocrine and endocrine functions are at a maximum. The activity of ER-resident PRX, which is essential for protein folding and maintaining the redox state in the ER, also is circadian. The strength of UPR activation in the ER is time-of-day dependent. Clock-mediated transcription of ATF4 and the circadian oscillation in Xbp1 pre-mRNA splicing are contributing mechanisms. Reciprocally, the UPR modulates the clock via feedback from IRE1-mediated splicing of Per1 mRNA and ATF4-driven transcription of Per2.

ia-inducible factor 1 $\alpha$  expression, a key player in the hypoxic response, is diurnal, and cells' sensitivity to oxidative stress is time dependent (Magnone et al., 2015).

Damaged mitochondria can be removed by mitophagy, and the cellular mitochondrial stock can be replenished through mitochondrial biogenesis. Peroxisome proliferator-activated receptor  $\alpha$  coactivator 1 $\alpha$  (PGC1 $\alpha$ ) is the master regulator of mitochondrial biogenesis and transcribed in a circadian manner in many metabolic organs. In heart-specific Bmal1-deficient mice, PGC1 $\alpha$  expression is reduced in myocytes. As a result, mitochondrial number and morphology are altered, and these animals develop congestive heart failure (Kohsaka et al., 2014). Moreover, PGC1 $\alpha$  controls Bmal1 expression, and PGC1 $\alpha$ -deficient animals have a disrupted circadian profile of locomotor activity (Liu et al., 2007). Thus, there is extensive bidirectional coupling between the circadian clock and mitochondrial dynamics and function.

**Circadian rhythmicity in lysosomes and autophagosomes.** Autophagy, which consists of the selective engulfment and digestion of cytosolic components, shows circadian modulation (Fig. 3, purple panels). Targets such as macromolecules or organelles are first isolated in an autophagosome, which fuses with a lysosome to form autolysosomes (Yorimitsu and Klionsky, 2007). Autophagy is critical in the starvation state, as micronutrients resulting from autophagic digestion provide nutrition and energy. Acute nutrient and energy deprivation can activate autophagy via the mammalian target of rapamycin and AMPK signaling pathways, respectively. The number of autophagic vesicles produced in hepatocytes and cardiomyocytes shows circadian rhythmicity and was described as early as 1981 using EM (Pfeifer and Strauss, 1981). Recent immunofluorescence studies have confirmed these results, showing that autophagy flux is diurnal, peaking at the end of the fasting phase (Ma et al., 2011). This diurnal rhythm is accompanied by circadian oscillation of autophagy gene expression,

likely caused by the clock-controlled expression of the regulatory gene CCAAT enhancer-binding protein  $\beta$ . The autophagy rhythm can be entrained by feeding cues but can also run as a cell-autonomous process (Ma et al., 2011). Furthermore, the AMPK energy sensor pathway can modulate the clock because AMPK phosphorylates CRY and primes it for degradation when the cellular energy level drops during fasting (Lamia et al., 2009). Thus, hepatocytes undergo daily nutrient and energy stresses that result in the circadian activation of autophagy as a normal physiological response to fasting.

Circadian rhythmicity of organelles' structure and activity suggest that cells segregate their functions both physically and temporally. These findings, in addition to the circadian control of genetic transcription to protein synthesis and modification, suggest that even cell fate could be affected by the circadian clock. In fact, recent studies show that circadian control is important in the cell cycle as well as cellular differentiation from progenitor stem cells.

### Circadian control of cell fate

The circadian clock plays an important role in cell division and differentiation of stem and progenitor cells during development and tissue regeneration in physiological conditions. In contrast, the circadian clock also plays an important role in senescence or cell death that results from the failure of repair mechanisms to recover from damages that occur in the face of intense or prolonged stress.

**Bidirectional coupling between the cell cycle and circadian clock.** During cell-cycle checkpoints, control mechanisms screen for DNA damage and, if necessary, initiate specific DNA-damage repair responses before the cell cycle can resume. In the previous section, we discussed the interplay between DNA repair activation and the circadian clock. In this study, we focus on connections between cell division and the circadian clock. In unicellular organisms that can divide more than once in 24 h, such as the cyanobacteria *Synechococcus elongates*, division only occurs at a certain phase of the circadian clock cycle. This phenomenon is called circadian "gating" (Mori et al., 1996). The number of gates varies with the speed of cell division (Yang et al., 2010). Another way that the circadian clock can influence cell division is by phase-locking. Two oscillating systems are phase-locked when they oscillate at the same frequency and with a constant relationship between their phases. For example, in single-cell cultures of NIH3T3, the cell cycle oscillations and the circadian clock oscillations are phase-locked. In unsynchronized cells, the cell cycle and the circadian clock are phase-locked in a 1:1 ratio of one cell division per 24 h (Bieler et al., 2014; Feillet et al., 2014). However, when the circadian clocks of the cells are synchronized with dexamethasone, subsets of cells display different ratios of phase-locking (Feillet et al., 2014). These results suggest that the coupling between the clock and the cell cycle is flexible and can adapt to environmental changes.

In vivo, the interaction between the cell cycle and the clock has been illustrated in regenerative tissues in various organisms. The clock is required for intestinal homeostasis in flies after chemical damage (Karpowicz et al., 2013) and in rodents (Mukherji et al., 2013). In rodents, the circadian clock gates the division of epidermal progenitor cells at different stages of the regenerative cycle (Lin et al., 2009; Plikus et al., 2013).

Whether in a gated or phased-locked model, the cell cycle and the circadian clock interact, possibly through bidirectional

regulation (Feillet et al., 2014). Various molecular mechanisms underlie this coupling. The circadian clock controls the transcription of several key cell cycle checkpoint regulators, such as the cyclin-dependent kinase inhibitors p21 by Rev-Erb (Gréchez-Cassiau et al., 2008), p16 by Nono and Per (Kowalska et al., 2013), and the activity of the mitosis checkpoint kinase CDK1 by the clock-associated kinase Wee1 (Matsuo et al., 2003). The cell cycle might also reciprocally control the circadian clock. The cell cycle regulator p53 can modulate Per2 expression by blocking the access of the BMAL1-CLOCK complex to its promoter (Miki et al., 2013).

The relationship between the circadian clock and senescence could be explained by the interaction between clock proteins and the mediators of senescence, namely p53 and RB-p16<sup>INK4A</sup> pathways (Kowalska et al., 2013; Miki et al., 2013). For instance, reactive oxygen species (ROS)-induced senescence is increased in Bmal1 knockout fibroblasts (Khapre et al., 2011).

The biological significance of the interaction between the circadian clock and the cell cycles likely reflects the necessity to gate the cell cycle to specific times of the day. In cyanobacteria, the presence of a circadian clock system oscillating in sync with the light/dark cycle during the growth phase confers a survival advantage (Ouyang et al., 1998). Current hypotheses include the timing of DNA replication away from DNA-damaging agents such as UV from solar radiation or more likely away from ROS produced by metabolic activity (Geyfman et al., 2012; Stringari et al., 2015). In mammals, the physiological and evolutionary relevance of this coupling is likely to be more complicated and very difficult to test.

This connection between the cell cycle and the circadian clock in dividing cells raises questions about the nature of this interaction in stem cells, differentiating cells, terminally differentiated nondividing cells, and senescence.

### Is clock silencing a property of stemness?

Mice that lack any circadian clock components are grossly normal at birth (van der Horst et al., 1999; Kondratov et al., 2006), indicating that the circadian system is dispensable for early differentiation. Pluripotent embryonic stem cells do not exhibit circadian oscillation in vitro (Yagita et al., 2010). As embryonic stem cells begin to differentiate, circadian oscillations in transcription appear. When differentiated cells are reprogrammed to induced pluripotent stem, circadian oscillations disappear (Yagita et al., 2010). In vivo evidence from mice suggests that independent cellular clock systems develop during embryogenesis but that a fully mature and synchronized circadian clock only appears after birth (Sládek et al., 2007; Dolatshad et al., 2010). If circadian oscillations are silenced in stem cells, it could reflect that certain factors required to maintain stemness might also functionally dampen the clock. This remains to be shown, but could shed light on the role of the circadian clock in stemness and differentiation.

The circadian clock is also required for the differentiation of some cell populations. For instance, in vivo studies in mice suggest that REV-ERB and ROR $\gamma$  are necessary for the lineage specification of T helper 17 cells (Yu et al., 2013). Bmal1 regulates adipocyte differentiation (Guo et al., 2012), and the adipocyte-specific deletion of Bmal1 leads to obesity in mice (Paschos et al., 2012). In mice, the colony-forming ability of bone marrow granulomonocytes varies with the time of day and is sustained in vitro (Bourin et al., 2002). The rhythm of bone marrow cell cycle and differentiation is sustained in

suprachiasmatic nucleus (SCN)–ablated animals (Filipski et al., 2004), suggesting that a cell-autonomous circadian clock controls the proliferation and differentiation capabilities of bone marrow progenitors.

**Circadian clock control of migratory properties.** The circulation of hematopoietic stem cells (HSCs) in the blood follows a circadian rhythm in both humans and mice. This rhythm is observed at both the steady state and after enforced mobilization with granulocyte colony-stimulating factor (Lucas et al., 2008; Méndez-Ferrer et al., 2008). The egress of HSCs is controlled by the circadian fluctuation of the chemokine CXCL12 produced in the bone marrow. The production of CXCL12 is controlled by the SCN. Nevertheless, the expression level of its receptor, CXCR4, exhibits time-of-day dependency on HSCs, suggesting a potential contribution of the cell-autonomous clock to migratory capacities of HSCs (Méndez-Ferrer et al., 2008).

The circadian regulation of cell migration can affect patient care. Efficient HSC collection is important for the successful engraftment and reconstitution of a recipient's hematopoietic system after transplantation. Cell adhesion and motility can influence harvest and engraftment (Lucas et al., 2008). The time of harvest can also affect HSC yield (Lucas et al., 2008). Furthermore, in mice, the success of HSC transplantation is decreased by 50% when the donor's circadian rhythms are affected by sleep deprivation caused by decreased migratory capacities of the transplanted cells in vitro and in vivo (Rolls et al., 2015). Thus, studies in the circadian field have revealed two parameters that can be taken into account to improve the harvesting and engraftment of donor HSCs.

## Conclusion

The circadian clock, a cell-autonomous timing system, temporally coordinates a range of cellular processes during the lifetime of a cell, from its differentiation to its death. At the molecular level, the circadian clock modulates gene expression at virtually all possible steps, from the control of DNA transcription to the regulation of protein activity by posttranscriptional modifications. At the organelle level, structural and functional properties display a diurnal rhythm. Spatial compartmentalization by organelles is essential to the highly specialized functions of eukaryotic cells. The temporal dynamics of this compartmentalization represent a further refinement of this adaptation. Cells not only physically but also temporally segregate cellular processes. At the cellular level, even cell fate can be affected by the time of the day. Temporal regulation of cellular processes is fundamental for proper cell function and cell health. For example, concurrent activation of some anabolic and catabolic pathways would result in futile cycles of some metabolites; DNA replication is favored at time when DNA-damaging agents like UV light or endogenous ROS production are low.

Circadian clock dysfunction is linked to a variety of ailments such as neurodegenerative and metabolic diseases (Barnard and Nolan, 2008) and cancer (Haus and Smolensky, 2013) and is associated with aging (Libert et al., 2012; Chen et al., 2014; Fonseca Costa and Ripperger, 2015). Not only genetic but also environmental perturbations can cause the circadian system to go awry. For example, disturbance of the circadian clock through shift or night work is associated with higher risk of cancer and metabolic disease (Haus and Smolensky, 2013). Further studies are required to define the permissive or causative role of circadian clock dysfunction in disease development.

Nevertheless, the recognition of the temporal orchestration of cell biology opens new therapeutic avenues. Chronotherapy, chronopharmacology, or chrononutrition could have a significant impact on clinical practice. Conceptually, cells are more susceptible to therapies at time when their target is primed and resistance mechanisms are ebbed, thus the potential success of optimizing the timing of pharmacotherapy (Dallmann et al., 2016). Additionally, using behavioral modifications that can counteract the clock dampening, like time-restricted feeding, can prevent and reverse metabolic diseases in mice (Hatori et al., 2012; Chaix et al., 2014). Thus, the recognition of the temporal orchestration of cell biology opens new therapeutic avenues and a deeper understanding of cellular processes.

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