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Circadian Clock Genes and the Transcriptional Architecture of the Clock Mechanism

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Abstract

The mammalian circadian clock has evolved as an adaptation to the 24-hour light/dark cycle on earth. Maintaining cellular activities in synchrony with the activities of the organism (such as eating and sleeping) helps different tissue and organ systems coordinate and optimize their performance. The full extent of the mechanisms by which cells maintain the clock are still under investigation, but involve a core set of clock genes that regulate large networks of gene transcription both by direct transcriptional activation/repression as well as the recruitment of proteins that modify chromatin states more broadly.

Keywords

mammalian; circadian clock; transcription; clock genes

Introduction

The ~24-hour rotation of the Earth has been a major evolutionary force on the development of intrinsic circadian clocks in most species (Pittendrigh, 1993). In plants that require light for energy production, it is obvious why there is a metabolic link to the day/night cycle (Greenham and McClung, 2015); however, animals have also adapted behavioral changes corresponding with light and temperature cycles to respond to and anticipate energetic demands (Bass and Takahashi, 2010). In addition to rhythmicity in sleep/activity cycles, in mammals there are also many other examples of ~24-hour physiological rhythms, including body temperature fluctuations (Buhr et al., 2010), circulating hormone levels (Lightman, 2016), and metabolism (Green et al., 2008).

An important (and defining) aspect of circadian rhythms is that they persist in the absence of external cues (Pittendrigh and Daan, 1976), yet external cues are important for synchronizing or entraining rhythms. It was originally thought that most circadian rhythms were entrained by light (Pittendrigh, 1960); however light is merely one of the many cues

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that can entrain the circadian clock. Moreover, while research on the mammalian circadian clock was long focused on the suprachiasmatic nucleus of the hypothalamus (SCN) as the central pacemaker (Welsh et al., 2010, Hastings et al., 2018), we now know that the circadian clock itself is actually an intrinsic property of cells in many different tissues (Yoo et al., 2004), with the SCN serving to synchronize “peripheral” clocks (Albrecht, 2012, Mohawk et al., 2012). The specific machinery underlying circadian clocks differ from organism to organism, but at the cellular level they depend on the transcription of sets of core clock genes, underscoring the evolutionary conservation of the core clock mechanism across species (Dunlap, 1999, Bell-Pedersen et al., 2005).

This review will describe what the field has learned about mammalian clock genes and the regulation of circadian gene transcription across tissues, with a focus on how these circadian genes influence metabolic pathways. While it is by no means exhaustive, it provides an overview of aspects of the circadian clock that the Takahashi lab continues investigating, and highlights unresolved questions that remain of great interest to the circadian field.

Cast of Characters: The Mammalian Circadian Clock

The first clock gene, *period*, was discovered through investigations of *Drosophila* mutants with abnormal behavioral cycles (Konopka and Benzer, 1971, Smith and Konopka, 1981, Reddy et al., 1984). These important studies laid the foundation for understanding the molecular basis of the clock, as the *per* gene was found to exhibit a circadian rhythm and the PER protein, itself, was found to regulate *per* gene expression (Hardin et al., 1990). Extending the studies in *Drosophila*, the first mammalian core clock gene, *Clock*, was discovered in a forward genetics screen for mice with abnormal circadian behavioral patterns (Vitaterna et al., 1994, King et al., 1997). The CLOCK protein In mice has features in common with *Drosophila* PER, including a PAS domain (for Per, ARNT, and Sim). However, CLOCK and its binding partner, BMAL1 (Gekakis et al., 1998), also have bHLH domains that allow them to bind DNA directly to regulatory elements (E-boxes) on rhythmic genes to influence their transcription.

The major targets of CLOCK/BMAL1 include other core clock genes that encode the mammalian *Period* ortholog (*Per1, Per2*, and *Per3*) (Shearman et al., 1997) and CRYPTOCHROME (*Cry1* and Cry2) (Kume et al., 1999) repressor proteins. These negative regulators heterodimerize then translocate into the nucleus where they repress their own gene transcription by interacting directly with CLOCK/BMAL1 (Michael et al., 2017, Rosensweig et al., 2018). In addition to this direct transcriptional feedback, the mRNA expression of *Per1/2/3* and *Cry1/2* is also regulated by various mechanisms (Kojima et al., 2011, Lim and Allada, 2013). The degradation of PER and CRY proteins is also regulated by the serine/threonine kinases, casein kinase δ (CK1δ) and CK1ϵ (Gallego and Virshup, 2007, Narasimamurthy et al., 2018), the F-box proteins, FBXL3 and FBXL21 (Hirano et al., 2013, Yoo et al., 2013), and other proteins (Reischl et al., 2007). Once negative transcriptional feedback and post-transcriptional and post-translational regulation of PER and CRY is sufficient to decrease PER/CRY protein levels in the nucleus, repression is relieved and CLOCK/BMAL1 start a new cycle of *Per*/*Cry* gene transcription (Takahashi, 2017).

Since the initial discovery of these core mammalian clock genes, several additional genes and feedback loops have been uncovered, increasing the complexity of the mammalian circadian clock gene network (FIGURE 1). In the second major transcriptional loop, CLOCK/BMAL1 activate transcription of genes for the nuclear receptors REV-ERBα and REV-ERBβ (Preitner et al., 2002). These proteins compete with the retinoic acid-related orphan receptors, RORα, RORβ, and RORγ for binding sites (ROR-binding elements) on the *BMAL1* gene, providing both positive (ROR) and negative (REV-ERB) regulation of transcription (Sato et al., 2004), and, as will be discussed later, they make an important link between the circadian clock and metabolism (Zhang et al., 2015). A third feedback loop involves the D-box binding protein (DBP) and the nuclear factor, interleukin-3 regulated protein (NFIL3, also known as E4BP4) which are regulated by CLOCK/BMAL1 (Ripperger and Schibler, 2006) and CRY1 (Stratmann et al., 2010), and bind to D-box elements on circadian promoters, including RORα and RORβ (Ueda et al., 2005). Together, these feedback loops that make up the "molecular clock" are governed by transcriptional (Takahashi, 2017), post-transcriptional (Kojima and Green, 2015), and post-translational (Gallego and Virshup, 2007) regulatory mechanisms that are sufficient to maintain circadian rhythms; however, external cues are still important for synchronizing rhythms of cells within and across tissues (Golombek and Rosenstein, 2010).

Circadian Rhythms Throughout the Body

Early studies of mammalian circadian rhythms suggested that the brain responds to light cues to regulate sleep/wake cycles and daily behavioral and neuroendocrine rhythms. The discovery of axons projecting from the retina to the suprachiasmatic nucleus of the hypothalamus (SCN) (Moore and Lenn, 1972) gave insights into the central pathway mediating these effects, and subsequent lesioning and transplantation studies established the SCN as a master regulator of circadian rhythms (Moore and Eichler, 1972, Stephan and Zucker, 1972, Ralph et al., 1990). It wasn't until several years later that a specialized population of retinal ganglion cells (intrinsically photosensitive "ipRGCs") containing the photopigment, melanopsin, were discovered (Provencio et al., 2000, Berson et al., 2002, Hattar et al., 2002). The light information transmitted by ipRGCs via the retinohypothalamic tract is sufficient to set the phase of the SCN (Guler et al., 2008), which responds by generating circadian patterns of action potentials (Hastings et al., 2018).

The SCN consists of a heterogeneous cluster of approximately 10,000 neurons in the ventral hypothalamus (Welsh et al., 2010). There are two main subdivisions of SCN neurons, defined based on their expression of the neuropeptides arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP). However, almost all SCN neurons express the inhibitory neurotransmitter GABA (Okamura et al., 1989), and there are several other neuropeptides that are expressed across the SCN, increasing the complexity of these subregions (Abrahamson and Moore, 2001, Hastings et al., 2018). The VIP-expressing neurons in the ventrolateral "core" of the SCN receive synaptic inputs from ipRGCs, and the response of these neurons is thought to be important for maintaining synchrony within the SCN. However, there is recent evidence to suggest that astrocytes within the SCN are also important for maintaining synchrony (Brancaccio et al., 2017, Brancaccio et al., 2019), so the story is likely not so simple.

The response of SCN neurons to incoming light signals is well-characterized and involves the activation of NMDA receptors on SCN neurons, calcium activation of CAMKII, and the activation of gene transcription (Golombek and Rosenstein, 2010). Of the core clock components, the *Per1* and *Per2* genes are particularly responsive to photic entrainment and have been used as a molecular marker for circadian oscillations (Yamazaki et al., 2000, Yoo et al., 2004). In addition, the expression of many other genes in the SCN, including immediate early genes are induced by light (Porterfield et al., 2007).

Aside from the SCN, the circadian clock is also intrinsic to cells in many other tissues (Mohawk et al., 2012). This has been shown in isolated cells (Balsalobre et al., 1998, Yagita et al., 2001, Welsh et al., 2004), in rodent models generated to visualize PER gene expression rhythms from various tissues (Yamazaki et al., 2000, Yoo et al., 2004) and in studies of rhythmic gene expression across different tissues (Panda et al., 2002, Storch et al., 2002, Zhang et al., 2014). As will be discussed in more detail later, these other tissues respond to the signals coordinated by the SCN, but can also entrain to signals other than light (Damiola et al., 2000, Stokkan et al., 2001, Vollmers et al., 2009). Therefore, although the SCN serves to synchronize these “peripheral” clocks, SCN inputs are not required for maintaining circadian timing in these other tissues (Albrecht, 2012, Mohawk et al., 2012, Hastings et al., 2018).

Mechanisms of Circadian Transcriptional Regulation

The main output of the core circadian clock includes genes regulated by CLOCK/BMAL1 (Takahashi, 2017), REVERBs/RORs (Ueda et al., 2002), and DBP (Ripperger and Schibler, 2006), but there is also evidence that PER1 and CRY1/2 regulate expression of genes outside of the core regulatory feedback loop (Lamia et al., 2011). Within the past decade, there has been great interest in understanding how circadian transcription factors drive the rhythmic expression of a variety of genes across different tissues (Koike et al., 2012, Menet et al., 2012). CLOCK and BMAL1 form a much larger complex with histone modifying enzymes (Katada and Sassone-Corsi, 2010) and transcriptional coactivators such as Sirtuin 1 and CBP/p300 (Nakahata et al., 2008, Lee et al., 2010) to open chromatin and promote gene expression (Menet et al., 2014), along with the rhythmic recruitment of RNA Polymerase (Takahashi, 2017).

Taking a single gene (*Dbp*) as an example, one can observe the core clock transcription factors binding to the gene promoter at varying times throughout the day, as well as cyclic changes in chromatin state (Ripperger and Schibler, 2006, Koike et al., 2012). When one starts to look genome-wide, it becomes apparent that there are large-scale changes in transcription and chromosomal organization mediated by the circadian clock (Figure 2) (Koike et al., 2012, Le Martelot et al., 2012, Menet et al., 2012, Vollmers et al., 2012, Takahashi, 2017). While some of these chromosomal changes are associated with promoters or enhancers, recent studies have shown that long-range chromatin interactions also show rhythmic changes (Xu et al., 2016, Kim et al., 2018, Mermet et al., 2018, Yeung and Naef, 2018, Pacheco-Bernal et al., 2019). The field is still just beginning to understand what factors mediate these large changes in topology, but this is an exciting area in circadian research, particularly since chromatin interactions may underlie tissue-specific regulation of

gene expression (Abruzzi et al., 2011, Yeung et al., 2018). Moreover, although most of the genome-wide studies have been performed using liver tissues, the latest evidence suggests that BMAL1 binding is highly variable across tissues and depends upon other tissue-specific transcription factors (Perelis et al., 2015, Beytebiere et al., 2019). Since some of the core clock transcription factors are also differentially expressed in specific tissues, it is likely that there are even more complex interactions of the circadian clock with tissue-specific factors.

Circadian Control of Metabolism

As major outputs of the circadian clock, CLOCK/BMAL1 regulate the transcription of thousands of genes (Koike et al., 2012, Menet et al., 2014, Beytebiere et al., 2019). In the liver there are about 3000 genes that display circadian rhythms in BMAL1 occupancy (Koike et al., 2012), and many of these genes are involved in regulating cellular metabolic pathways (Figure 3). CLOCK/BMAL1 regulation of whole-body metabolism has been noted previously, both in genomics studies and also in *Clock* and *Bmal1* mutant mice, which display obesity and features of metabolic syndrome, such as altered glucose homeostasis, as well as disrupted skeletal muscle metabolism (Turek et al., 2005, Marcheva et al., 2010, Perelis et al., 2015, Harfmann et al., 2016). In addition, the transcriptional targets of REV-ERBs also connect the core clock machinery with metabolic pathways by regulating glucose and fatty acid metabolism (Cho et al., 2012, Delezie et al., 2012, Zhang et al., 2015), and Cry1 expression is associated with a reduction in gluconeogenesis in the liver (Zhang et al., 2010). Post-transcriptional regulation of core clock components also influences circadian gene expression in the liver (Wang et al., 2018), and many recent studies have shown that large-scale changes in the circadian epigenome (Sun et al., 2011, Vollmers et al., 2012, Masri et al., 2013) accompany the changes in metabolic gene expression. There are also several examples of genes involved in metabolic pathways that directly impact the expression of core clock genes (Asher et al., 2008, Lamia et al., 2009, Eckel-Mahan et al., 2013, Furlan et al., 2019). Thus, the core circadian clock is intimately linked to metabolism at the molecular level (Bass and Lazar, 2016, Challet, 2019).

However, links between the circadian clock and metabolism were first made in studies showing that the liver circadian clock could be entrained by feeding time independently from the central SCN clock (Damiola et al., 2000, Stokkan et al., 2001). Since that time, many different feeding paradigms have shown that circadian gene expression in peripheral tissues is altered when the type or timing of food intake is manipulated (Vollmers et al., 2009, Eckel-Mahan et al., 2013, Mukherji et al., 2015). The circadian clock within several peripheral tissues, including the liver, skeletal muscle, and pancreas, is sensitive to hormonal signals and glucose levels (Saini et al., 2013, Dyar et al., 2014, Perelis et al., 2015, Schibler et al., 2015, Harfmann et al., 2016, Ikeda et al., 2018, Crosby et al., 2019), providing mechanisms through which food entrainment could occur. Interestingly, recent evidence suggests that, at least in the liver, the cell-autonomous circadian clock also depends on light synchronization and that food intake *per se* has large effects on transcription independent of effects on circadian gene expression (Atger et al., 2015, Greenwell et al., 2019, Koronowski et al., 2019). Thus, the simplistic view of liver clock being entrained by food, while the SCN is entrained by light, does not give sufficient credit to the complexity of the peripheral clock (Albrecht, 2012, Izumo et al., 2014).

What is clear, is that synchronization of central and peripheral clocks is important for overall health (Di Francesco et al., 2018, Dyar et al., 2018, Challet, 2019), and one of the most salient factors for this circadian synchronization appears to be the timing of food intake (Barclay et al., 2012, Hatori et al., 2012, Chaix et al., 2019). Notably, while caloric restriction paradigms have been successful in improving overall health and extending lifespan (Weindruch et al., 1986), these paradigms inadvertently impose temporal restriction of food intake. This was shown recently by my laboratory in experiments using automatic feeder cages that allowed us to regulate food intake as well as record activity of hundreds of mice simultaneously. We found that, under caloric restriction, mice consolidate their feeding to a 2-hour time interval, thus, self-imposing a time-restricted feeding pattern (Acosta-Rodriguez et al., 2017). These findings strongly suggest that for optimal metabolic performance, the timing of food intake must align with other circadian rhythms (i.e. activity, hormone secretion, temperature fluctuations).

Conclusions/Perspectives

While this review has only been able to touch on some of the highlights of work on circadian transcriptional regulation, the data show that the circadian regulation of gene expression is pervasive and extends far beyond CLOCK/BMAL1 occupancy on gene promoters, including RNA polymerase recruitment, the modulation of chromatin states, chromatin architecture, and nuclear localization. In addition, clock genes and the pathways they regulate are undoubtedly embedded in metabolic pathways as shown both by the effects of the timing of food intake as well as the intrinsic links to metabolic gene networks. Thus, multi-faceted levels of regulation of circadian gene transcription allow the organism to anticipate metabolic demands and optimize energy utilization by consolidating gene expression to certain times of day. Interestingly, emerging results from my laboratory suggest that the circadian regulation of the timing of metabolic events may be critical for maintaining health and extending lifespan. Using circadian gene transcription as a window into the overall synchrony of an organism, we hope to continue to learn about additional factors involved in the circadian regulation of transcription, which will no doubt give us perspective on the underlying basis for many human diseases.

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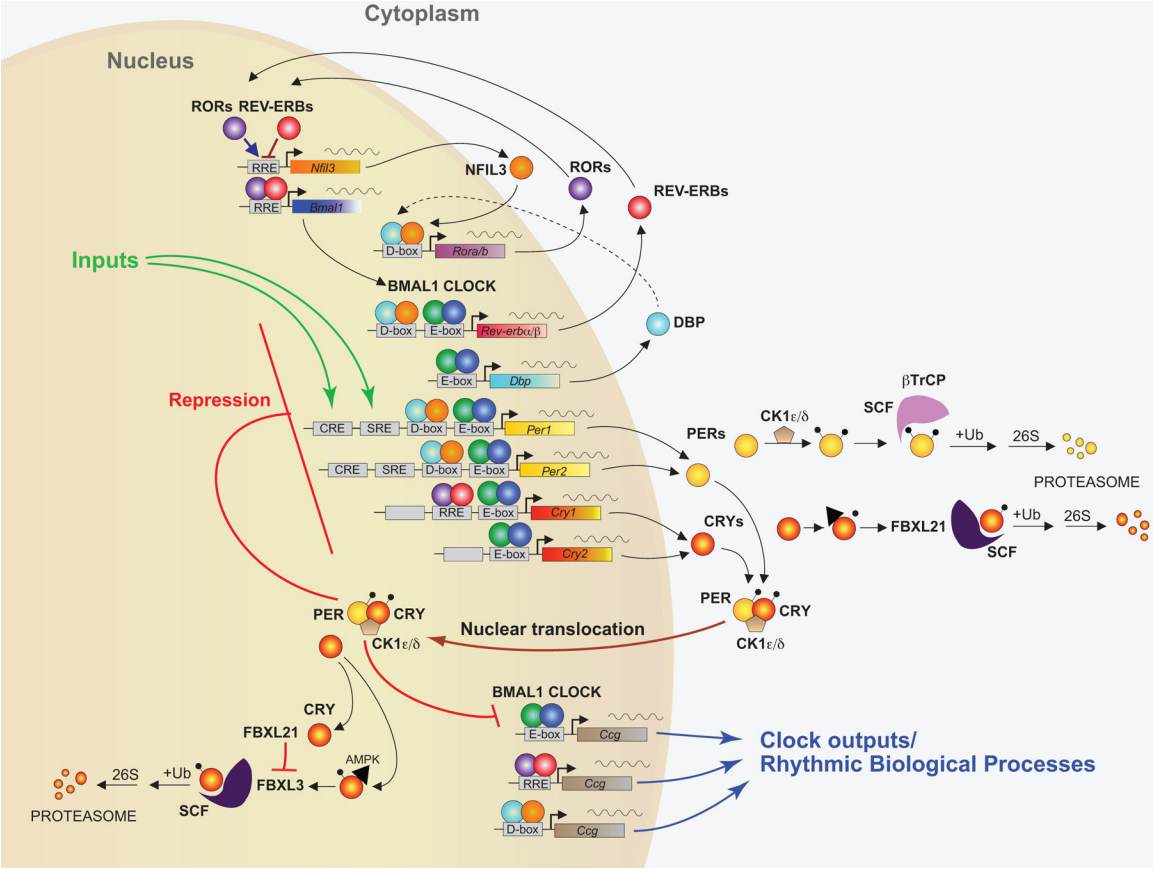

Figure 1: Core components of the mammalian circadian clock.

In the core feedback loop, the transcription factors BMAL1 (green circles) and CLOCK (blue circles) bind to E-box domains on gene promoters, including the genes for *Per1* and *Per2* (yellow) and *Cry1* and *Cry2* (red/yellow). PERs (yellow circles) and CRYs (red/yellow circles) dimerize and translocate to the nucleus after binding with casein kinase δ (CK1δ) or CK1ϵ, where they repress their own transcription. The stability of PER and CRY is regulated both in the cytoplasm and within the nucleus by several proteins, including FBXL21 and FBXL3. In a second feedback loop, CLOCK and BMAL1 also regulate the transcription of genes for the nuclear receptors REV-ERBα and REV-ERBβ (red circles), which compete with the retinoic acid-related orphan receptors, RORα, RORβ, and RORγ (purple circles) for binding to RRE elements on the *BMAL1* gene promoter, providing both positive (ROR) and negative (REV-ERB) regulation of *BMAL1* transcription. A third feedback loop is mediated by CLOCK/BMAL1-mediated transcription of the gene *Dbp* (light blue) and the ROR/REV-ERB-mediated transcription of *Nfil3* (orange). DBP (light blue circles) and NFIL3 (orange circles) dimerize and bind to D-box elements on the promoters of many of the core clock genes, providing additional layers of regulation. In addition, CLOCK/BMAL1, ROR/REV-ERB, and DBP/NFIL3 regulate the transcription of many other clock output genes (Figure modified from (Takahashi, 2017)).

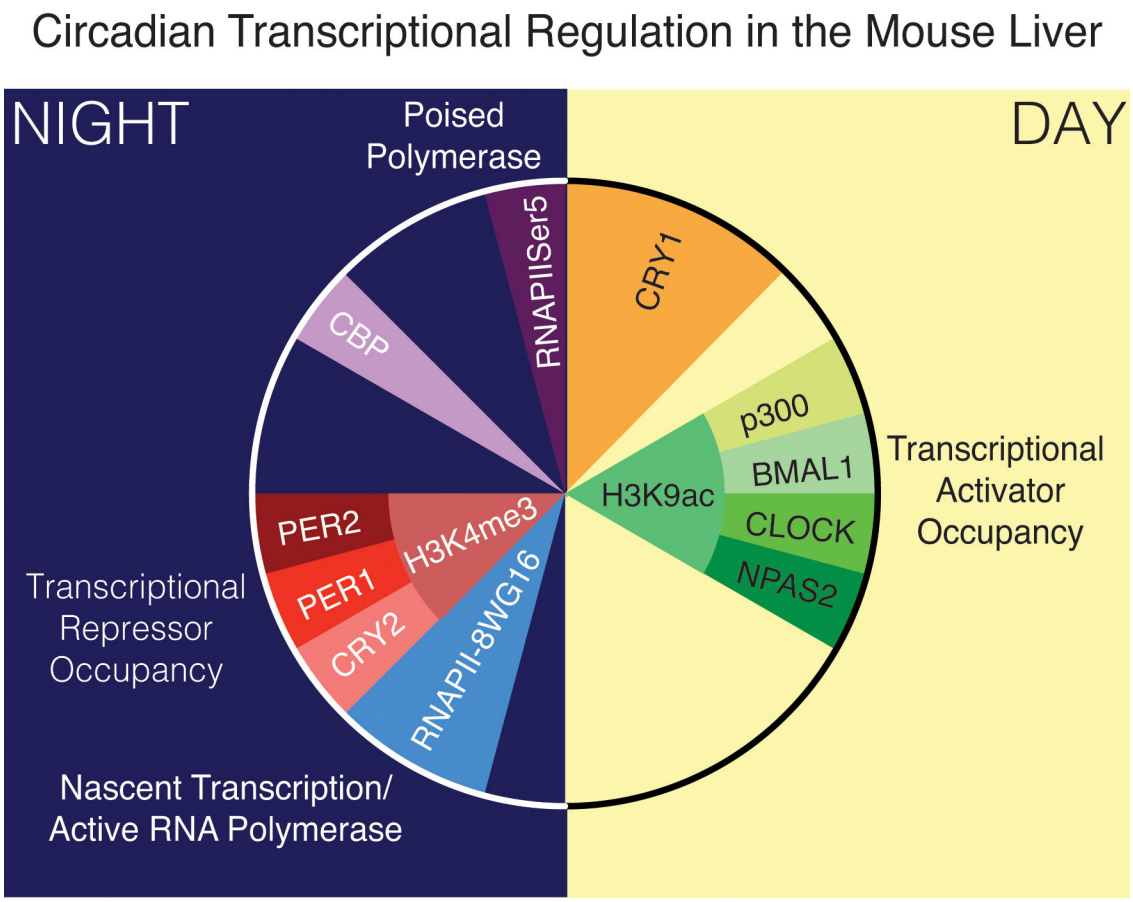

Figure 2: 24-hour depiction of genome-wide circadian transcriptional regulation in the mouse liver.

Peak occupancy of transcriptional activators at gene promoters occurs in the middle of the day and corresponds with a peak in H3K9acetylation. Peak transcription occurs shortly after nightfall, as indicated by activated RNA polymerase binding. Transcriptional repressor occupancy peaks shortly thereafter, and corresponds with a peak in Hk34 tri-methylation. Additional transcription factors and co-factors, such as CRY1 and CBP appear to occupy promoters at different times, and poised RNA polymerase occupancy peaks just at the end of the 24-hour cycle (Based on data from (Koike et al., 2012) and figure from (Takahashi, 2017)).

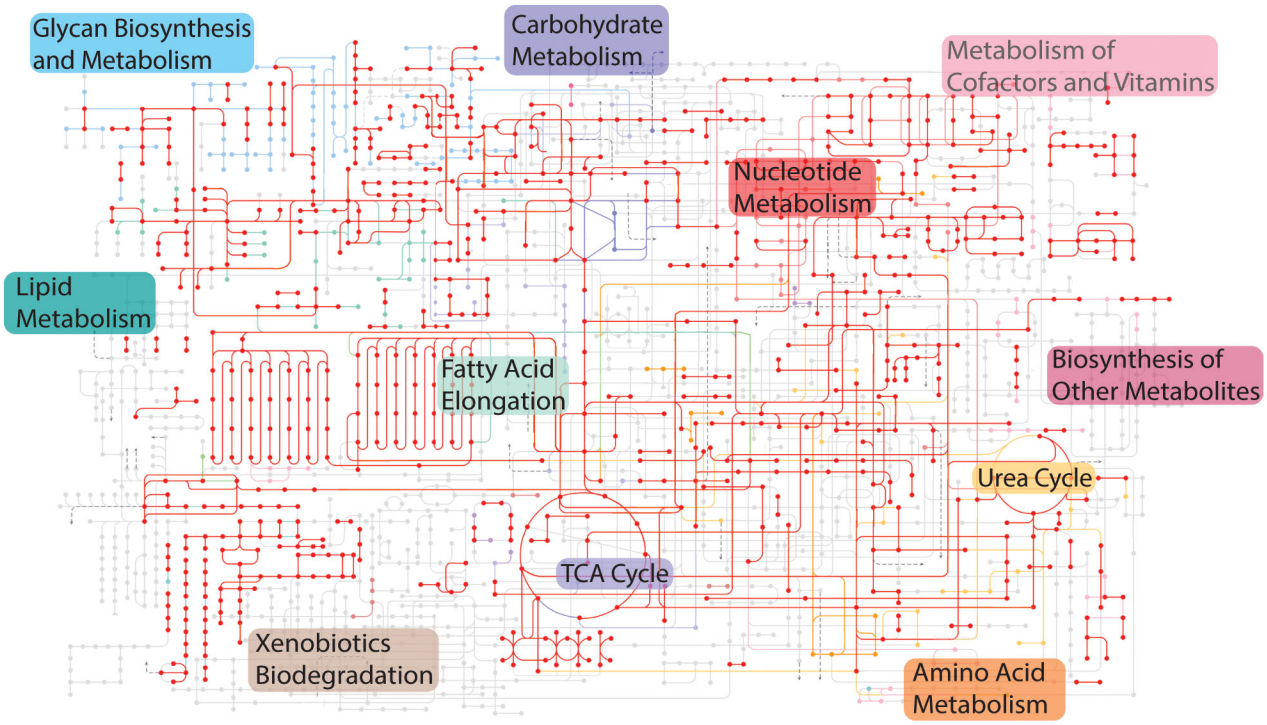

Figure 3: BMAL1 regulation of metabolism.

Overlay of BMAL1 target genes (indicated in red) on diverse metabolic pathways in the liver. BMAL1 occupancy data are from a previously published ChIP-seq dataset (Koike et al., 2012). The original metabolic pathway is from a KEGG analysis (used with permission) and has been simplified to show major nodes (Kanehisa and Goto, 2000, Kanehisa et al., 2017). In KEGG, nodes indicate enzymes and lines indicate connections in metabolic pathways, with colors indicating pathways serving similar functions. The red dots and lines indicate BMAL1 interactions with genes involved in these pathways.