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## The circadian clock and cell cycle: Interconnected biological circuits

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### Abstract

The circadian clock governs biological timekeeping on a systemic level, helping to regulate and maintain physiological processes, including endocrine and metabolic pathways with a periodicity of 24-hours. Disruption within the circadian clock machinery has been linked to numerous pathological conditions, including cancer, suggesting that clock-dependent regulation of the cell cycle is an essential control mechanism. This review will highlight recent advances on the ‘gating’ controls of the circadian clock at various checkpoints of the cell cycle and also how the cell cycle can influence biological rhythms. The reciprocal influence that the circadian clock and cell cycle exert on each other suggests that these intertwined biological circuits are essential and multiple regulatory/control steps have been instated to ensure proper timekeeping.

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The circadian clock is a remarkable timekeeping system that regulates numerous biological processes with a high degree of specificity, to ensure proper 24-hour rhythms. Light is the major zeitgeber, or time giver, that provides synchrony to the organism. The central circadian clock resides in the brain, within the suprachiasmatic nucleus (SCN), which is able to transmit signals to the peripheral clocks, such as liver, muscle, skin, that maintain their rhythms in a tissue-specific manner<sup>1, 2</sup>. The clock system is remarkably plastic and adapt to external cues, such as temperature and food intake, which are able to reset the clock system and maintain homeostasis of the organism.

The molecular circadian clock is driven by the transcription factors, circadian locomotor output cycles kaput (CLOCK) and aryl hydrocarbon receptor nuclear translocator-like (ARNTL or BMAL1), which are responsible for directing the positive arm of transcription, and are subsequently antagonized by the circadian transcriptional repressors period (PER) and cryptochrome (CRY) family members<sup>3</sup>. In addition to transcriptional control, the circadian clock is regulated at the level of translational and post-translational modifications<sup>4, 5</sup> that are able to fine tune the circadian system. Similar to the circadian cycle, the cell cycle is a tightly regulated system with checkpoints that exist at key transitions in the cell cycle to regulate fidelity of DNA replication and mitosis. How do

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these cycles converge and regulate the other? Are there cues in place, such as metabolic signals, that can direct the regulatory checkpoints? Given, the excellent reviews on cell cycle and the circadian clock<sup>6-8</sup>, this review will focus on new and unexplored areas of circadian and cell cycle coordinated control and how these pathways can be influenced by external cues.

## Gating controls of the circadian clock and the cell cycle

It has been previously shown in plants<sup>9</sup>, cyanobacteria<sup>10, 11</sup>, zebrafish<sup>12-14</sup>, and mouse<sup>15</sup> that the circadian clock specifically regulates or 'gates' key phases of the cell cycle. Gating of the cell cycle by the circadian clock has been reported at the entry to S-phase<sup>12, 16</sup>, though the defined mechanism(s) of this phenomenon are unclear. Circadian clock-dependent regulation of S-phase is important for vulnerability to UV-induced DNA damage in proliferating skin cells<sup>17</sup>. Also, it has been reported that time-of-day dependent susceptibility to UV radiation that has been linked to skin cancer in mice and is dependent on DNA damage repair through the xeroderma pigmentosum group A (XPA) protein<sup>18</sup>. Also, recent data has revealed that *p20* and *p21*, important regulators of the G<sub>1</sub>/S transition, are clock-controlled genes that are temporally expressed in a tissue-specific manner<sup>19, 20</sup> (**Figure 1**).

Similarly, the circadian clock has been reported to specifically gate the G<sub>2</sub>/M checkpoint in proliferating hair follicles<sup>21</sup> and a proliferative liver regeneration mouse model, whereby impaired liver regeneration was observed in arrhythmic *Cry1/Cry2*-deficient mice<sup>15</sup>. Furthermore, WEE1 kinase is responsible for regulating the CYCLIN B1/CDC2 (cell division control protein 2 also known as cyclin-dependent kinase 1, CDK1) complex and subsequent entry into mitosis<sup>15</sup>. *Wee1* mRNA and protein expression was found to be highly circadian, along with its kinase activity that regulates mitotic entry<sup>15</sup>. The *Wee1* promoter contains three E-box sequences<sup>15</sup>, the sites to which CLOCK and BMAL1 bind. Of particular interest, the *Wee1* promoter is subject to chromatin remodeling and hyperacetylation at the histone H3 tail (H3K14) in response to light<sup>13</sup>. Not only are cell cycle genes such as *Wee1* (and others such as *c-Myc*, *Cyclin D1*, *Cyclin B1* and *Cdc2*) subject to circadian oscillation in expression, but the extent to which chromatin modifications play a role in light-dependent remodeling at cell cycle gene promoters is unclear. The CLOCK complex is known to have intrinsic histone acetyltransferase (HAT) activity, which contributes to BMAL1 and H3 tail acetylation<sup>22, 23</sup>. Similarly, the histone methyltransferase mixed-lineage leukemia (MLL1) is responsible for H3K4 tri-methylation, an active mark for gene expression which permits circadian oscillation<sup>24</sup>. What is the role that MLL1 plays in chromatin remodeling and subsequent recruitment of the CLOCK/BMAL1 transcriptional complex to clock-dependent cell cycle gene promoters? It would be expected that dynamic and circadian changes in both H3 methylation and acetylation establish a permissive chromatin state for transcription of cell cycle genes.

The control that the circadian clock exerts on the cell cycle seems to be extensive. Yet, little is known about cell cycle control over the circadian clock. Nagoshi *et al.* reported that oscillations in gene expression persisted during the cell cycle and that daughter cells maintained the circadian rhythm of the maternal cell after mitosis was complete<sup>25</sup>. Also, it

was shown that the circadian period length of proliferating NIH3T3 fibroblasts is longer than the period of non-proliferating fibroblasts, suggesting the cell cycle can influence the period of the circadian clock<sup>25</sup>. The authors suggest that cell division could alter PER/CRY repressor protein concentrations and subsequently alter circadian rhythms, though the precise mechanisms are not understood. Recent data shows that an RNA binding protein called p54nrb or NONO partnered with PER proteins to activate the *p16-Ink4A* cell cycle checkpoint gene in a circadian manner<sup>26</sup>. Furthermore, it was noted that WT fibroblasts demonstrated circadian variation in the proportion of cells in S-phase. A greater than 2-fold variation in the number of cells that had entered S-phase was observed between circadian time (CT) 7 and CT 19<sup>26</sup>. Remarkably, this diurnal effect was abolished in NONO-null fibroblasts and *Per1/Per2* mutant cells, which divided equally during the day and night, indicating a strong relationship between these proteins and circadian control of cell cycle gating. What remains to be determined is the extent to which this coordination occurs; are there cell cycle proteins that could work in concert with the circadian clock machinery, and vice-versa?

## Common circadian and cell cycle proteins

The idea that proteins can be conserved among different pathways is not new and most likely is taking place between the circadian clock molecular machinery and that of the cell cycle. The NONO/PER coordination is one such example. What about other factors that have been reported to participate in both biological circuits? The mammalian Timeless (TIM) protein shares homology with the reported drosophila clock protein TIM<sup>27</sup>, but is most closely related to cell cycle regulators and involved in DNA damage response. Mammalian TIM was found to interact with the circadian protein CRY2, checkpoint kinase 1 (CHK1) and ataxia telangiectasia and rad3 related (ATR), resulting in regulation of S phase and DNA damage response<sup>28</sup>. Furthermore, mammalian TIM was found to be important for ataxia telangiectasia mutated (ATM)-dependent activation of checkpoint kinase 2 (CHK2) and subsequent regulation of the G<sub>2</sub>/M checkpoint in response to DNA damage<sup>29</sup>, and CHK2 and ATM were also reported to interact with PER1<sup>30</sup>. As the role of TIM in the mammalian circadian clock machinery appears pleiotropic<sup>31, 32</sup>, is it possible that this protein has evolved from the circadian circuit to regulate the cell cycle? Potentially, this could explain why TIM retains interaction with the clock machinery via PER and CRY and coordinates DNA damage response (**Figure 2**).

The histone deacetylase (HDAC) SIRT1 is an NAD<sup>+</sup>-dependent mammalian sirtuin that deacetylates PER2, BMAL1 and the H3 tail and is important for maintaining circadian gene expression<sup>33, 34</sup>. Remarkably, SIRT1 was reported to be phosphorylated by CYCLINB1/CDK1 (CDC2) which modulates its HDAC activity and subsequent progression through the cell cycle, yet the targets of SIRT1 during mitosis remain to be determined<sup>35</sup>. Also, SIRT1 deacetylates p53<sup>36, 37</sup> which is involved in DNA damage response and apoptosis, and forkhead box O3 (FOXO3)<sup>38</sup> which is involved in G<sub>1</sub>/S and G<sub>2</sub>/M checkpoints, DNA damage response and apoptosis. The function of SIRT1 as an HDAC is extensive, targeting both circadian and cell cycle proteins. Yet, a crosstalk may exist in that SIRT1 can target the cell cycle machinery, which can feedback and phosphorylate SIRT1. There is also an additional layer of complexity involving NAD<sup>+</sup>, which will be discussed in the next section.

Overall, there seems to be common regulators between the circadian and cell cycles and bidirectional regulation is in place involving both biological circuits, potentially to attain proper cellular homeostasis depending on stress response or metabolic state.

## Influence of metabolism on the clock/cell cycle

It has been suggested that the circadian gating mechanism of the cell cycle may not be restricted to specific checkpoints, but could be an overarching mechanism with multiple points of control<sup>39</sup>. This brings into question the metabolic state of the cell and how this can influence the decision of a cell to replicate its DNA and divide. This concept has been highlighted in yeast where an ultradian rhythm has been reported for the cellular metabolic state which cycles between a reductive and non-respiratory state to an oxidative/respiratory phase<sup>40</sup>. Microarray analysis revealed that expression of genes with similar functions was compartmentalized into specific phases of the yeast metabolic cycle. Genes involved in DNA replication and cell cycle are coordinately expressed and the cell cycle occurred specifically during the reductive phase of the yeast metabolic cycle<sup>40</sup>. More recently, it was also proposed that circadian gating of the cell cycle may follow complex pathways in mammalian cells. *Cry1/2*-deficient fibroblasts display differences in their rates of proliferation as compared to WT cells, but the authors propose that this is due to global cellular changes, as many alterations in gene expression were observed in BMAL1-dependent targets<sup>41</sup>. The authors also highlight differences in proliferation rates in *Cry1/2*-deficient cultured fibroblasts<sup>41</sup> versus previously reported *Cry1/2*-deficient mice<sup>15</sup> and therefore suggest that systemic cues likely play a larger and unappreciated role in global circadian control of the cell cycle. Similarly, Sancar and colleagues reported that DNA damage response maybe very different in cells grown in culture, unlike an intact organism that relies on various inputs to regulate homeostasis<sup>42</sup>.

Based on these ideas that systemic cues likely play an important role in understanding circadian control of the cell cycle, it is imperative to extend our understanding of cellular metabolites that are under circadian control. It has been shown that nicotinamide adenine dinucleotide (NAD<sup>+</sup>) oscillates over the circadian cycle and its levels are directly controlled by the clock machinery<sup>43, 44</sup>. As previously discussed, SIRT1 is NAD<sup>+</sup>-dependent and plays an important role in regulating the clock machinery and is itself regulated by cell cycle factors. Given that the metabolic state of the cell can influence the cell cycle and that many metabolites are under control of the circadian clock, this suggests that the level of gating or control by the circadian clock could be quite extensive. The question is to what extent do these metabolites influence cell cycle commitment and progression? For example, a key metabolite, ATP, oscillates in a circadian manner<sup>45</sup>. Kinases require ATP and the G<sub>2</sub>/M checkpoint that is controlled by WEE1 could be tightly regulated by circadian oscillations in ATP levels. While experimental evidence is lacking, it could be speculated that cyclic levels of ATP may influence the many cyclin-dependent kinases that rely on ATP to phosphorylate and regulate their targets throughout the cell cycle. The extent to which the circadian clock regulates the cellular metabolome is becoming evident<sup>46-48</sup>, therefore it will be intriguing to understand how metabolic state fully influences the cell cycle.

The circadian clock and cell cycle are two very different biological circuits with many layers of coordinated regulation. Timing for both the circadian and cell cycles is critical and this maybe the reason for such elaborate levels of control. The circadian clock controls multiple aspects of the cell cycle, conferring gating mechanisms at key checkpoints of the cell cycle to ensure fidelity in DNA replication and cell division. How this is accomplished is not fully understood. Yet, it is clear that the circadian clock controls oscillatory expression of several cell cycle genes. The role of epigenetic control by the circadian clock is relatively unexplored, but most likely plays a critical role in dynamic changes in cell cycle gene expression. Also, common factors, such as the HDAC SIRT1, are involved in both circadian clock and cell cycle regulation. An additional layer of complexity exists with metabolites that could influence both circadian and cell cycles and the extent to which metabolic state is critical in gating mechanisms remains to be determined. Overall, the specific mechanisms in place that regulate both the clock and cell cycles, including bi-directional modulation between these two pathways, might be essential to protect the organism from rampant cycling that could lead to diseases such as cancer.

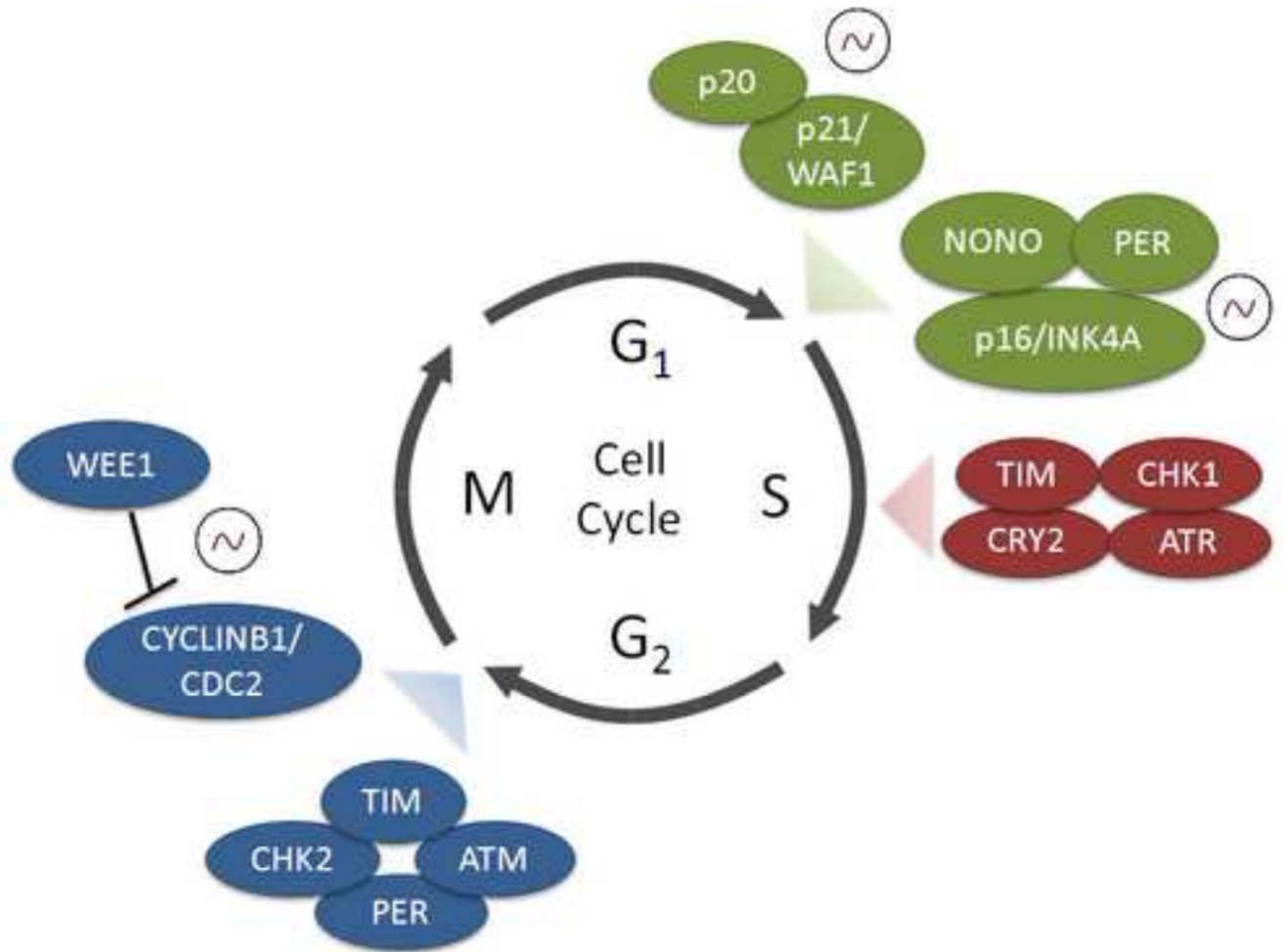
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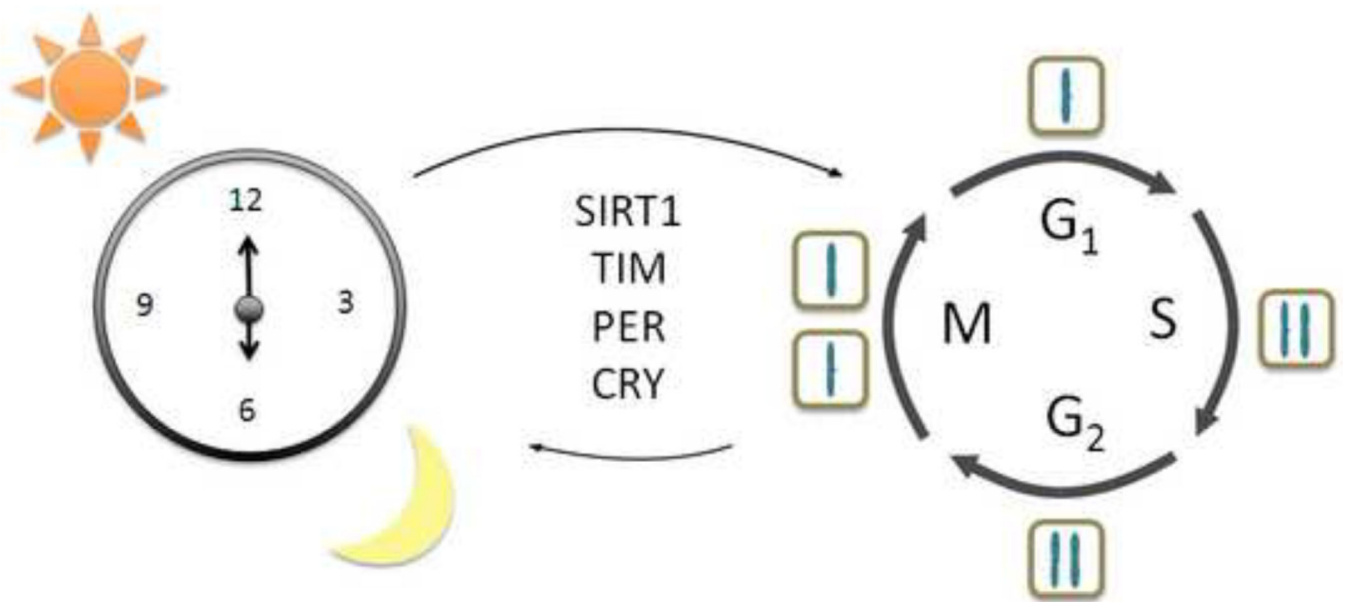
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**Figure 1. Gating of the cell cycle by the circadian clock**

The circadian clock machinery regulates the cell cycle at G<sub>1</sub>/S, S-phase and G<sub>2</sub>/M checkpoints of the cell cycle. Expression profiles of certain genes have been reported to oscillate in a circadian manner, and are indicated (~). Clock and cell cycle complexes that regulate the G<sub>1</sub>/S checkpoint are indicated in green, S-phase proteins shown in red and G<sub>2</sub>/M checkpoint regulatory complexes are presented in blue. Other factors such as Cyclin D1 that controls the G<sub>1</sub>/S checkpoint and c-Myc that regulates proliferation via the G<sub>0</sub>/G<sub>1</sub> transition are also important clock targets not shown.



**Figure 2. Common proteins that function in both circadian and cell cycles**

The circadian clock is regulated by the light/dark cycle that helps maintain periodicity of the system to approximately 24 hours. The cell cycle, comprised of G<sub>1</sub>, S, G<sub>2</sub> and M phases, whereby the cell makes the decision to replicate its DNA and subsequently divide, is also under strict timing cues. Many proteins seem to have overlapping functions in both biological circuits. Shown are the mammalian Timeless protein (TIM), the mammalian Sirtuin (SIRT1), and Period (PER) and Cryptochrome (CRY) regulatory proteins that are involved in modulation of multiple points of both circadian and cell cycles.