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# Circadian clocks, epigenetics, and cancer

**Selma Masri**, **Kenichiro Kinouchi**, and **Paolo Sassone-Corsi**

Department of Biological Chemistry, Center for Epigenetics and Metabolism, University of California, Irvine, Irvine, California, USA

## Abstract

**Purpose of review—**The interplay between circadian rhythm and cancer has been suggested for more than a decade based on the observations that shift work and cancer incidence are linked. Accumulating evidence implicates the circadian clock in cancer survival and proliferation pathways. At the molecular level, multiple control mechanisms have been proposed to link circadian transcription and cell-cycle control to tumorigenesis.

**Recent findings—**The circadian gating of the cell cycle and subsequent control of cell proliferation is an area of active investigation. Moreover, the circadian clock is a transcriptional system that is intricately regulated at the epigenetic level. Interestingly, the epigenetic landscape at the level of histone modifications, DNA methylation, and small regulatory RNAs are differentially controlled in cancer cells. This concept raises the possibility that epigenetic control is a common thread linking the clock with cancer, though little scientific evidence is known to date.

**Summary—**This review focuses on the link between circadian clock and cancer, and speculates on the possible connections at the epigenetic level that could further link the circadian clock to tumor initiation or progression.

### Keywords

cancer; cell cycle; circadian clock; epigenome; metabolism

## INTRODUCTION

The circadian clock is an endogenous, self-sustaining pacemaker that operates with a periodicity of 24 h, in order to maintain proper rhythms in sleep–wake cycles, behavior, metabolism, hormone secretion, and cell cycle [1,2]. Disruption in proper circadian timekeeping results in detrimental effects on mammalian physiology, and a number of clues from the clinic and laboratory suggest that these disturbances result in uncontrolled cell growth and cancer [3,4]. In humans, circadian disruption found in shift workers puts them at increased risk for breast cancer [5]. Also, mice with an ablation of the central clock located within the suprachiasmatic nucleus (SCN) exhibit increased growth of tumor xenografts compared with mice with an intact circadian pacemaker [6]. Overall, a link exists between

Correspondence to Paolo Sassone-Corsi, Department of Biological Chemistry, Center for Epigenetics and Metabolism, University of California, Irvine, Irvine, CA 92697, USA. Tel: +1 949 824 4540; psc@uci.edu.

**Conflicts of interest**

The authors declare no conflicts of interest.

cancer and disruption of circadian rhythms, although its extent and molecular mechanisms are not fully elucidated.

At the heart of the circadian machinery are the core DNA-binding transcription factors, CLOCK and BMAL1, that drive the oscillation of approximately 10% of transcripts in the genome in a defined tissue-specific program [7,8]. CLOCK:BMAL1-dependent transcription of core clock and clock-controlled genes (CCGs) peaks during the day, whereas transcription is inhibited by the circadian repressors, Period (PER) and Cryptochrome (CRY), at night [9,10]. In addition to the core transcriptional–translational feedback loop, regulation of circadian transcription is also subject to vast modifications in the epigenetic state that change dynamically over the day–night cycle [9,11].

## CIRCADIAN RHYTHMS AND CANCER

A number of genetic mouse models and human clinical studies reveal that the core clock transcriptional machinery is genetically altered in numerous cancer models. The human *Clock* gene is expressed in colorectal cancer, and its expression level is correlated with hypoxia-inducible factor 1-alpha (HIF-1α), aryl hydrocarbon receptor nuclear translocator, and vascular endothelial growth factor, molecules implicated in hypoxia and tumor angiogenesis [12]. CLOCK expression has also been reported to be upregulated in high-grade human glioma tissue, whereas the glioma suppressor miR-124 has been shown to directly target CLOCK expression and subsequently modulate glioma proliferation [13]. CLOCK has also been involved in breast cancer cell proliferation [14] and CLOCK is reported to interact with estrogen receptor alpha (ERα), whereas estrogen appears to enhance both CLOCK and ERα driven transcription via CLOCK-dependent sumoylation [15]. In addition to CLOCK, BMAL1 has also been reported to be involved in cancer. *Bmal1*$^{-/-}$ mice display increased salivary gland hyperplasia, and when irradiated, a fraction of these mice exhibit lymphomas in the chest cavity and salivary glands [16].

The PER repressors of the circadian clock have also been linked to cancer. The *Per2*$^{m/m}$ mice are highly sensitive to gamma-irradiation and display increased rates of salivary gland hyperplasia [17]. Recent studies also demonstrate that low levels of *Per1* and *Per2* gene expression are associated with poor prognosis in gastric cancer [18]. *Per1* mRNA is degraded by IREα, and inhibition of IREα signaling reduces tumorigenesis [19]. *Per2* has been implicated in preventing tumor invasion and epithelial–mesenchymal transition (EMT) gene expression profiles [20]. Thus, the core clock machinery has been overall implicated in the regulation of cancer cell growth and survival in mouse models. In addition, clinical data also support a role for clock proteins in cancer.

## CIRCADIAN CLOCK AND CELL CYCLE

The circadian clock has been previously reported to regulate or ‘gate’ the cell cycle at the G1/S [21–23] and G2/M [24,25] checkpoints, and recent evidence confirms that the clock and cell cycle exhibit phase-locking characteristics and are coordinately synchronized [26]. The expression of a number of cell-cycle regulators is also under the control of the clock: *Wee1, c-Myc, p20, p21, and Cyclin D1* all exhibit circadian gene expression [27,28]. Specifically, critical circadian regulators that link the clock to cell-cycle control are the

PER1 and PER2 repressors. The expression of a number of cell-cycle genes is abolished in PER2-mutant mice, and PER1 and PER2 interact with checkpoint kinases CHK1/2 [29] and NONO/p16-Ink4A to control cell-cycle progression [30]. In addition, the importance of circadian clock-dependent gating of the cell cycle was recently reported in intestinal stem cells and neural progenitor cells, suggesting circadian control of the cell cycle has far-reaching implications [31,32].

One of the most important features in cancer cells is deregulation of the cell cycle, which can also be linked to the clock. Recent reports revealed that about 30% of circadian transcripts in colon mucosa regulate the cell cycle and specifically mitotic control, and the expression levels of these genes were found to be critical in the response of colon epithelial cells to anticancer agents such as cyclin-dependent kinase (CDK) inhibitors [33]. Also, it is well known that mutations in oncogenes and tumor suppressor genes are critical for tumor development. Two notable examples of cell-cycle regulators that are linked to the circadian clock are the tumor suppressor p53 and c-Myc oncogene. p53 controls multiple checkpoints of the cell cycle [34] and p53 also regulates *Per2* expression by blocking CLOCK:-BMAL1-dependent recruitment to the *Per2* promoter [35▪▪]. Strikingly, p53-null mice exhibit a shorter circadian period and impaired photo-entrainment [35▪▪]. *c-Myc* is a known regulator of cell-cycle progression [36,37] and similar to CLOCK:BMAL1, MYC binds E-box sequences to drive its transcriptional program. What has not been determined is the possible interplay between these two transcription networks, and whether, in the case of uncontrolled cell growth, MYC could interfere in the expression of known CLOCK:BMAL1 dependent genes. As an example of this, a recent computational approach linked gene signatures of the circadian clock to oncogenic Ras signaling. Using an inducible system, Ras expression was able to alter the circadian period length, suggesting potential common control mechanisms [38] (Fig. 1). Overall, these examples suggest the possibility that circadian transcriptional networks could overlap with oncogenic signaling pathways, possibly at the level of cell cycle and proliferative control. It could be of critical importance to determine the changes of CLOCK:BMAL1 genome-wide re-distribution in response to loss of p53 expression or activation of oncogenic Myc and Ras signaling in cancer cells.

## CIRCADIAN EPIGENOME AND CANCER

The vast genomic reprogramming that occurs in tumors has prompted in-depth investigations on the epigenetic changes and chromatin transitions occurring in cancer cells. The emerging view is that key chromatin remodelers involved in histone modifications play a central role in the development and establishment of a cancerous state for a given cell or tissue, directing a specialized set of histone modifications [39]. The remarkable role played by chromatin remodeling in circadian control begs the question on whether the epigenetic reprogramming that occurs during tumorigenesis could involve the clock system.

Circadian transcription is coupled with rhythmic chromatin modifications that regulate oscillations in gene expression (Fig. 1). The promoter regions of CCGs exhibit rhythmic histone acetylation at H3K9 and H3K14 [9,11,40], which has been attributed to the histone acetyltransferase (HAT) p300 [41] and the intrinsic HAT activity of CLOCK [40,42]. Conversely, circadian acetylation of histone and nonhistone proteins is counterbalanced by

the $NAD^+$-dependent deacetylases sirtuin 1 (SIRT1) [43,44] and SIRT6 [45]. Moreover, histone methylation is known to be rhythmic at H3K4, H3K9, H3K27 and H3K36, and these marks are mediated by a number of histone methyltransferases (HMTs) and demethylases that will be discussed below [9,46–48].

A number of histone-modifying enzymes that regulate the circadian clock have also been implicated in cancer. The mammalian sirtuins, SIRT1 and SIRT6, have been shown to participate in circadian control [44,45], but are also involved in aging and cancer. The role of SIRT1 in cancer is currently unclear as SIRT1 targets a number of acetylated proteins including Myc, p53, HIF, TGF-β, and Wnt signaling, apparently acting both as tumor suppressor and tumor promoter depending on the biological system studied [49–51]. Striking evidence illustrates that SIRT1 expression is elevated in leukemia stem cells, and a cross-talk exists between SIRT1 and MYC oncogenic signaling that is responsible for driving FLT3 receptor tyrosine kinase resistance in acute myeloid leukemia (AML) [52▪]. SIRT6 was recently described as a tumor suppressor and a potent regulator of aerobic glycolysis in cancer cells, which is a key mechanism for energy production upon which cancer cells are reliant for growth [53]. The role of the sirtuins in cancer could be regulated at the level of the circadian clock, and further work is needed to validate this idea experimentally. In addition to the sirtuins, liver-specific deletion of histone deacetylase 3 (HDAC3) results in hepatocellular carcinoma (HCC) [54] and the HDAC3–nuclear receptor corepressor 1 (NcoR1)–Rev-Erb axis has been implicated in the circadian control of gene expression [55,56].

Mixed lineage leukemia 1 (MLL1) operates as a critical regulator of rhythmic H3K4 tri-methylation and recruitment of CLOCK:BMAL1 to CCG promoters [46], and recent reports show that also MLL3 contributes to histone methylation and circadian gene expression in the liver [57]. The MLL protein family has been long implicated in leukemia through multiple mechanisms pertaining to loss of MLL expression, mutation, amplification, or translocation events, whereby oncogenic fusion proteins are formed between MLL and multiple partners [58]. The enzymatic HMT activity of MLL is critically involved in the epigenetic regulation in cancer and recent work has identified a small-molecule inhibitor for MLL1 that inhibits its interaction with WD repeat-containing protein 5 (WDR5) to repress H3K4 methylation, gene expression, cell-cycle arrest, and apoptosis in leukemia cells [59▪]. Furthermore, MLL3 is frequently mutated in multiple human cancers and was recently identified as a tumor suppressor located at a commonly deleted chromosomal locus in AML. MLL3-dependent changes in gene signatures corresponding to cellular differentiation and immune response suggest that H3K4 methylation profiles are also altered in these AML cancers [60]. As the HMT activity of MLL proteins controls rhythmic histone methylation, it could be envisioned that this circadian regulation of histone methylation is altered or abolished in cancer cells, potentially linking the circadian clock to tumorigenesis at the epigenetic level. In addition to the HMT activity of the MLL family of proteins, MLL is targeted by microRNAs [61–63], which could also be a common control mechanism with the circadian clock, as microRNAs are known to be involved in the circadian output and gene expression [64–66].

The histone demethylase LSD1 targets H3K4 and H3K9 methylation, and was recently reported to be a key component of the circadian machinery and regulator of CCG expression [67]. Interestingly, LSD1 functions as a histone demethylase in Sox2-expressing lung squamous cell carcinomas [68] and also controls proliferation and metastasis of colon cancer cells [69]. Another H3K4 demethylase, Jarid1a, demethylates H3K4 and has been implicated in circadian control by interacting directly with CLOCK:BMAL1 and regulating circadian gene expression [70]. Some clues suggest that Jarid1a could be involved in the tumor suppressor network of Retinoblastoma (Rb) [71], though how this is linked to the circadian clock remains unclear.

Finally, DNA methylation could also play an important role in linking the clock to cancer. Striking evidence for dynamic DNA methylation in the central clock region of the SCN identified light-induced changes in DNA methylation at specific promoters that correspond to circadian gene expression [72▪▪]. Yet, what is currently unclear is the extent to which changes in DNA methylation are rhythmic, considering CpG methylation is believed to exert long-lasting suppressive effects on gene expression. Global alterations in DNA methylation have been reported in cancer and not surprisingly, the *Per* and *Cry* promoters have been reported to be methylated in specific cancers [73,74]. Also, DNA methyltransferases and histone-modifying enzymes, such as HDACs, HMTs, and histone demethylases, are known to cross-talk and regulate the recruitment of one another, suggesting major complexity in this epigenetic control axis [75].

## CIRCADIAN CONTROL OF TUMOR METABOLISM

Cancer cells have adapted alternative methods of energy production, such that the rates of aerobic glycolysis are dramatically elevated to maintain the energetic needs of the tumor, termed the ‘Warburg effect’ [76]. Additionally, a revised view of cancer cell metabolic reprogramming beyond glycolysis also includes enhanced glutamine metabolism for lipogenesis, which is needed for membrane synthesis and proliferation, fatty acid beta-oxidation for energy production, and methionine dependency which is needed for methylation reactions and polyamine synthesis [77,78▪]. Not surprisingly, the circadian clock is heavily implicated in metabolic control and a number of metabolites, like glucose and fatty acids, display diurnal rhythms [79–81]. It is conceivable that as cancer cells are highly energy-consuming, a possible loss or deregulation of circadian metabolic control can lead to exacerbated cell proliferation in cancer cells. The details of this remain fully unexplored, but factors such as p53, mechanistic target of rapamycin (mTOR), Ras, and c-Myc, which are implicated in clock control, are known to also regulate metabolic processes in cancer cells.

## CIRCADIAN RHYTHMS AND CANCER TREATMENT

Targeting the circadian machinery may be valuable in the treatment or intervention of human cancers. The administration of chemotherapeutic agents at optimal times (chronotherapy) has been considered to maximize the antitumor effects and minimize the toxic influence on other organs. For instance, evaluation of *Bmal1* and *Rev-erb*α transcription profiles could help minimize the toxicity of chemotherapy [82]. Also, *Bmal1*

overexpression reduces cancer cell proliferation and improves the sensitivity to oxaliplatin in colorectal cancer [83]. Furthermore, mTOR protein expression is rhythmic, and administration of mTOR inhibitors in renal cell carcinoma during the peak expression phase improves survival [84]. At a time when personalized medicine is vastly valued, this set of findings suggests that the timing of chemotherapy should be adjusted to each patient, depending on the cyclic expression of clock genes and sensitivity of drug target – thereby following the internal circadian rhythm of the patient.

## CONCLUSION

The elevated incidence of cancer in modern society parallels the epidemiology data, showing elevated cancer risk in shift workers. Regarding this point, the detrimental effects of light pollution on the circadian clock are a growing concern. A number of clinical and laboratory results suggest that genetic and epigenetic changes in cell-cycle control and cell proliferation link the circadian pacemaker to cancer. In addition to the accumulating evidence discussed in this review, an area that remains completely unexplored is the connection between tumor metabolism and the circadian clock. The link between the circadian clock, cancer, epigenetics, and possibly metabolism opens up multiple avenues that require further exploration and could result in potential therapeutic intervention.

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## KEY POINTS

- Mouse models as well as human clinical studies have suggested that disruption of circadian rhythms facilitates tumorigenesis.
- The circadian clock has been shown to ‘gate’ the cell cycle: the clock and cell cycle display phase-locking characteristics and are coordinately synchronized.
- Circadian transcription is coupled to rhythmic changes of histone modifications and a number of histone-modifying enzymes are also implicated in cancer.

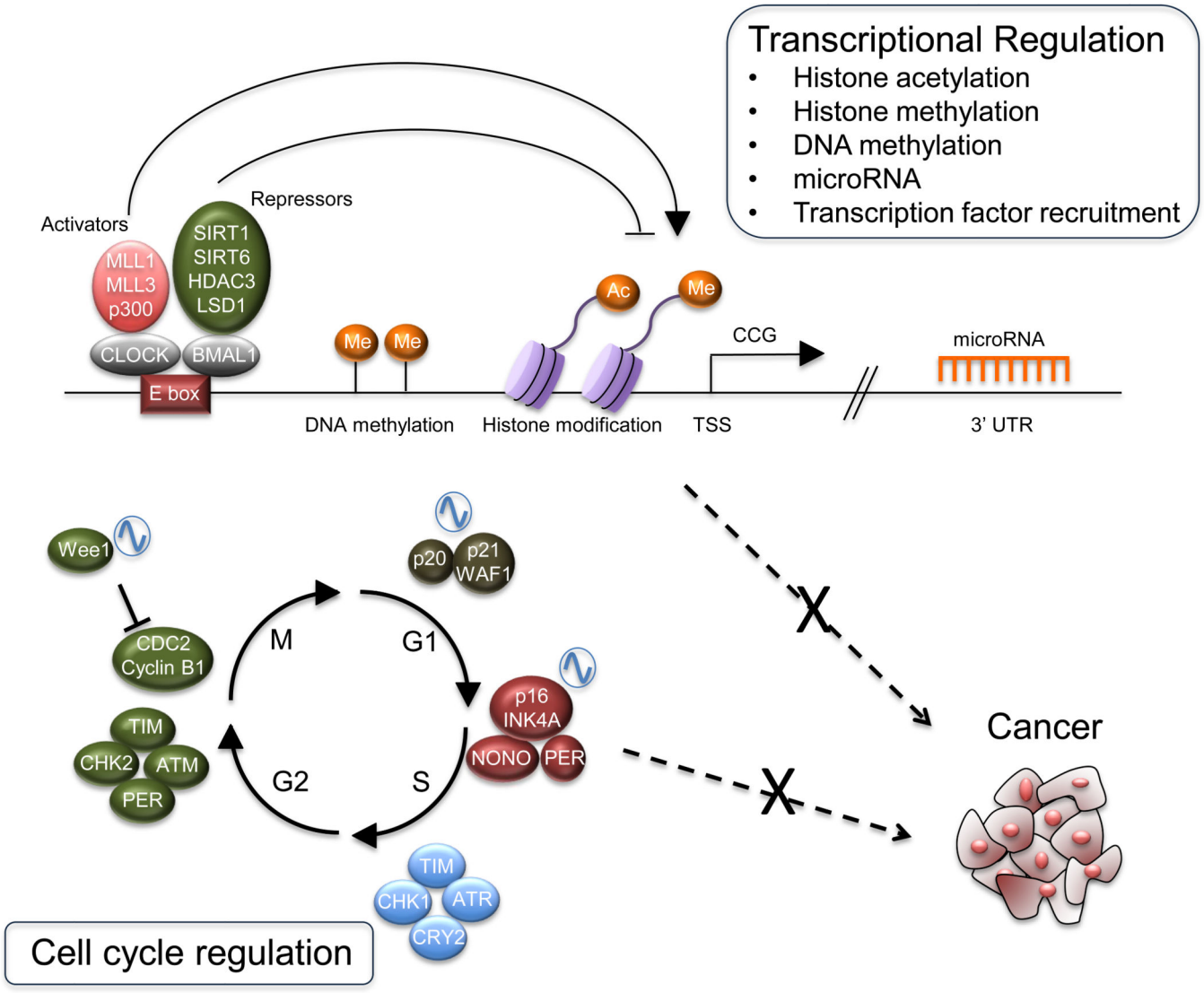


**FIGURE 1.**

Circadian epigenome and cell-cycle regulation in cancer. Schematic representation of the core clock machinery is shown. The activating heterodimer CLOCK:BMAL1 binds to the E-box elements on the genome, controlling a large number of genes. CLOCK:BMAL1 action is counteracted by the PER and CRY repressor proteins. Additional regulators and chromatin remodelers contribute to circadian gene expression. Among the genes controlled by the clock, a number of them are key cell-cycle regulators. The molecular clock has also been shown to interplay with oncogenes and tumor suppressor genes. CRY, Cryptochrome; MLL, mixed lineage leukemia; PER, Period.