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Cancer and the Circadian Clock

Ayesha A. Shafi[1,2], **Karen E. Knudsen**[1,2,3,4,5]

[1]Department of Cancer Biology, Thomas Jefferson University, Philadelphia, Pennsylvania.

[2]Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, Pennsylvania.

[3]Department of Medical Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania.

[4]Department of Urology, Thomas Jefferson University, Philadelphia, Pennsylvania.

[5]Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, Pennsylvania.

Abstract

The circadian clock is a master regulator of mammalian physiology, regulating daily oscillations of crucial biological processes and behaviors. Notably, circadian disruption has recently been identified as an independent risk factor for cancer and classified as a carcinogen. As such, it is imperative to discern the underpinning mechanisms by which circadian disruption alters cancer risk. Emergent data, reviewed herein, demonstrate that circadian regulatory functions play critical roles in several hallmarks of cancer, including control of cell proliferation, cell death, DNA repair, and metabolic alteration. Developing a deeper understanding of circadian-cancer regulation cross-talk holds promise for developing new strategies for cancer interception, prevention, and management.

Introduction

The circadian clock is an evolutionarily conserved, molecular time-keeping mechanism that regulates daily oscillations of biological processes and behaviors (1–4). The central clock is generated and maintained in the suprachiasmatic nucleus (SCN) of the hypothalamus, but cell-autonomous subordinate clocks also exist in peripheral tissues (e.g., liver, kidney, skin, intestine, lung, pancreas, ovary, and heart), which synchronize with one another by the SCN clock through neural and humoral inputs. The SCN synchronizes to environmental cues, such as ambient light, to coordinate circadian outputs and manage selected molecular and physiologic functions on a 24-hour cycle (5, 6). Although the basic molecular architecture of the SCN and peripheral clocks is the same, the SCN clock is the “master clock,” which signals and synchronizes peripheral clocks and others via circadian output pathways, including the autonomic nervous system and the neuroendocrine system. On balance, the circadian clock is vital to maintaining physiologic homeostasis and normal function of all organisms.

Corresponding Author: Karen E. Knudsen, Thomas Jefferson University, 233 South 10th Street, Bluemle (BLSB) 1050, Philadelphia, PA 19107. Phone: 215-503-5692; Fax: 215-923-4498; karen.knudsen@jefferson.edu.

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As a result of both population and laboratory-based findings, the World Health Organization designated circadian disruption as a likely carcinogen (7–9), thus raising interest in understanding how disruption of diurnal patterns promotes tumor development. Epidemiologic studies indicate that circadian rhythm disruptions (e.g., via jet lag, shift work, sleep disruption, and exposure to light at night) are associated with increased cancer risk, including cancers of the prostate, breast, colon, liver, pancreas, ovary, and lung (10–13). Furthermore, loss of circadian control is associated with poor efficacy of anticancer treatments and early mortality amongst patients with cancer (14, 15). In addition, visually impaired individuals who are insensitive to light changes in the environment, and thus depend largely on free-running endogenous circadian clocks to synchronize daily physiology, have a lower overall cancer risk (16). While mechanistic understanding of observed increased cancer risk is incompletely understood, recent findings have begun to uncover the molecular impact of circadian disruption on cancer phenotypes. As will be discussed, circadian processes impact key pathways affecting cancer development and progression, including cell-cycle control, apoptosis, metabolic regulation, and the DNA damage response (DDR; Fig. 1).

Circadian Dysfunction and Cancer

Circadian clock regulation

The core clock machinery is composed of an autoregulatory network consisting of positive and negative transcription-translation feedback loops (TTFL; Fig. 1; refs. 17–19). Transcriptionally, the clock is driven by positive regulators of the loop. Basic helix–loop–helix heterodimeric transcription factors (CLOCK/BMAL1 or BMAL1/NPAS2) regulate expression of key circadian genes including *Cryptochromes* (*CRY1* and *CRY2*) and *Period* (*PER1, PER2*, and *PER3*) genes, which are the negative regulators of the circadian loop. CRY and PER form a transcriptional repressor complex that enters the nucleus to repress CLOCK/BMAL1 activity, thus creating a negative feedback loop to control the clock. *Bmal1* is also rhythmically controlled by its own transcriptional target. In brief, *Rora, Rev-erbα*, and *Rev-erbβ*. RORα stimulate *Bmal1* expression, while Rev-erbα, and β suppress *Bmal1* expression. The importance of these master clock regulators is underscored by the observation that CLOCK/BMAL1 controls expression of approximately 10% of clock-controlled genes, which regulate molecular, biochemical, and physiologic processes (1–4). Furthermore, posttranslational modifications of CRY and PER regulate protein stability, control nuclear entry of CRY/PER repressors, and impact the autoregulatory clock feedback loops. These overlapping mechanisms conferring daily rhythmicity of cellular, metabolic, and physiologic functions for homeostatic maintenance are depicted in Fig. 1 (17, 20, 21). In sum, the circadian clock is tightly controlled through a discrete set of transcriptional regulatory factors; as will be discussed, recent findings link alteration of clock-regulatory factors as contributing to cancer phenotypes.

Tumor-specific functions of CLOCK and BMAL

Numerous studies have linked disruption of circadian clock function to tumorigenesis. Studies to date indicate that CLOCK and BMAL1 may harbor tumor-suppressive roles that are conserved among humans and rodents (2). In humans, single-nucleotide polymorphisms

(SNP) in *Clock* and/or *Bmal1* genes are associated with increased susceptibility to prostate, breast, ovarian, and pancreatic cancers (22–26). SNPs associated with increased cancer susceptibility are located in rs3749474 and rs11943456 (CLOCK) and in rs117104877, rs2290035, rs2278749, and rs969485 (BMAL1). Functional studies will be needed to determine how these alterations may contribute to tissue-specific cancers. Conversely, mice expressing dominant negative *Clock* mutation ($Clock^{\Delta 19}$) incur an expected disruption of circadian rhythm, altering the expression of genes controlling metabolism, chromatin remodeling, DDR, and tumor suppression (27, 28). Moreover, $Clock^{\Delta 19}$-mutant mice have significantly decreased survival when compared with wild-type mice, resulting from cardiac dysfunction and metabolic dysregulation. While Clock-mutant mice do not generate spontaneous tumors, this may be attributed to the decreased overall survival time, and transcriptional profiling reveals an induction of protumorigenic signaling. Similarly, there is significant evidence to suggest that *Bmal1* also serves to restrict tumor development. Suppression of *Bmal1* expression significantly increased the metastasizing potential of prostate, lung, and glioma cancers, both *in vitro* and *in vivo*. Mechanistically, tumor-suppressive qualities of BMAL1 are posited to occur through regulation of the PI3K–AKT signaling axis (29, 30). For instance, the AKT pathway component, ribosomal S6 protein kinase 1 (S6K1), phosphorylates BMAL1 allowing for BMAL1 to both associate with translational machinery and to also stimulate protein synthesis to impact tumorigenesis (31). Furthermore, upstream regulators may play a role in modulating tumor-suppressive potential of CLOCK and BMAL1, as studies have shown that the unfolded protein response induces a phase shift in circadian oscillations via direct regulation of miR-211 to suppress *Clock* and *Bmal1* expression impacting tumor progression (32). While these preliminary studies indicate that Clock and BMAL1 may serve tumor suppressor–like functions, exceptions exist in colorectal cancer, wherein *Clock* and *Bmal1* expression is elevated, and modeling studies linked high CLOCK expression to increased proliferation (33, 34). In addition, in acute myeloid leukemia (AML), *Clock* and *Bmal1* are required for growth of AML (35). Taken together, early data suggest that CLOCK/BMAL1 serve tumor-protective roles, but these functions may be context- and disease-specific.

Tumor-suppressive functions of the CRY and PER family

In addition to CLOCK/BMAL1, evidence exists to implicate *CRY* and *PER* genes in tumor suppression. SNPs and/or upregulation of *Cry1,2* and *Per1, 2,* or *3* are associated with increased susceptibility to prostate, breast, endometrial, colorectal, and skin cancer (22–26). Similar to CLOCK/BMAL1, PER's role as pro or antioncogenic need to be further defined; although, current data indicate tumor-suppressive roles. For instance, several mouse models have demonstrated that mice lacking both alleles of *Per1* and/or *Per2* display an increased risk of spontaneous and radiation-induced tumor development compared with their wild-type counterparts, and this phenotype was further amplified in circadian phase–shifted conditions (36–38). In addition, *Per2*-inactivating mutations in mice exhibit increased risk of neoplastic growth. Specifically, suppression of *Per2* increased cell proliferation in human colon cancer models through regulation of β-catenin and c-Myc, highlighting the tumor-suppressive role of *Per2* (39). PER1 directly interacts with ATM to mediate its effect on tumor-suppressive genes, including *TP53* and *CHK2* to impact tumorigenesis. This interaction is maintained in the presence of DNA damage, where overexpression of PER1 sensitized human cancer cells

to DNA damage–induced apoptosis (40). Thus, PER1 and PER2 clearly exhibit tumor-suppressive roles.

Similarly, mice lacking both alleles of *Cry1* and/or *Cry2* also display an increased risk of spontaneous and radiation-induced tumor development compared with their wild-type counterparts, which was further amplified in circadian phase–shifted conditions (36–38). Interestingly, mice with *Cry1* and *Cry2* mutations are arrhythmic, further supporting their role in maintaining circadian homeostasis (41). Inhibition of *Cry2* expression in breast cancer models leads to dysregulation of genes involved in proliferation, apoptosis, migration, and invasion, again suggestive of a link to tumor development (42). While these collective observations link CRY and PER gene disruption to increased cancer susceptibility, functional dissection of CRY and PER pathways in controlling tumor development remain nascent.

Mechanisms linking clock dysfunction to the hallmarks of cancer

Molecular understanding of Clock, BMAL1, CRY, and PER family functions in circadian regulation are well understood, but data are emergent with regard to the molecular basis of tumor-suppressive functions. As described herein, preliminary findings have identified cross-talk of clock-regulatory proteins with key hallmark pathways controlling cancer development and progression.

Cell-cycle cross-talk.—The mitotic cell cycle and the circadian clock share many similarities as biologic oscillators in dividing cells, as each displays periodic phases of activation and repression. In organisms from cyanobacteria to unicellular eukaryotes (43–46), there is molecular coupling of the processes, wherein the molecular clock serves as an additional “checkpoint” for mitosis that restricts cell division to specific circadian phases (47, 48). However, the relevance of this coupling mechanism is unclear in mammalian cells and is the basis of controversy; whereas a subset of studies reported that most cell divisions occur in specific phases of the circadian cycle, others failed to identify a gating requirement of the cell cycle on circadian clock positioning (49–51). Although the basis of these divergent observations is not known, molecular observations in mammalian cells strongly support the contention that circadian pathways cross-talk with the cell-cycle machinery through transcriptional control or direct protein–protein interactions (Fig. 1).

Studies have demonstrated that circadian clock components can induce or repress cell-cycle progression depending on the time of day, inducing rhythmic transcriptional and posttranscriptional control of the cell cycle. Thus, each phase of the cell cycle has the potential to be influenced by the circadian clock. For example, in G_1 phase, Rev-erbα and RORα/γ repress transcription of the cyclin-dependent kinase (CDK) regulator $p21^{cip1}$, thereby promoting cell-cycle progression (52–56). Conversely, the clock-controlled gene, NONO, regulates the CDK inhibitor $p16^{ink4a}$ expression in a PER-dependent manner at the G_1–S transition causing cellular senescence (52–56). In addition, PER1 and the circadian gene Timeless (TIM) inhibit the G_1–S transition through interaction with ataxia-telangiectasia–mutated (ATM) and checkpoint 2 (CHK2), causing cell-cycle arrest (40). Similar paradigms exist for the G_2–M transition, wherein both positive and negative

influence of circadian clock factors has been reported. CRY1 promotes cell-cycle progression by inhibiting WEE1, the G_2–M regulatory kinase, and thereby inducing mitotic entry. CLOCK/BMAL1 also regulates WEE1 controlling WEE2 rhythmic transcription in a manner that is sufficient to control cell-cycle arrest (52–56). Conversely, in different analyses it was shown that CRY1 restricts mitosis by modulating the ATM, ATR, CHK1-mediated G_2–M transition by interacting with TIM in a circadian-controlled manner (57, 58). Lastly, expression of several known oncogenes (*β-catenin, c-Myc*, and *Mdm2*), cyclins (CCND1, CCNB, and CCN1), and additional cell-cycle regulators (*Cdk4, Wnt3*, and *Tcf4*) are all clock-controlled (59, 60). Thus, tight circadian control at key checkpoints is necessary to promote proper cell-cycle control at the G_2–M checkpoint and maintain physiologic homeostasis. Taken together, these observations indicate circadian factors significantly influence both the G_1–S and G_2–M transition, but elicit distinct effects, dependent on context and the phase of circadian rhythm.

Conversely, cross-talk exists wherein the cell-cycle regulatory machinery impinges on circadian clock function, especially as related to transcriptional silencing occurring during mitosis. As observed, the pivotal tumor suppressor protein p53 is central to coupling circadian and cell-cycle oscillators. Molecular studies demonstrated that p53 directly binds to *Per2* promoter and represses *Per 2* expression, thus disrupting CLOCK/BMAL1 regulation and shifting the circadian cycle (61). In addition, a second tumor suppressor, PML, binds to and promotes PER2 nuclear localization, thus altering circadian timing and homeostasis (62). The overall impact of circadian clockcell-cycle cross-talk on tumor risk is complex, and likely contributes to the impact of circadian disruption on tumor development. Future studies are needed to link these molecular observations to cancer risk mediated by circadian disruption.

Regulation of cancer cell signaling.—Sustaining proliferative signaling remains a key factor among hallmarks of cancer (63, 64), and preliminary evidence exists linking circadian factors to regulation of growth factor processes in cancer. For example, upstream components of the JNK and p38 pathways exhibit the high circadian rhythmicity, including the following: ASK2, MKK7, MMK3, MMK6, p38γ, p38α, and JNK3 (65, 66). There is also evidence of cross-talk in that MKK7-mediated JNK activation increases the half-life of PER2 through phosphorylation, resulting in altered circadian timing (67). Furthermore, GADD45 family members that directly interact with JNK/p38 components also respond to circadian clock–regulated signaling (68). Both *CRY1* knockdown *in vitro* and *PER*-mutant mice demonstrated impaired the circadian expression of *GADD45α* increasing cellular proliferation (38, 42). Finally, downstream components of the ERK1/2 pathway, ERK2 and MKK2, also show significant circadian rhythmicity, implicating connectivity of multiple growth factor signaling pathways with the circadian clock (65, 66). How these observations connect to specific growth factor responses in cancer remains an open question to be addressed.

At the tissue level, the central clock controls cell proliferation in peripheral tissues via the sympathetic nervous system (SNS), which innervates all peripheral organs to control intracellular signaling (69, 70). Studies showed that deregulated SNS signaling, either through surgical ablation or in jet-lagged mouse models, abolishes circadian oscillation and

promotes tumor initiation (36, 71). Deregulated SNS signaling causes loss-of-function in the peripheral clock abolishing CLOCK/BMAL activation and leading to *Myc* oncogenic activation (36, 72). Taken together, balanced circadian control of cellular proliferation through transcriptional control and kinase regulation is key to cellular homeostasis and preventing tumor development.

Clock influence on cell death.—Recent studies established direct relationship between the core circadian clock and apoptosis. Similar to what was observed with cell-cycle regulation, circadian factors can both promote and restrict apoptosis, dependent on cellular context and clock status. With respect to promoting cell death, CRY1/2 and PER1 influence the extrinsic TNFα-dependent pathway and intrinsic apoptotic pathways, respectively (73). Mechanistically, PER2 sensitizes cancer cells to radiation-induced apoptosis through activation of *Myc*-mediated proapoptotic pathways. In addition, knockdown of PER1 results in downregulation of antiapoptotic BCL-2 and upregulation of proapoptotic BAX in hepatocellular carcinoma cells, increasing apoptosis. Thus, circadian factors can promote apoptosis through multiple mechanisms. Conversely, Clock can inhibit apoptosis. Mice defective in CLOCK show decreased expression of apoptosis-inducing factors, which contributes to increased tumor growth (74). In addition, the apoptotic regulators DEC1 (proapoptotic) and DEC2 (anti-apoptotic) repress CLOCK/BMAL–induced transactivation of the *Per1* promoter, thereby influencing circadian regulation of apoptosis (75–77). These collective observations underscore the need to more fully understand the factors that control circadian-mediated cell death regulation, and the impact of these processes on tumorigenesis.

Clock and the DDR.—Perturbed DDRs contribute to cancer phenotypes (78, 79), and a multitude of evidence links circadian clock to DDR competence. In murine models, clock disruption results in accumulation of DNA damage and increased risk of neoplasia. The link between these processes is likely evolutionarily conserved, as *Cryptochromes* are structurally related to DNA photolyases that catalyze light-dependent DNA repair in plants and *Drosophila* (80). The direct role of CRYs in DDR in mammals still has to be fully defined mechanistically; however, several causative studies have shown the importance of *CRY1,2* in DDR. UVB irradiation in the epidermis of $Cry1^{-/-}$; $Cry2^{-/-}$ mice exhibits dampened circadian rhythm in the nucleotide excision repair gene XPA (81, 82). Time-restricted feeding also shifts the phase and amplitude of the epidermis circadian clock, ultimately altering sensitivity to UVB-induced DNA damage and expression of XPA, hindering repair (83). Furthermore, UV-induced DNA damages induce CRY2 interaction with ATR and CHK1 to regulate intra-S checkpoint function (84). The overall involvement of CRYs with DDR regulation underscores the need to fully investigate the contribution of tumor-derived CRY alterations in not only cancer development, but response to therapeutic intervention.

Importantly, other components of the molecular clock including PER1, PER2, and TIM play pivotal roles in multiple DDR processes. PER1 directly interacts with ATM/CHK2 in response to radiation-induced DSBs (40), PER1 overexpression activates *Myc*-mediated apoptosis in response to radiation-induced DSBs, and conversely, downregulation of PER2

confers resistance to radiation-induced apoptosis due to delayed CHK2 activation (38, 85). Accordingly, *Per2*$^{-/-}$ mice incur an increased risk of lymphoma (38, 86). TIM also has functions in DDR, including modulation of CHK1 and ATR downstream of single-strand DNA breaks, and activation of CHK2 via ATM modulation downstream of double strand breaks (87). Taken together, distinct circadian components are necessary to elicit canonical DDR for both single-strand and double-strand DNA breaks.

Complementing these findings, the positive circadian component *Bmal1* has been preliminarily linked to DDR. *Bmal1* knockdown abolishes radiation-induced p53 activation, releasing cells from cell-cycle arrest (88). In addition, *in vivo* keratinocyte-specific deletion of *Bmal1* dampens UVB-induced DDR and increases accumulation of DNA lesions in the epidermis of mice (89). Conversely, the DNA repair factor CCAR2 represses BMAL1 and CLOCK expression and can modulate circadian rhythm (90), providing yet more evidence of cross-talk between DDR and circadian pathways. Understanding the specific timing and pathway regulation by each circadian gene will be pivotal for discerning proper therapeutic regimens to induce sustained responses to genotoxic therapies.

Cancer cell metabolism and the clock.—Coordinated interaction between the molecular circadian clock and the intricate network of metabolic pathways is required for maintenance of physiologic homeostasis in healthy cells. First identified in mammalian red blood cells (91), the metabolic circadian clock is independent of transcriptional activity and is sustained through the redox cycle of peroxiredoxin/thioredoxin/NADPH enzymes (92–94). This complex displays a 24-hour redox fluctuation metabolizing H_2O_2 in various tissues throughout the body. Multiple redox pairs, including: thiols (glutathione-GSH/GSSG) and coenzymes ($FADH_2/FAD^+$, $NADH/NAD^+$, and $NADPH/NADP^+$), dictate the global cellular redox state to influence electron flux and cellular homeostasis (95, 96). In particular, NADPH is able to extend or shorten the 24-hour circadian rhythm in drosophila, mouse tissue, and human cells (97). Thus, NADPH is a critical cofactor that has the potential to function as a circadian-regulated and cancer-promoting metabolite.

Cancer-associated reprogramming of energy metabolism to predominantly utilize glycolytic activity, despite aerobic conditions (Warburg effect), is characterized with higher NADPH formation, decreased TCA cycle activity, and increased fatty acid synthesis (98), and recent studies established a relationship between this process and the circadian clock. For example, melatonin elevation due to light exposure changes leads to decreased growth of prostate and breast cancer xenografts due to disruption of the Warburg effect (99–103). In addition, alterations in the pentose phosphate pathway, which generates NADPH, is tightly controlled in a circadian manner (96). Moreover, sirtuins (SIRT), a family of NAD^+-dependent proteins, interact with the circadian clock to control chromatin remodeling and metabolic output (104). SIRT1 expression is regulated by CLOCK/BMAL; conversely, SIRT1 directly interacts with CLOCK and is known to deacetylate PER2 altering the circadian clock (105–107). This SIRT-circadian system also impacts the TCA cycle through SIRT3 and BMAL, and fatty acid metabolism through SIRT6 governing CLOCK/BMAL recruitment of SREBP1 to circadian promoters (108, 109). On the basis of these findings, evidence is strong that circadian disruption influences metabolic adaptions in favor of cancer development.

Consistent with these findings, controlled feeding times improve metabolic disease even when mice are fed a high-fat diet (110, 111). For example, clock-mutant mice exhibit impaired cholesterol metabolism and promotion of atherosclerosis (112). In addition, ROR$\gamma^{-/-}$ mice display reduced hepatic gluconeogenesis and improved insulin sensitivity; while cell-specific deletion of *Bmal1* led to hypoglycemia (113, 114). The influence of the circadian clock on metabolism also impacts lipogenesis, bile acid synthesis, cardiovascular disease, and inflammation (115). For instance, chronic jet-lag to disrupt the circadian rhythm induced spontaneous hepatocellular carcinoma (HCC) in wild-type mice due to deregulated nuclear receptor–controlled cholesterol/bile acid and xenobiotic metabolism, in addition to global liver metabolic dysfunction similar to the pathway observed in obese patients (116). Moreover, recent studies showed that 50% of detected metabolites oscillate in a mouse liver, and 18 of those metabolites also oscillate in human cell-autonomous U2OS cells (117). Intriguingly, *BMAL1, CRY1*, and *CRY2* knockdown decouples transcriptional and metabolite rhythms by shortening, lengthening, or diminishing rhythms, respectively. Conversely, metabolic alterations can alter the circadian oscillation as well. For example, AMPK is a key nutrient sensor that can destabilize CRY1 and PER2 through phosphorylation, which alters the circadian rhythm (118, 119). Moreover, UBE3A binds and degrades BMAL1 in a ubiquitin ligase–dependent manner to disrupt circadian oscillation (120). In addition, MYC directly activates negative regulators of CLOCK/BMAL1, leading to disruption of circadian metabolic oscillation (121). The insulin-FOXO3-Clock signaling cascade mediates function in hepatic metabolism and oxidative sensitivity (122, 123). Lastly, a recent study showed that a high-fat diet influenced the circadian transcriptome and metabolome due to impaired BMAL1 and PPARγ recruitment (124). Thus, through transcriptional remodeling and posttranslational modifications, the circadian clock regulates metabolism and integrates nutrient signaling critical to maintaining tumorigenesis.

Leveraging circadian rhythm function in cancer management (chronotherapy)

Given the substantial data linking circadian clock dysfunction of cancer pathways, it is reasonable to consider how this process might be modulated to influence tumor growth and survival. The concept of chronotherapy, which considers the body’s natural rhythms and cycles to treat an illness or disorder, was utilized even before the molecular mechanism of the core circadian clock was defined (125). For example, the chemotherapeutic agent, cisplatin, exhibits significant difference in outcomes for patients with prostate, breast, cervical, and ovarian cancer when morning and evening doses were compared, indicating chronotherapy improves the toxic therapeutic ratio of cisplatin and enhances efficacy (126). Furthermore, additional chemotherapeutic drugs exhibited optimal dosing timings to improve outcome in bladder, colorectal, endometrial, and renal cancer (127–130). The activity of several anticancer drugs may be restricted by their side effects and toxicities to healthy cells. Hence, chronotherapeutics aims to maximize the antitumor effects of cancer chemotherapy by minimizing toxicity and undesirable side effects, while simultaneously increasing tolerability to improve the survival rate for patients with cancer.

The role of the circadian clock in chemotherapy administration has also been evaluated using wild-type and circadian clock–mutant mice (131). *Clock*-mutant and *Bmal1* knockout mice are sensitive to chemotherapy regardless of the time of administration of treatment

(132), whereas *Cry1*$^{-/-}$ *Cry2*$^{-/-}$ mice are more resistant to chemotherapy compared with wild-type (133). These *in vivo* studies also revealed that both host tolerability and drug efficacy are affected by circadian timing. Accordingly, it was inferred that response to chemotherapy varies with the time of day, indicating the circadian clock plays an important role in therapeutic outcome (131). In addition, genome-wide circadian gene expression profile studies in mice, nonhuman primates, and human lung and liver tissues indicated that at least 80% of the FDA-approved drugs tested exhibited daily rhythm in their targets and respective downstream functions (134, 135).

Consequently, the successful chronotherapeutic preclinical results were used as justification for several randomized clinical trials for advanced cancers, which revealed that anticancer chronotherapy is most beneficial to patients who maintain their endogenous circadian clock and rhythm (136). This highlights the intricate connection of therapeutic efficacy with individual innate circadian function for ideal outcome. However, a dysregulated circadian clock could alter the efficacy of anticancer drugs, so additional investigation needs to be performed to discern optimal timing for treatment in those disease states. On the basis of these collective data, discerning the mechanisms by which the circadian clock alters cancer therapy may provide insight into refining and augmenting outcomes for the therapeutic intervention.

Conclusions

Circadian disruption is an independent risk factor for cancer and has been classified as a carcinogen. As described herein, perturbations of the circadian clock strongly influence neoplastic transformation and tumor growth through alterations of multiple cancer regulatory pathways including cell cycle, apoptosis, DDR, and metabolism. While the robust link between circadian dysfunction and cancer is well established, mechanistic understanding is nascent. Therefore, it is imperative to continue to elucidate the mechanisms by which the mammalian circadian clock regulates cancer progression.

Key questions remain that must be addressed to delineate the complex roles of the molecular clock in human malignancy. First, is a circadian lifestyle change that incorporates timing of sleep, physical activity, and nutrition enough to diminish disruption of circadian rhythm to reduce cancer incidence? It is intriguing to speculate that cancer risk reduction could be achieved through behavior modification and/or pharmacologic normalization of the circadian cycle. Second, what molecular mechanisms are involved in tissue-specific circadian gene expression and how does that impact tumorigenesis? Peripheral clocks are found in several tissue types, but not all, and the lack of coordinated circadian rhythm leads to differential expression of core circadian genes. The impact of circadian expression on tumorigenesis and other age-related diseases needs to be evaluated. Third, because circadian genes have been associated with high concentrations of sex hormones (137), it would be intriguing to discern the possible role of circadian genes in hormone-related cancers to uncover novel mechanisms of action. Finally, to establish a rational chronotherapeutic strategy, determining the underlying basis of effectivity and optimal implementation strategy will be critical. Future studies will prove instrumental in enriching our understanding of circadian influence on tumor initiation and progression. In conclusion, discerning the

intricate workings of the circadian clock on cancer development and progression has the potential for transformative impact with respect to cancer prevention and management.

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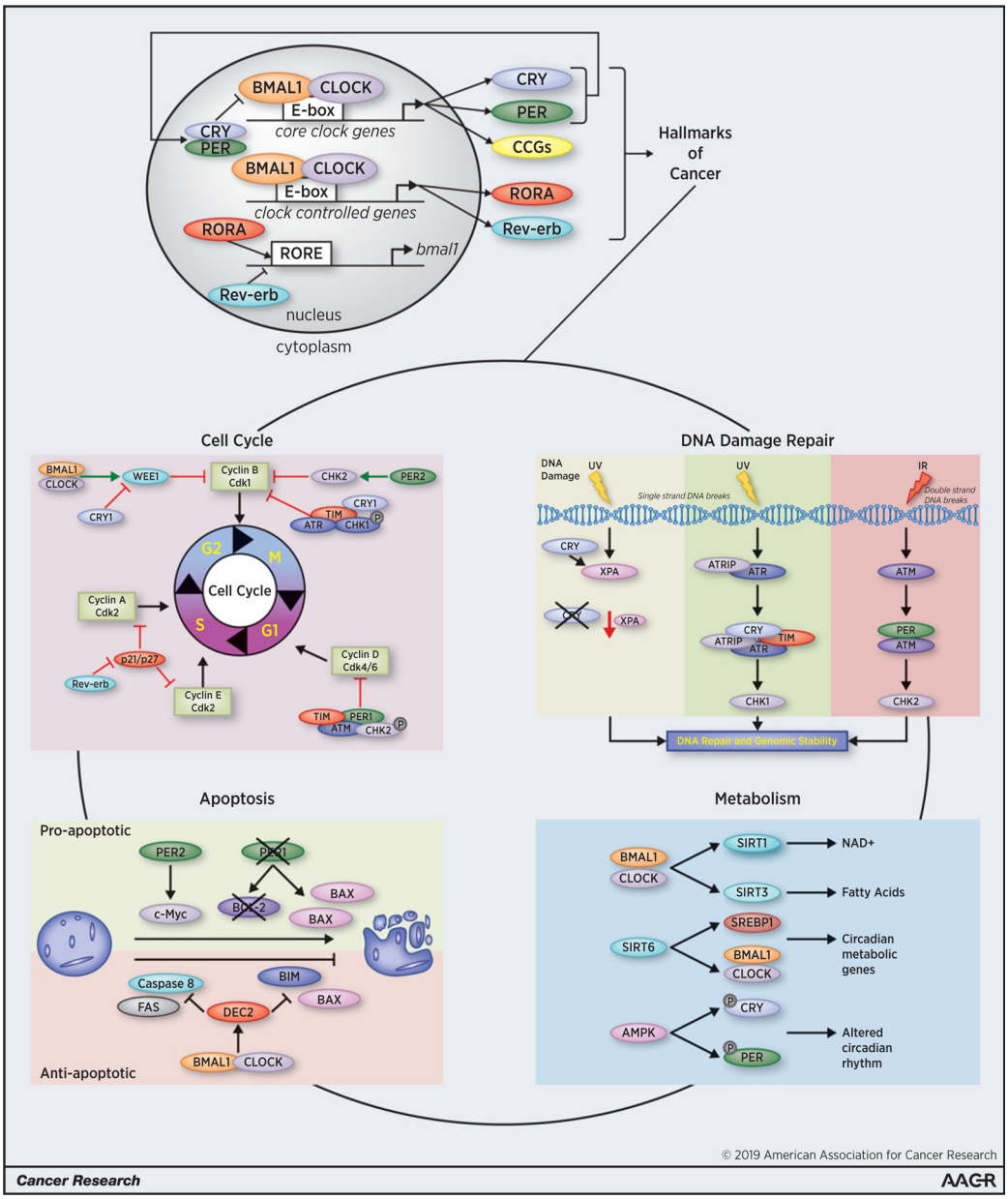

Figure 1.

"Hallmarks" of the circadian clock. The core clock machinery consists of positive (CLOCK and BMAL1) and negative [Cryptochrome (CRY) and Period (PER)] regulators that maintain daily rhythmicity throughout an organism, impacting cell cycle, apoptosis, DNA repair, and metabolic regulation. CLOCK/BMAL1 heterodimers bind to E-box sites to regulate expression of core clock genes (CCGs), including CRY1, CRY2, PER1, PER2, and PER3. CLOCK/BMAL1 also regulates expression of additional clock-controlled genes, such as RORA and Rev-erb, which, in turn, regulate expression of BMAL1 through binding to ROR response elements (RORE). Thus, this autoregulatory network consisting of positive and negative transcription-translation feedback loops confer daily rhythmicity for homeostatic maintenance. The circadian clock influences several biological processes

impacting tumor development and progression. Circadian-controlled processes are vast, including cell cycle, apoptosis, metabolic regulation, and DDR, which are all crucial for physiologic homeostasis. Disruption of circadian homeostasis through various factors is associated with increased cancer incidence and is an important, independent risk factor of cancer development in humans.