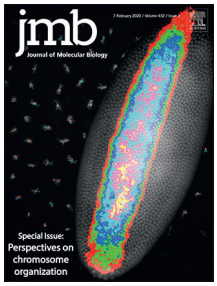

Molecular Links between the Circadian Clock and the Cell Cycle

Elham Farshadi, Gijsbertus T.J. van der Horst and Inês Chaves

Department of Molecular Genetics, *Erasmus University Medical Centre, Rotterdam, the Netherlands*

Correspondence to Inês Chaves: *Department of Molecular Genetics, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. i.chaves@erasmusmc.nl*
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Abstract

Circadian control of cell division is well established in diverse organisms. Recent single-cell studies on mouse fibroblasts have shown that the circadian clock and cell cycle systems are robustly phase-coupled in a bidirectional manner. In healthy cells, coupling of clock and cell cycle results in timed mitosis and rhythmic DNA replication. However, little is known about the interplay between these two oscillators in cancer cells, which often display de-regulated cell proliferation and circadian gene expression. Here we review the molecular organization of the circadian clock and the cell cycle, as well as the reciprocal interaction between the circadian clock and the cell cycle in normal and in cancer cells. Understanding how the circadian clock and cell cycle are coupled in cancer cells will be instrumental to optimally take advantage of chronotherapy in cancer treatment, as efficiency of therapy benefits from asynchrony in timed mitosis between the host and the malignant cells in order to predict the optimal time of treatment.

The Circadian System

As a result of the earth rotation, organisms are exposed to environmental changes (e.g. light–dark and temperature cycles) that are associated with the day and night. Most organisms have developed an internal timing system with a near (circa) 24-h (dies) rhythm that is referred to as the "circadian clock" [1]. This biological clock regulates timing of cellular processes in order to optimize and adapt physiology and metabolism to the time of day [2,3]. One important process that is connected to the circadian clock is the cell cycle, as will be discussed in detail in the following sections.

The circadian clock system is conserved among all the species from prokaryotes, such as cyanobacteria [4,5], to eukaryotes such as mammals [6]. The mammalian circadian system consists of a central clock in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks in almost all other cells and tissues of the body [7]. In order to stay in phase with the day/night cycle, the master clock is entrained by external environmental cues, notably light [8–10]. The photic information is received by photoreceptors located in the retina and is transmitted to the SCN*via* the retinohypothalamic tract [11]. The SCN neurons keep synchrony and stay coupled to each other through synaptic connections [12]. This intercellular coupling between the SCN neurons is critical for robust circadian rhythmicity in output processes. Accordingly, synchronizing signals are transmitted from the SCN clock to the peripheral clocks *via* neural and hormonal stimuli to achieve coherent rhythms in the entire organism [13,14].

Importantly, circadian rhythmicity persists in isolated cells *in vitro[15,16]*. However, in contrast to cultured SCN cells, the oscillation of peripheral tissues and cells in culture dampens in time and can be re-synchronized using serum or other synchronizing agents [17,18]. *In vivo*, these peripheral cellular clocks receive entraining signals from the SCN to maintain synchrony [14]. Interestingly, increasing evidence demonstrates an independent

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synchronization of peripheral clocks *via* light directly, or *via* organ to organ communications [19,20].

The Molecular Circadian Oscillator

The peripheral and SCN clocks share the same molecular mechanism to generate circadian oscillations, which is based on auto-regulatory transcription–translation feedback loops composed of positive (activating) and negative (inhibitory) elements [6,21,22]. The transcription–translation feedback loop drives cyclic expression of clock genes and proteins with a period of approximately 24 h. The activator (positive) elements of the circadian oscillator are Brain Muscle Arnt-Like protein-1 (*Bmal1*) and Circadian Locomotor receptor Cycles Output Kaput (*Clock*) ([21,23,24] (Figure 1). CLOCK and BMAL1 heterodimerize to form an active transcription factor that binds to the Enhancer-box (E-box) elements (5′-CACGTG-3′) of their target genes. Period (*Per1, Per2*) and Cryptochrome (*Cry1, Cry2*) comprise the negative elements of the circadian machinery ([21,23,25]. Transcription of *Per* and *Cry* genes is induced by the CLOCK/BMAL1 complex. CRY and PER proteins are synthesized, accumulate in the cytoplasm, and after

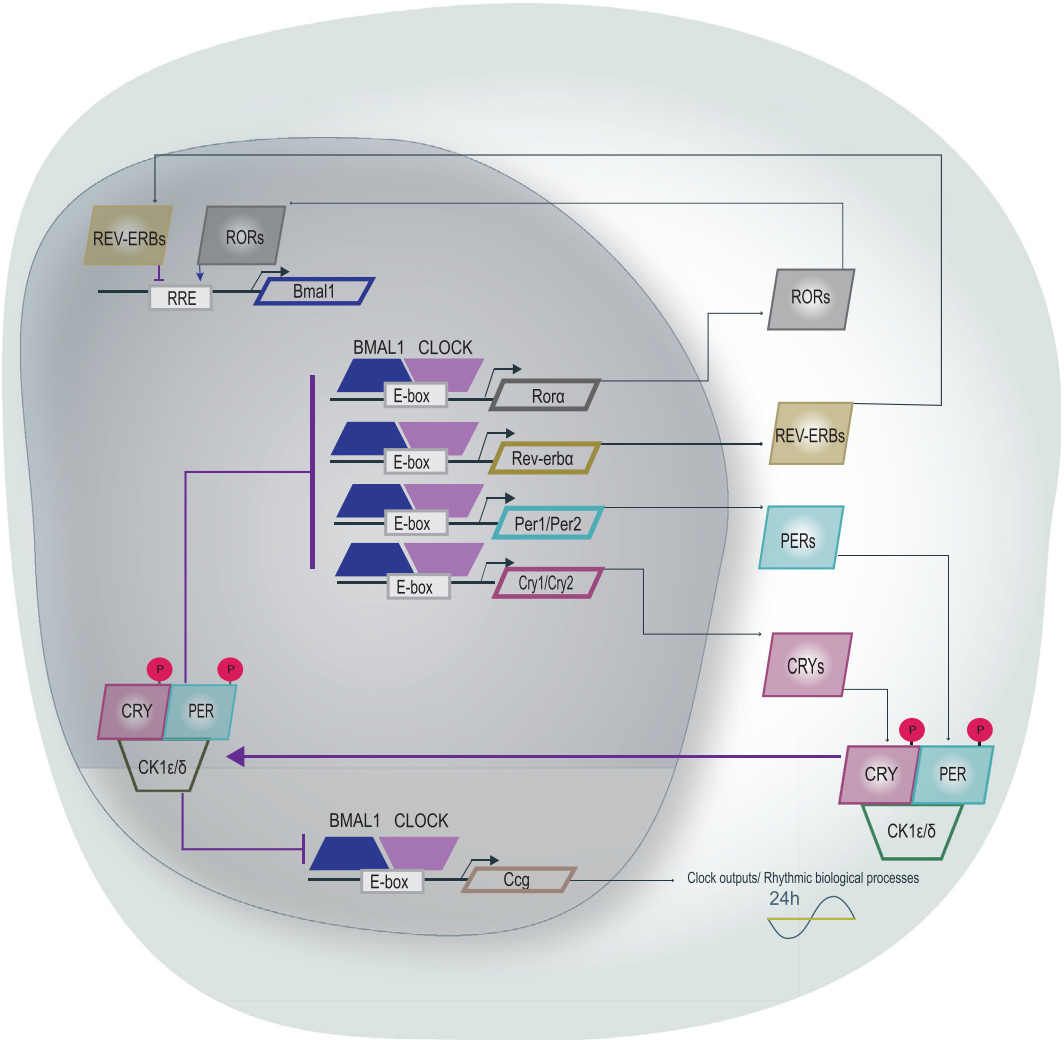

Figure 1. Transcriptional–translational network of the mammalian circadian oscillator. Representation of the mammalian molecular circadian oscillator. The primary negative feedback loop of the circadian oscillator involves *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2* genes. CLOCK/BMAL1 heterodimer activates E-box-dependent transcription of *Per* and *Cry* genes. Subsequently, PER and CRY proteins heterodimerize and translocate to the nucleus to inhibit CLOCK/BMAL1-driven transcription. The secondary auto-regulatory feedback loop is composed of REV-ERBα and RORα, which compete to bind retinoic acid-related orphan receptor response elements (RRE) located in the promoter of the *Bmal1* gene. REV-ERBα represses *Bmal1* transcription, and RORα activates expression of *Bmal1*. PER and CRY proteins are mainly phosphorylated by Casein Kinase 1 Delta (CK1 δ) and Casein Kinase 1 Epsilon (CK1 ε), and these phosphorylations define the circadian periodicity.

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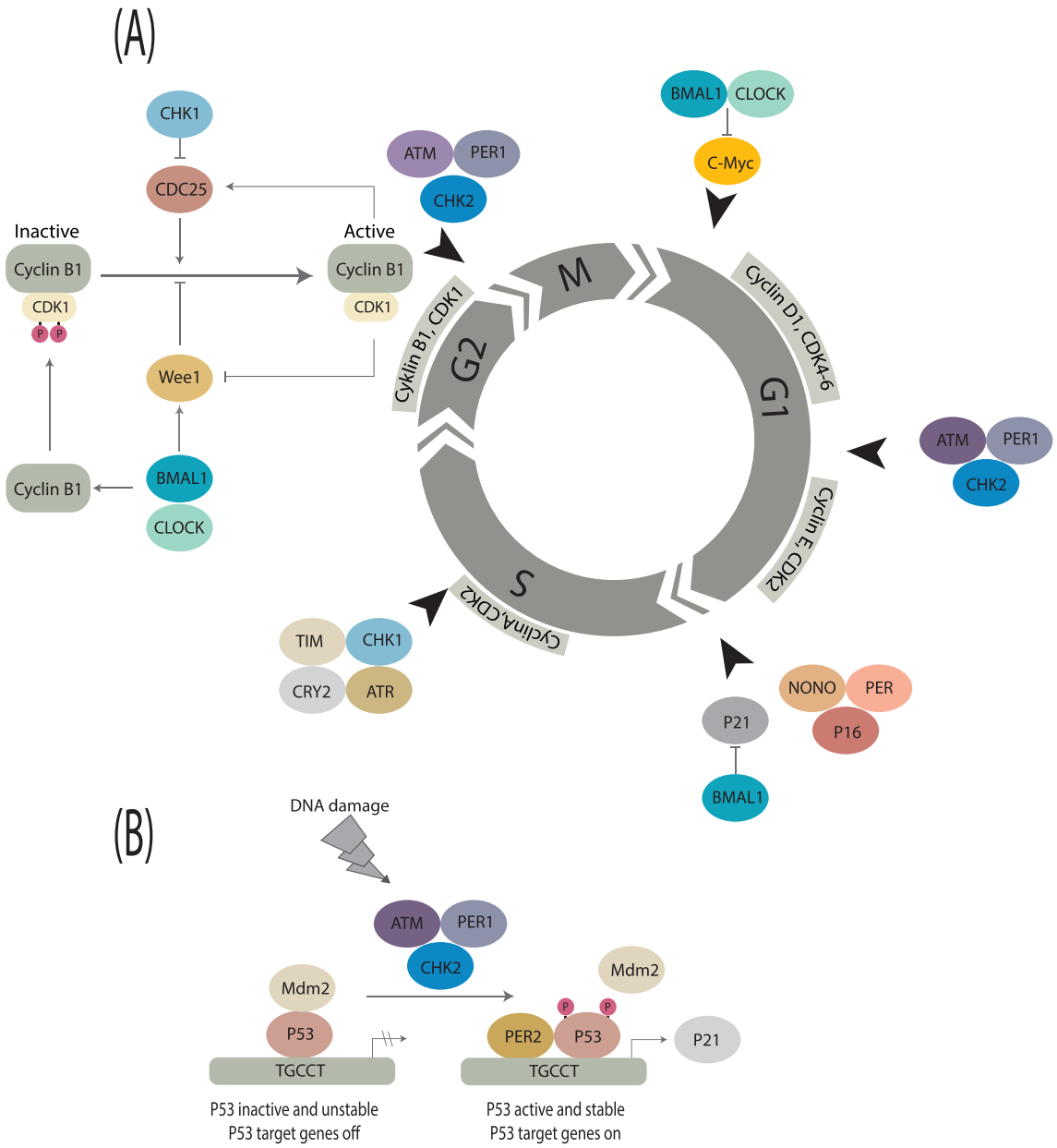

Figure 2. Schematic representation of the cell division cycle and molecular interaction with the circadian clock. (a) Cyclin–CDK complexes regulate progression of the cells through different cell cycle phases. Interaction between circadian clock proteins and cell cycle proteins is indicated, as described in the text. Black arrows next to p21, ATM–PER1–CHK2, and ATR–Chk1–CRY–TIM indicate pathways of G1/S, Intra-S, and G2/M checkpoints, respectively. (b) Representation of how the DNA damage checkpoint is regulated by circadian clock proteins (as described in the text). PER2-dependent stabilization of p53 results in phosphorylation of p53 and enhanced activation of p53 target genes, such as the cell cycle inhibitor p21. This PER2-dependent activation of p53 is regulated by the ATM–PER1–CHK2 complex.

heterodimerization shuttle between the cytoplasm and the nucleus [26]. Once nuclear levels of PER/CRY complexes are sufficiently high, they inhibit transcription of E-box genes (including their own genes) by blocking CLOCK/BMAL1-mediated transcription (Figure 1).

An additional feedback loop reinforces the strength of the CLOCK/BMAL1 and PER/CRY loop. CLOCK/BMAL1 heterodimers also drive the transcription of two nuclear receptors: *Rev-Erbα* and RORα. REV-ERBα inhibits gene expression of *Bmal1,* and to a lesser extent of *Clock*, by binding to ROR responsive elements that are located in the promoters of these genes ([21,24,27,28]. While REV-ERBα inhibits transcription of *Bmal1*, RORα activates it. The net result is a high-amplitude

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circadian oscillation of *Bmal1* mRNA. A number of other clock components can be noted such as *Per3*, *Timeless (Tim)*, *Dec1*, *Dec2,* and *E4BP4,* but their roles have not been clearly specified. [24,25].

Circadian transcription of the core clock genes gives rhythmicity to the expression of numerous genes that are involved in various biological processes. These so-called clock-controlled genes comprise from at least 10% of a tissue's transcriptome, to almost 50%, according to the most recent publications [29–32]. Importantly, clock-controlled genes that are under circadian transcription differ in each specific tissue, which means that the circadian regulation of cellular physiology and metabolism is tissue specific [7]. These oscillating genes bring rhythmicity to many physiological processes, including hormone secretion, drug and xenobiotic metabolism, glucose homeostasis, and cell proliferation [25]. Considering the importance of the circadian clock and the wide range of physiological events that are regulated in a circadian manner, it is not surprising that genetic disruption or environmental disturbance (such as jet lag) of circadian rhythmicity predispose to a range of diseases, including metabolic syndrome, cardiovascular disease, and cancer [33–35].

Cell Cycle Control

The cell cycle represents another oscillatory system that co-exists with the circadian clock in proliferating cells. The circadian clock and the cell cycle share many common features to drive their oscillatory events. Both systems follow sequential rounds of transcription, translation, post-translational modification, and protein degradation to govern their cyclic events. During a cell division cycle (Figure 2(a)), cells copy their genome in S phase and divide the genome into two daughter cells in mitosis (M phase). The S phase and mitosis are separated by two gap phases (G1 and G2). In G1, cells are prepared for DNA replication by protein synthesis and cell growth. In G2, the DNA damage check point is active to avoid passing a damaged genome to daughter cells [36,37]. Progression through the cell cycle is controlled by the rhythmic activity of Cyclin–CDK kinase complexes (Figure 2(a)). Within these complexes, cyclins are oscillating and form the regulatory subunits, whereas CDKs are present at constant levels and comprise the catalytic subunits. [38]. Specific combination of Cyclin–CDK complexes triggers various cell cycle events, such as DNA replication and mitosis, at a particular time during the cell cycle.

Cyclin D is synthesized in response to growth stimuli in early G1 phase and associates with CDK4 and CDK6 kinases to form an active complex [39]. The active Cyclin D and CDK4 complex phosphorylates tumor suppressor RB protein in G1 phase [40,41]. Hyper-phosphorylatedRB dissociates from the RB/E2F complex resulting in activation of E2F complex, a positive regulator of the cell cycle. E2F in turn induces transcription of the genes regulating G1/S transition, such as Cyclin E [42]. In mid-G1, the Cyclin E–CDK2 complex facilitates G1/S transition [43]. Cyclin A rises at the beginning of S phase, and in complex with the catalytic subunit CDK2, is essential for DNA replication and S phase progression [44–46]. Cyclin B1 levels rise from the late S phase till late G2 phase allowing the protein to form complexes with CDK1 [47].

To avoid premature initiation of mitosis, Cyclin B1–CDK1 is initially kept in an inactive form through phosphorylation of the CDK1 subunit by WEE1 and MYT1 kinases ([48,49]. High concentration of Cyclin B1, and therefore high activity of Cyclin B1–CDK1 complex can set off a double feedback loop in which Cyclin B1–CDK1 can inhibit its inhibitor (WEE1) and activate its activator (CDC25) allowing cells to enter mitosis [50,51]. Timed degradation of the cyclins is equally important as their timed expression for cell cycle progression. For instance, Cyclin B1 destruction is essential for mitotic exit [52]. Persistent activity of Cyclin B1–CDK1 complex interferes with chromosome segregation and stalls the cells at the end of anaphase [52,53]. Destruction of Cyclin A starts right after nuclear envelope break down and is complete before reaching metaphase [54,55]. As a consequence, overexpression of Cyclin A in late G2 phase cells delays chromosome alignment, subsequently delaying mitosis [54].

Transition of the proliferating cell from one cell cycle phase to another is tightly regulated by cell cycle checkpoints. Restriction point R in the late G1 phase is an important check point in the mammalian cell cycle, which occurs 2 to 3 h before the onset of DNA synthesis. Before this restriction point, the cell cycle depends on external stimuli (growth factors) to proceed through G1. After the restriction point, the cell becomes independent of external mitogenic stimuli and can complete the cell division cycle autonomously [56,57]. One other important cell cycle check point is the G2/M check point. This checkpoint ensures genome stability before cells enter M phase, avoiding that a defective genome passes to the next generation of the cells. When cells are exposed to genotoxic agents, or in case of defective replication in S phase, DNA damage response pathways are activated [58]. As it is mentioned before, the main driver of mitotic entry is the activity of Cyclin B1–CDK1. Therefore, DNA damage response pathways modulate regulators of Cyclin B1–CDK1 complex to pause the cells in G2 [59]. The DNA damage response is mainly triggered by two signaling cascades: Ataxia–Telangiectasia Mutated and Check Point Kinase 2 (ATM/CHK2) and ATM-Rad3-related and Check Point Kinase 1 (ATR/CHK1) [60]. The G2/M check point is regulated by

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CHK1-dependent phosphorylation of CDC25 phosphatase, which is an important activator of Cyclin B–CDK1 complex. Phosphorylation of CDC25 prevents activation of Cyclin B–CDK1 complex and stalls the cells in G2 phase [50].

The Interaction between the Circadian Oscillator and the Cell Cycle Machinery

Several studies suggest a cross-talk between the circadian clock and the cell cycle. For instance, it has been shown that a light-induced phase shift in mouse behavior leads to a corresponding shift in the proliferation timing of cells in the intestine [61]. Additionally, DNA damage phase-advanced circadian rhythms in a dose- and time-dependent manner [62–64]. This phenomenon was attributed to stabilization and de-ubiquitination of CRY1 [65]. On the other hand, increased accumulation of DNA damage or genome instability is reported in $Cry2^{-/-}$ cells, suggesting a particular role of cryptochromes on transcriptional regulation of DNA repair in response to genotoxic stress [65]. These studies highlight reciprocal influences of these two systems on each other.

Research on human oral mucosa and skin has provided a first clue to an association between clock gene expression and cell cycle phase [66,67]. This was achieved through the analysis of rhythmic expression of clock genes and cell cycle proteins in human oral mucosa and skin biopsies over 24 h. In these tissues, expression of *Per1* mRNA was shown to peak in the morning and to coincide with the peak of p53 expression, which is considered a G1 cell cycle phase marker. In contrast, *Bmal1* transcripts reached their highest level at night, showing synchrony with the peak expression of Cyclin B1, a marker of G2 and M phase. Rhythmicity in DNA synthesis and mitosis has also been demonstrated in hematopoietic cells, immune system cells, gastrointestinal tract, liver, and skin cells of rodents [68,69].

In a study by Matsuo and colleagues, it has been shown that in critical situations such as partial hepatectomy, the circadian rhythm affects the onset of proliferation *in vivo* [70]. In wild-type mice, partial hepatectomy causes hepatocytes to enter M phase at a specific time of the day. This M phase gating was not seen in circadian clock-deficient Cry1/Cry2 double-knockout mice [70]. Recently, the dynamics of, as well as the interaction between the circadian clock and cell cycle machineries has also been addressed at the level of the individual cell [71–73]. In fluorescent Rev-Erbα-VNP clock reporter protein expressing NIH3T3 cells frequency of cell division was plotted against circadian time in a interval time between 24 and 60 h after dexamethasone pulse [73]. Interestingly, three specific and non-random circadian time windows for mitosis have been identified, indicative of cell division gating by the circadian clock. However, at the same time, the period and phase of the circadian clock were influenced and altered after each cell division event. This observation was attributed to the decreased concentration of PER and CRY proteins during cytokinesis when components of the cells are split between the two daughter cells [73]. Later, using the same circadian clock reporter (Rev-Erbα-VNP) but in combination with two cell cycle markers (FUCCI reporter system: hCDT1-mKOrange for G1 and hGeminin-CFP for S/G2/M), a tight synchrony between the circadian clock and the cell cycle has been reported at the single cell level ($NIH3T3^{3C}$ cells; [72]). It has been shown that the circadian clock and the cell cycle are tightly phase coupled and are oscillating with the same frequencies (1:1 ratio). A remarkable shortening of the circadian period was observed in dividing cells compared to non-dividing cells, indicating the influence of the cell cycle on the circadian clock [71,72]. In line with these observations, but at the single cell level, we observed circadian and cell cycle periods of approximately 17 h in proliferating cells [74]. Notably, after cells reached confluency, the circadian period was close to 23 h. This suggests that the circadian clock in proliferating cells is no longer free running, but rather is entrained or reset by the cell cycle, likely each mitotic event.

Bieler and colleagues, making use of clock reporter (Rev-Erbα-VNP), have also reported a tight synchrony between the circadian clock and cell cycle [71]. They reported a uni-directional link between the circadian clock and the cell cycle, suggesting that in the absence of external cues (clock synchronizers), the effect of the cell cycle on circadian period is dominant [71]. In contrast, in the study by Feillet and coworkers, a bi-directional link between these two oscillatory systems has been uncovered [75]. Fiellet and co-workers have shown that synchronization of the circadian clock by physiological cues, such as dexamethasone, clustered cell division. This indicates that when the circadian oscillator is exposed to synchronizing cues, the effect of circadian system on the cell cycle is dominant. In contrast, in the absence of clock synchronizers, the influence of the cell cycle on the circadian cycle is dominant.

Molecular Cross-Talk between the Circadian Clock and the Cell Cycle

Our knowledge regarding the molecular mechanisms underlying the interaction between these two oscillatory systems is gradually increasing. Circadian clock genes regulate important cell cycle check points by either transcriptional control of critical regulatory genes or direct protein–protein interactions. Figure 2 highlights the current knowledge regarding the molecular cross-talk between the circadian clock and the cell cycle, as will be

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described below. For instance, transcription of oncogene *c-Myc* (involved in G0/G1 transition) is regulated by BMAL1/CLOCK [76]. G1 and G1/S checkpoints are under circadian control through cyclic transcription of the tumor suppressor genes *p21WAF1/CIP1* and *p16-Ink4A* [77,78]. *p21* is negatively regulated by BMAL1, as suggested by a high level of P21 protein reported in *Bmal1*$^{-/-}$ hepatocytes [77]. The multifunctional nuclear protein NONO binds to the *p16* promoter and drives its circadian transcription in a PER-dependent manner [78]. In the absence of PER or NONO, the circadian expression of *p16* is abolished.

ATR/CHK1 signaling cascade is activated in response to UV DNA damage [60]. It has been shown that CRYs are involved in activating ATR/CHK1 DNA damage signaling pathway *via* direct interaction with Timeless (TIM) protein [79,80]. Downregulation of *Tim* disrupts both the circadian oscillation and ATR/CHK1 signaling pathway [60]. Similarly, it has been shown that PER1 participates in the ATM–CHK2 protein complex, which is activated upon DNA double-strand breaks caused by ionizing radiation (IR) [60]. PER1 interacts with both ATM and CHK2 proteins for an efficient activation of the signaling cascade, which results in cell cycle arrest or activation of DNA repair pathways (Figure 2(b)). A direct interaction between PER2 and p53 tumor suppressor protein has also been reported. PER2 prevents MDM2-mediated ubiquitination of p53 by binding to the C-terminal domain of p53, and blocking access of MDM2 to its substrate [81]. PER2-dependent stabilization of p53 results in enhanced activation of p53 target genes such as the cell cycle inhibitor p21 (Figure 2(b)).

Expression of the *Wee1* gene (an important G2/M checkpoint kinase) is under direct control of BMAL1/CLOCK complex [70]. As it is mentioned earlier, Cyclin B1 protein levels rise gradually during G2 to form active Cyclin B1–CDK1 complex for mitotic entry, which is kept in inactive format by kinase activity of Wee1 to avoid premature mitosis. We have shown that knockdown of *Clock* or *Bmal1* in NIH3T3^{3C} cells resulted in reduced levels of Cyclin B1 protein at G2/M transition where a threshold concentration of Cyclin B1 is essential to bypass the inhibitory effect of WEE1 and for mitotic entry [74]. Consequently, decreased induction of Cyclin B1 slowed down the cell cycle by delaying exit from G2 [74]. Thus, it appears that the CLOCK/BMAL1 complex has a dual role in controlling G2/M check point by simultaneously regulating an activator (Cyclin B1) and an inhibitor (WEE1) of mitotic entry. However, the increased cell cycle length in *siClock* and *siBmal1* cells suggests that the regulatory effect of CLOCK/BMAL1 complex on the activator (Cyclin B1) of G2/M check point is dominant over the effect on the repressor (WEE1) of G2/M transition (Figure 2(a)) [74]. There is also evidence regarding the molecular influence of the cell cycle on the circadian clock. The cell cycle gene *p53* negatively regulates *Per2* expression, thereby affecting circadian period [82]. Importantly, it has been shown that FBXW7, a critical tumor suppressor protein, and CDK1 kinase are coordinately mediating degradation of REV-ERBA, therefore affecting circadian clock amplitude [83].

The circadian clock [84,85] and cell cycle [86,87] have also been studied making use of mathematical models, which can been integrated into computational models that enable the study of the interaction between the two oscillatory systems *in silico* [88]. Such models enable predictions based on biological data. Traynard and co-workers [89] developed a model to study entrainment of phase and period, which in part reproduces biological data [71,72], and could predict an upregulation of RevErbα during mitosis. Similarly, the effect of knocking down *Bmal1* or *Clock* on the dynamics of the cell cycle could be mimicked using computer simulations [74]. Finally, the bi-directional nature of the coupling between circadian clock and cell cycle has been addressed using computational modeling [90]. The authors conclude that this bi-directionality underlies the robust synchronizations between the two systems.

As a consequence of these complex interconnectivities between the circadian clock and the cell cycle, it is not surprising that loss of circadian control can be considered as a key factor for abnormal cell growth. It has been reported that osteoblasts from *Per1*/*Per2* or *Cry1/Cry2*-deficient mice display an accelerated G1/S transition resulting in increased bone mass [91]. This result was attributed to high expression levels of G1 cyclins such as Cyclin D1 [91]. Likewise, Destici and co-workers have shown accelerated cell cycle progression and a high proliferation rate in primary *Cry1*$^{-/-}$*Cry2*$^{-/-}$ mouse fibroblasts, as compared to wild-type cells [92]. In contrast, primary hepatocytes from *Bmal1* knockout mice showed a decreased proliferation rate, which was related to the altered expression of tumor suppressor gene *p21* [77].

Taken together, the above data suggest a unique effect of clock genes on cell cycle progression. Clock genes impact different cell cycle phases in a specific manner, and circadian positive regulators appear to have opposite an effect of circadian negative regulators (e.g. CLOCK/BMAL1 *versus* CRY).

The Circadian Clock, Cell Cycle, and Cancer

Genetic disruption and environmental disturbance of the circadian system have been associated with a range of physiological disorders [93–95]. For instance, altered insulin and glucose levels in the *Clock*-deficient mice lead to a range of metabolic disorders such as obesity, hyperlipidemia, and hypoinsulinemia [96]. Some of the health complications observed in night

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shift workers, such as autoimmune disease and obesity, are associated with disruption of the circadian immune function [93]. Epidemiological studies have shown that human night shift work is linked to increased risk of breast, colon, lung, prostate, and non-Hodgkin's cancer [97–100]. Night shift work is considered as a carcinogenic factor, as the risk of cancer development is increased by the number of the years an individual spends working at night [68,94,99]. Several studies have shown that loss of circadian homeostasis in mice leads to accelerated mammary tumor growth. For instance, breast cancer-prone *p53* mutant mice show accelerated tumor development under a jetlag protocol [101]. In addition, ablation of the SCN in mice increases the growth rate of implanted tumors ([102,103].

Many of the genes that are mutated in human cancers are directly involved in the regulation of cell division. Likewise, altered expression of circadian clock genes that are involved in the regulation of different cell cycle check points has been reported by various studies [76,94,104]. For instance, mutations in the *Per1* and *Per2* genes were detected in breast and colon cancer patients [105]. Exposure of cancer cell lines over-expressing*Per1* to IR revealed an increased apoptosis sensitivity. In contrast, suppression of *Per1 expression* by siRNA in IR exposed cancer cell lines results in a reduction of the apoptotic rate [106]. Furthermore, *Per2* mutant mice showed increased tumor development upon exposure to IR [76,107]. Altered expression of cell cycle-related genes such as *p53* and *c-Myc* is proposed as an underlying mechanism. In addition, downregulation of the *Per2* gene in breast cancer cells accelerates the proliferation rate by increasing Cyclin D and Cyclin E levels *in vitro* [108]. All the above data suggest that *Per1* and *Per2* are tumor-suppressor genes. Therefore, mutations in circadian clock components can predispose to cancer by increasing the cell growth and cell proliferation rate through general cell cycle dysregulation.

Outlook

Abnormal cell growth is characterized by impaired cell cycle progression. The circadian clock and the cell cycle have been considered as two independent oscillators for a long time. However, increasing evidence has challenged this view by showing that there is a strong bi-directional link between these two oscillatory systems [72,75], and we have shown the involvement of the clock genes in the regulation of important cell cycle check points [74]. Although our knowledge is steadily increasing, still many questions remain to be answered.

Understanding the nature of the coupling between the circadian clock and the cell cycle in cancer cells will be important to dissect the interplay between these two systems in cancer cells and facilitate further improvement of cancer treatment. Drugs used in cancer therapy often target specific cell cycle phases [68,69,109]. For instance, chemotherapeutic drugs such as 5-fluorouracil act on S-phase cells, whereas other drugs such as taxanes exert their highest toxicity on M-phase cells. The 24-h rhythmicity in cell proliferation allowed the development of new cancer chemotherapeutic approaches, which focus on the determination of the best treatment time [69]. Chronotherapy is benefiting from the differences in circadian physiology between the host and cancer tissues in order to optimize the anti-cancer treatment, by reducing the toxicity of the treatment for the host cells and increasing the efficiency for the cancer cells [68,109]. Extending the current knowledge of the circadian clock–cell cycle coupling mechanism in cancer cells will enable the development of new chronotherapeutic approaches in which the clock–cell cycle coupling in the normal tissue is used to predict the optimal time of treatment: for example, by choosing a time window in which normal cells are less sensitive to the treatment, while malignant cells undergo random cell division independent of the circadian phase.

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Abbreviations used:
SCN, suprachiasmatic nucleus; *Bmal1*, Brain Muscle Arnt-Like protein-1; *Clock*, Circadian Locomotor receptor Cycles Output Kaput; IR, ionizing radiation.

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