

Chapter 2

Circadian Rhythms and Cellular Networks: A Systems Biology Perspective

2.1 Systems Biology of Circadian Rhythms: A Schematic Overview

The emerging field of systems biology represents the switch of the gear from reductionist approaches toward the recognition and understanding of complex systems and behaviors. Systems biology emphasizes the interactions among individual elements such as genes and proteins. Such focus makes the circadian timekeeping systems a valuable model. This is because the circadian oscillating systems have the features of robustness, periodicity, nonlinearity, adaptation, temperature compensation, as well as synchronization (Ueda 2007; Hogenesch and Ueda 2011). As an essential adaptive function, the organism's internal physiological and behavioral rhythms can be entrained and synchronized to environmental signals.

Figure 2.1 provides a schematic overview of the roles of the clock systems in various psychophysiological processes at different levels. Specifically, the environment (e.g., the light/dark cycle) and lifestyles (e.g., sleep patterns) may influence the central and peripheral clocks. While the suprachiasmatic nucleus (SCN) of the hypothalamus harbors the master clock, the peripheral clocks in the heart, lung, liver, kidney, and muscles also regulate the behavioral and physiological activities. The central SCN clock may orchestrate the circadian oscillators in peripheral tissues with light signals as the foremost synchronizer.

In addition, various rhythmic signals from the hypothalamic–pituitary–adrenal (HPA) axis and immune–endocrine systems such as hormones (e.g., melatonin) and cytokines (e.g., TGF β) also participate in the oscillations. At the molecular and cellular levels, the circadian genes and pathways interact with multiple cellular networks in the regulation of cell cycle, transcription, metabolism, electrical activities, DNA repair, and stress responses (see Fig. 2.1). More details of these processes and their relevant pathogenesis will be discussed in Chaps. 3–7.

As illustrated in Fig. 2.1, the 24-h cycle systems are critical for understanding the biomedical complexity across various spatiotemporal scales (see Chap. 1).

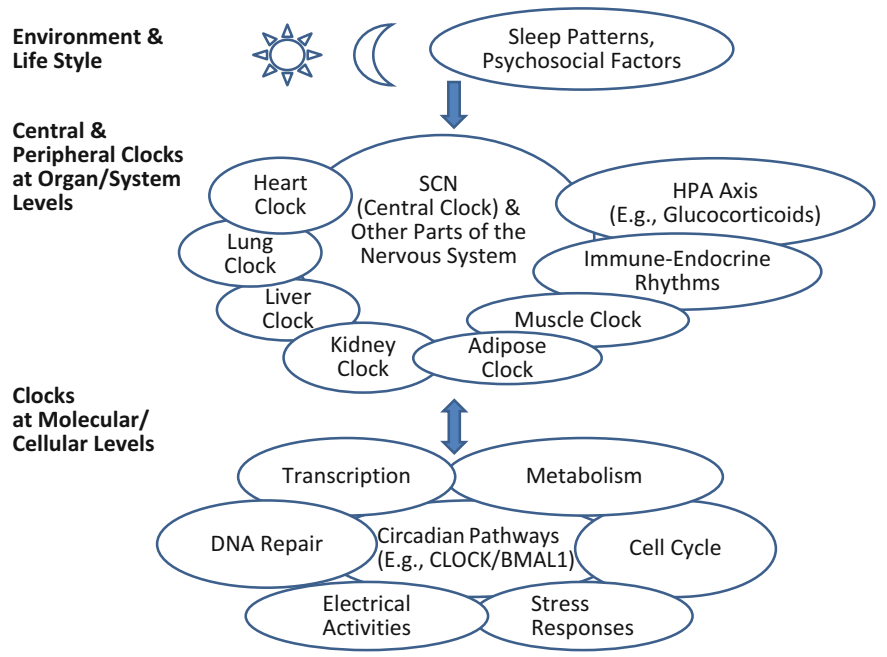


Fig. 2.1 The roles of the clock systems in psychophysiological activities at different levels

The endogenous oscillators control daily rhythms from cis elements to genes, from transcriptional circuits to cellular pathways, from the SCN network to behaviors in various timeframes (Yamada and Forger 2010; Ukai and Ueda 2010; Baggs and Hogenesch 2010). Such intrinsic clocks allow for the adaptation to environmental changes and efficient utilization of energy sources (Zhang and Kay 2010). The adaptive advantages are pivotal for health maintenance and recovery from illnesses.

At the molecular and cellular levels, biological rhythms come from the feedback loops generated in the regulatory networks. Table 2.1 shows some examples of the proteins with core roles in the regulation of the circadian clocks. The relevant interactions and diseases are also included. A more complete list can be found in the Database of Biological Rhythms (DBBR 2015). For example, the protein PER1 is an essential member of the PER/CRY and CLOCK/BMAL1 feedback loops. It is critical for circadian-associated locomotor activity, metabolism, and behaviors. Abnormal functions of PER1 have been associated with pancreatic cancer (Sato et al. 2009), prostate cancer (Cao et al. 2009), buccal squamous cell carcinoma (BSCC) (Zhao et al. 2013), and skin tumorigenesis (Lengyel et al. 2013) (see Table 2.1).

Studies of such rhythmic proteins and networks would help elucidate a spectrum of oscillatory processes including those of p53 and NFκB, as well as the associations between the dynamics of cyclin-dependent kinases and cell cycle (Goldbeter et al. 2012; also see Sects. 2.2 and 2.3). Furthermore, cell-based screening and proteomics examinations would enable the identification of novel

Table 2.1 Examples of circadian-associated proteins and relevant diseases

Core proteins (interactions)	Roles in circadian rhythms	Associated diseases (references)
ARNTL (also known as BMAL1) (CLOCK/BMAL1, PER/CRY)	Circadian feedback loop	Atherosclerosis (Lin et al. 2014); bipolar disorder (Rybakowski et al. 2014); colorectal cancer (Zeng et al. 2014); gestational diabetes mellitus (Pappa et al. 2013)
CLOCK (CLOCK/BMAL1, PER/CRY)	Circadian regulation	Breast cancer (Truong et al. 2014); obesity (Dashti et al. 2015); sleep quality (Vanderlind et al. 2014)
CRY1 (CLOCK/BMAL1, PER/CRY)	Circadian regulation	Chronic lymphocytic leukemia (Lewintre et al. 2009); colorectal cancer (Yu et al. 2013); glioma (Luo et al. 2012); major depressive disorder (Hua et al. 2014)
CRY2 (CLOCK/BMAL1, PER/CRY)	Circadian regulation	Bipolar type 1 disorder, winter depression (Kovanen et al. 2013); cancer (Hoffman et al. 2010); rapid cycling in bipolar disorder (Sjöholm et al. 2010); type 2 diabetes (Liu et al. 2011)
NR1D1 (BMAL1/CLOCK)	Metabolic, inflammatory and cardiovascular processes	Bipolar disorder (Partonen 2012); mood disorders (Kishi et al. 2008); mycobacterium tuberculosis (Chandra et al. 2013)
PER1 (CLOCK/BMAL1, PER/CRY)	Circadian associated locomotor activity, metabolism, behaviors	Buccal squamous cell carcinoma (BSCC) (Zhao et al. 2013); pancreatic cancer (Sato et al. 2009); prostate cancer (Cao et al. 2009); skin tumor (Lengyel et al. 2013)
PER2 (CLOCK/BMAL1, PER/CRY)	Circadian associated locomotor activity, metabolism, behaviors	Colorectal carcinoma (Štorelová et al. 2013); familial advanced sleep-phase disorder (FASPD) (Chong et al. 2012)
PER3 (CLOCK/BMAL1, PER/CRY)	Circadian associated locomotor activity, metabolism, behaviors	Non-small cell lung cancer (NSCLC) (Couto et al. 2014); sleep-loss-related attentional lapses (Maire et al. 2014)
TIMELESS (PER1, PER2, PER3, CLOCK/BMAL1)	Cell survival, DNA polymerase epsilon activity, telomere length, epithelial cell morphogenesis	Bipolar mood disorder (Rybakowski et al. 2014); breast tumor (Fu et al. 2012); lung cancer (Yoshida et al. 2013)

clock components and modifiers (Baggs and Hogenesch 2010). The multi-scale view of circadian rhythms on the basis of systems biology would empower the discovery of novel therapeutic strategies such as chronotherapy (see Chap. 7).

2.2 Circadian Rhythms, Protein–Protein Interactions, and Cellular Networks

As the internal timekeepers, the circadian clocks enable the organisms to adapt to the cyclic environmental fluctuations of light and temperature (Schöning and Staiger 2005). They form the essential cellular timing mechanisms that synchronize vital physiological processes. The major molecular clock elements have periodic expression patterns that are driven by cell-autonomous transcriptional feedback loops. Such oscillation is kept in the central clockwork and transmitted to the downstream genes. Post-transcriptional and post-translational processes are critical for maintaining the normal functions of the clock proteins that interact with other proteins. In another word, the circadian rhythm circuitry depends on the interlocked transcription–translation feedback loops with multiple molecules and complex protein–protein interactions involved.

One of such loops is a positive feedback loop operated by the CLOCK/BMAL1 heterodimer that may start the transcription of target genes with elements of the E-box cis-regulatory enhancer sequences (Ko and Takahashi 2006). In addition, a negative feedback loop contains the rhythmic transcription of the clock genes PER1, PER2, and PER3, as well as the cryptochrome genes CRY1 and CRY2. The combination of PER and CRY proteins can construct a heterodimer that may interact with the CLOCK/BMAL1 heterodimer to inhibit its own transcription (Ko and Takahashi 2006). PER and CRY proteins can be phosphorylated by casein kinase epsilon (CKIepsilon) and result in the starting over of the cycle. Another regulatory loop involves the interactions between the CLOCK/BMAL1 heterodimers and the retinoic acid-related orphan nuclear receptors (RORs). While RORs may activate the transcription of BMAL1, REV-ERBs (also known as NR1Ds) may inhibit the transcription process, forming both positive and negative regulations (Ko and Takahashi 2006).

The activation of several signal transduction cascades may be involved in the circadian regulation, such as the cAMP signaling pathways and mitogen-activated protein kinase (MAPK) signaling pathways (Zhang et al. 2010a; Goldsmith and Bell-Pedersen 2013). These pathways are associated with essential physiological functions such as hepatic gluconeogenesis and stress responses (see Table 2.2). Another important phase shifting-associated component is melatonin that may provide the feedback of the immune responses on circadian timing (Fernandes et al. 2006).

Table 2.2 lists some examples of the protein–protein interactions (PPIs) and cellular pathways associated with the regulation of circadian rhythms. The relevant diseases are also included. A more complete list can be found from the Database of Biological Rhythms (DBBR 2015). The processes and timing of the PPIs are essential for all biological activities and normal regulatory functions. Using systems

Table 2.2 Examples of circadian-associated pathways and relevant disorders

Pathways (interactions)	Circadian associations	Relevant disorders	References
AHR signaling pathway (AHR, BMAL1)	Behaviors, cell proliferation, circadian disruptions	Disorders in behaviors, metabolism, immune responses	Shimba and Watabe (2009)
cAMP signaling pathways (CRY1)	Circadian regulation of gluconeogenesis	Type 2 diabetes	Zhang et al. (2010a)
Dopamine signaling (PER2)	Circadian and interval timing	Impaired interval timing and time perception	Bussi et al. (2014)
Leptin and CCK pathways	Circadian regulation of energy balance	Disorders in food intake and energy balance	Merino et al. (2008)
Leptin signaling pathway (SOCS3, JAK)	Circadian patterns, macronutrient storage, energy balance	Metabolic disorders	Pittsytyn and Gimble (2007)
Leptin signaling pathway (STAT-3)	Circadian rhythms of metabolic activity	Obesity, physical inactivity, higher food intake	Hsuehou et al. (2013)
Melatonin synthetic pathway (TNF α)	Circadian timing in immune responses	Inflammatory responses	Fernandes et al. (2006)
Mitogen-activated protein kinase (MAPK) pathways	Clock cycling	Stress responses	Goldsmith and Bell-Pedersen (2013)
mTOR pathway (Fbxw7)	Circadian oscillations of mTOR activity	Cancer, renal cell carcinoma	Okazaki et al. (2014)
mTOR/4E-BP1 pathway (VIP)	SCN entrainment, synchrony	Circadian disruptions	Cao et al. (2013)
NF κ B pathway	NF κ B oscillation	Inflammatory responses	Wang et al. (2015)
NF κ B pathway (CRY, p53, TNF α , GSK3 β kinase)	Apoptosis	Cancers	Lee and Sancar (2011)
REV-ERB α (NR1D1) pathway (NF κ B, NrF2)	Circadian regulation of cellular metabolism	Lung inflammation, oxidative stress	Yang et al. (2014)
ARNTL (BMAL1)-p53 pathway	Circadian dysfunctions	Cancer	Mullenders et al. (2009)
p53 signaling pathway (PER2)	DNA damage responses	Genotoxic stress responses	Gotoh et al. (2015)
SIRT1-BMAL1 pathway	Tobacco/cigarette smoke caused circadian disruption	Chronic obstructive pulmonary disease (COPD), lung inflammation/injury	Hwang et al. (2014)
Wnt/beta-catenin pathway (PPAR gamma-BMAL1)	Cardiovascular rhythms, circadian variations in BP and heart rate	Cardiac dysfunction, arrhythmogenic right ventricular cardiomyopathy, type 2 diabetes	Lecarpentier et al. (2014)
Wnt pathway (β -catenin, BMAL1)	Circadian and cell proliferation	Premature aging	Lin et al. (2013)
Wnt signaling pathway	Circadian disruptions	Cancer, tumorigenesis, tumor growth	Yasuniwa et al. (2010)

biology approaches and systematic circadian phenotyping, recent studies have found that dynamic circadian PPIs and networks are the key connections among various cellular processes from signal transductions to cell cycles (Wallach et al. 2013).

As shown in the examples in Table 2.2, the temporal regulations of cellular physiology and pathology rely on these dynamical networks. For instance, the proteins CRY, p53, TNF α , NF κ B, and GSK3 β kinase may be involved in the NF κ B signaling pathways associated with apoptosis. Abnormal functions in these interactive networks have been related to cancers (Lee and Sancar 2011; also see Chap. 6). In another example, the leptin signaling pathway is involved in the circadian regulation of metabolic activities with malfunctions related to metabolic disorders and obesity (Hsueh et al. 2013; Merino et al. 2008).

2.3 Two Essential Cellular Rhythms: The Circadian–Cell Cycle Interactions

The two essential cellular rhythms are the cell division cycle and the 24-h circadian pattern. These two coupled oscillators are tightly connected in multiple manners. The ‘gating’ controls of the circadian systems at different checkpoints of the cell cycle and the impact of cell cycle on the biological rhythms indicate that these intertwined bidirectional circuits are critical in physiological and pathological processes (Masri et al. 2013). Multiple regulatory steps and complex feedback loops are involved to warrant such timekeeping. Studies using temperature, genetic, and pharmacological perturbations have suggested that the two interacting cellular oscillators may adopt robust synchronization over a broad range of parameters (Bieler et al. 2014). The circadian regulation of the cell cycle may cover various stages including S, G1 and G1/S, G2 and G2/M (Weigl et al. 2013). The G1/S transition may also influence the local clocks in the proliferating tissues.

Many molecular elements of the cell cycle network are regulated in a circadian way (Gérard and Goldbeter 2012; El Cheikh et al. 2014). The circadian clock is involved in the regulation of the cell cycle and check-point-associated proteins, which in turn also participate in the regulation of the circadian proteins. For instance, the network of cyclin-dependent kinases (CDKS) controls the development of the consecutive stages of the cell cycle (Gérard and Goldbeter 2012). In this network, the generation of the kinase WEE1 that suppresses the G2/M transition can be promoted by CLOCK-BMAL1, the complex essential in the circadian rhythm network. Another element in the circadian network, REV-ERB α (also known as NR1D1), may suppress the production of the CDK inhibitor p21. The CLOCK-BMAL1 complex may also inhibit the generation of the oncogene c-MYC, while c-MYC may enhance the production of G1 cyclin (Gérard and Goldbeter 2012).

In addition, the multifunctional nuclear protein NONO serves as not only a partner of the circadian PER proteins, but also the linkage between the circadian gating and the cell cycle. Such connection has been found essential for wound healing in mice (Kowalska et al. 2013). NONO may interact with the p16-Ink4A cell cycle checkpoint gene and be involved in the circadian activation that is PER-dependent.

On the other hand, this activation as well as the circadian cell cycle gating may not happen with the depletion of NONO or PER (Kowalska et al. 2013). The loss of NONO may lead to defective wound repair. Such effects indicate that NONO may have a key role in the coupling of the cell cycle to the circadian clock.

The circadian–cell cycle interactions may also affect the cell population growth rates. The coupling of the circadian clock and cell cycle may be mediated via the protein WEE1 and involved in a proliferating cell population (El Cheikh et al. 2014). Mutations in the clock genes CRY1 and CRY2 may lower the growth rate of cells, while PER2 mutations and BMAL1 knockouts may promote it for autonomous stages of the cell cycle shorter than 21 h (El Cheikh et al. 2014). The combination of a molecular model with a population model has been proposed to explain the impacts of the circadian system on the cell population growth (El Cheikh et al. 2014).

Furthermore, alterations such as DNA damage may affect both of the circadian patterns and the cell cycle. The circadian proteins PER1 and TIMELESS (TIM) may interact with the cell cycle checkpoint components including ataxia telangiectasia mutated (ATM)-checkpoint kinase 2 (CHK2) and ataxia telangiectasia and Rad3-related (ATR)-CHK1. Such interactions are critical for the activation of CHK1 and CHK2 in DNA damage (Kondratov and Antoch 2007). In addition, in both normal and stress states, the complex of TIM and TIM-interacting protein (TIPIN) may interact with the DNA replication components to control the DNA replication activities (Kondratov and Antoch 2007).

The circadian regulation of cell cycle may provide the molecular and cellular connections between the rhythmic patterns and problems such as aging and cancer. Factors such as the circadian effects on cell proliferation, metabolism, stress responses, as well as DNA repair may all be involved in the cellular pathogenesis of aging-associated disorders and carcinogenesis (Khapre et al. 2010; also see Fig. 2.1). The circadian genes including PERs, BMAL1, and CRYs may have pivotal roles in such mechanisms.

For example, transgenic mice with mutations in the clock genes have been found to develop cancer and premature aging, as genome integrity and cell proliferation are critical in such disorders (Khapre et al. 2010). In addition, studies have identified circadian variations in the expression of genes associated with genotoxic stress responses (Kondratov and Antoch 2007). These mechanisms may have implications for chronotherapy to promote drug efficacy and tolerance by adjusting the administrative time (see Chap. 7).

2.4 Systems Biology Approaches for Modeling the Circadian Networks

In conclusion, systems biology studies would allow for the integrative description of the individual elements and interactive networks within and among cells toward the understanding of the dynamical principles (Ueda 2007; De Haro and Panda 2006). Both experimental and theoretical modeling methods can be applied to map the interactions at the genome-wide scale to explore the regulatory networks underpinning cellular rhythms.

Systems biology methods such as genetic perturbations and computational modeling within each scale may contribute to the advancement of systems and dynamical medicine (see Chap. 1). Approaches including gene expression profiling and proteomic analyses are re-shaping our understanding of the circadian system. Perturbation analysis and synthetic methods may enhance our knowledge of the mechanisms underlying the transcriptional regulations and robustness of the oscillators (Baggs and Hogenesch 2010).

Such approaches can be applied to identify patterns at various levels including the expression patterns of circadian genes. For example, by analyzing RNA data, promoter elements, and phase information, a circadian transcriptional network was developed with the discovery of the gene-expression patterns around the 24-h clock (Hayes et al. 2005). Factors associated with circadian expression were presented in the network, especially the transcriptional circuits including the REV-ERB/ROR-regulatory element (RRE).

In addition to experimental methods, theoretical frameworks can be applied for studying the dynamical systems using systems theory and nonlinear dynamics. Such frameworks can be useful for modeling the dynamic properties of the “network motifs” and interactions in the molecular and cellular circuits (Zhang et al. 2010b). The network motifs of the feedback and feedforward loops such as those described above are essential for cellular functions including homeostasis and oscillations. The elucidation of the functional networks may help improve the understanding of the complex cellular responses to environmental changes and therapeutics (Zhang et al. 2010b). Such understanding may contribute to the discovery of systemic biomarkers and strategies in chronotherapy (see Chap. 7).

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