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The Circadian Clock in Cancer Development and Therapy

Loning Fu[1,2,3,4] and **Nicole M. Kettner**[1,2]

[1]Department of Pediatrics/U.S. Department of Agriculture/Agricultural Research Service/ Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX, USA

[2]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA

[3]Dan L. Duncan Cancer Center, Baylor College of Medicine, Houston, TX, USA

Abstract

Most aspects of mammalian function display circadian rhythms driven by an endogenous clock. The circadian clock is operated by genes and comprises a central clock in the brain that responds to environmental cues and controls subordinate clocks in peripheral tissues via circadian output pathways. The central and peripheral clocks coordinately generate rhythmic gene expression in a tissue-specific manner *in vivo* to couple diverse physiological and behavioral processes to periodic changes in the environment. However, as the world industrialized, activities that disrupt endogenous homeostasis with external circadian cues have increased. This change in lifestyle has been linked to increased risk of diseases in all aspects of human health, including cancer. Studies in humans and animal models have revealed that cancer development *in vivo* is closely associated with the loss of circadian homeostasis in energy balance, immune function and aging that are supported by cellular functions important for tumor suppression including cell proliferation, senescence, metabolism and DNA damage response. The clock controls these cellular functions both locally in cells of peripheral tissues and at the organismal level via extracellular signaling. Thus, the hierarchical mammalian circadian clock provides a unique system to study carcinogenesis as a deregulated physiological process *in vivo*. The asynchrony between host and malignant tissues in cell proliferation and metabolism also provides new and exciting options for novel anti-cancer therapies.

Introduction

Circadian rhythms in physiological and behavioral processes in plants and animals have been known since fourth century BC. These rhythms were originally attributed to a passive response of organisms to diurnal changes in external light cues, but were later discovered to be generated by an endogenous clock in all species studied[1]. In mammals, circadian rhythms are generated by a central clock located in the hypothalamus suprachiasmatic nucleus (SCN) that constantly synchronizes with environmental cues via circadian input pathways and controls the peripheral clocks through circadian output pathways[2,3].

[4]Corresponding author: loningf@bcm.edu, 713-798 -0342, fax 713-798-7101.

Both central and peripheral clocks are operated by the same set of circadian genes expressed in all tissues studied. The molecular clockwork in mammals has been described in detail in several recent reviews[4–6]. Briefly, it is based on autoregulatory transcriptional feedback loops driven by the heterodimer of bHLH-PAS transcription factors BMAL1/CLOCK or BMAL1/NPAS2 that activate their downstream transcriptional repressor targets *Cryptochrome* (*Cry1*,*2*) and *Period* (*Per1–3*) at the beginning of a circadian day. The accumulation of PER and CRY proteins in the cytoplasm at the end of a circadian day, controlled by the SCF (Skp1-Cullin-F-box protein) E3 ubiquitin ligase complexes, casein kinase 1ε/δ (CK1ε/δ) and AMP kinase (AMPK), leads to the formation of a PER/CRY repressor complex that translocates into the nucleus at the beginning of a circadian night to inhibit the activity of BMAL1/CLOCK or BMAL1/NPAS2 heterodimers and recruit the transcriptional termination complex to the *Per* and *Cry* genes[7]. In addition, the transcription of *Bmal1* is alternatively regulated by its own transcription targets, the nuclear receptors *Rev-erb*α/β (the repressors) and *Ror*α (the activator)[8–10]. The multiple interlocked autoregulatory feedback loops result in a robust circadian variation in the expression and activity of *Bmal1* over a 24 hour period, providing a driving force for circadian oscillation of the molecular clockwork.

The circadian regulators also target clock-controlled genes to generate circadian rhythms in all major cellular processes in both SCN neurons and peripheral organs, resulting in a rhythmic expression of 3–10% of all mRNAs expressed in a given tissue due to time-dependent interactions between the circadian regulators with specific gene promoter sequences, transcription factors, or transcriptional initiation, elongation and termination complexes, as well as the key factors controlling chromatin remodeling[7,11–15]. The clock-controlled genes usually do not share overlapping expression patterns between tissues, suggesting a key role for the circadian clock in controlling tissue-specific function *in vivo*. Clock-controlled genes expressed in all tissues studied include the key regulators of cell proliferation, metabolism, senescence and DNA damage response[16–23].

The molecular clock in SCN neurons and peripheral tissues can be entrained or phase-shifted by cellular signaling. The most potent circadian time cue for the SCN clock is light which is received by a subset of melanopsin-expressing retinal ganglion cells and transmitted directly to the SCN neurons via the retinohypothalamic tract (RHT). Upon activation, the RHT produces neurotransmitters that activate a cascade of signal transduction events leading to circadian phase resetting[24,25]. Although the SCN clock on its own is capable of generating autonomic circadian outputs, the constant coupling of the central clock with environmental cues provides a survival advantage by synchronizing daily physiology and behavior with local time cues[25,26]. A shift in environmental cues, such as traveling across several times zones on an aircraft, induces a phase-shift in the central clock and the subsequent SCN-controlled phase-shift in peripheral tissues via circadian output pathways to reestablish the endogenous circadian homeostasis to the new local time. The number of days needed to fully adjust to the new time zone is dependent on the number of time zones crossed during the trip. Constant back-and-forth phase-shifts of environmental light cues resulted from rotating work schedules or chronic jet-lag, disrupts endogenous circadian homeostasis by uncoupling the central and peripheral clock coordination[27–29].

The best studied circadian output pathways include the autonomic nervous system (ANS) and neuroendocrine system (NES) that control all aspects of mammalian physiology as well as the peripheral clocks via cellular signaling. The rhythmic activities of these systems provide a mechanism for the central clock to control peripheral tissues directly and indirectly via peripheral clocks[24,29–33].

Dramatic changes in lifestyles since the industrial revolution due to increased use of artificial lighting, nightshift working schedules, or rapid long-distance transmeridian travelling have led to frequent disruption of endogenous circadian homeostasis in modern societies. These changes in lifestyle are coupled with a significant increase in the risk of diseases in all aspects of human health including cancer.

Circadian dysfunction promotes cancer development in humans

Circadian disruption is an independent cancer risk factor for humans

Recent epidemiology studies have linked circadian disruption to increased susceptibility of cancer development in all key organ systems in humans. The cancers observed from these studies included breast, ovarian, lung, pancreatic, prostate, colorectal and endometrial cancers, non-Hodgkin's lymphoma (NHL), osteosarcoma, acute myeloid leukemia (AML), head and neck squamous cell carcinoma, and hepatocellular carcinoma[34–49]. Circadian dysfunction-induced cancer risk increases with the number of years, the frequency of rotating work schedules, and the number of hours per week working at night among human night-shift workers[45,46,50–52]. Together, these findings suggest that loss of circadian homeostasis could be an independent cancer risk factor for humans[53]. Due to the prevalence of night shift-work schedules in modern societies, the World Health Organization’s International Agency for Research on Cancer (IARC) listed "shiftwork that involves circadian disruption" as a probable carcinogen in 2007.

Circadian disruption is associated with poor prognosis and early mortality of cancer patients

Loss of circadian homeostasis not only promotes cancer development, but is also associated with poor performance to anticancer treatments and early mortality among cancer patients. After adjusting for other factors that might affect survival, circadian rhythm in salivary and serum cortisol levels as well as daily rest/activity patterns are used as independent prognosis factors for survival and therapeutic response of patients with metastatic breast, lung and colorectal cancers[54–61].

Disruption of the molecular clockworks in human cancers

Ample evidence has linked dysfunction of the molecular clock with pathogenesis of human cancers (Table 1). The mechanisms of dysregulation of the core circadian genes in human cancers discovered to date include epigenetic silencing by promoter methylation, deregulation at the transcriptional and post-transcriptional levels, and structural variations of clock proteins due to circadian gene polymorphisms.

When compared to normal host tissues, decreased expression and polymorphism of the core circadian genes *Per1*, *Per2* and *Per3* are frequently found in human breast, endometrial, prostate, pancreatic, colorectal and non-small cell lung cancers (NSCLC), as well as hepatocellular carcinoma, neck squamous cell carcinoma, glioma, AML and chronic myeloid lymphoma (CML)[62–73]. In CML, breast, endometrial and NSCLC, this deregulation is often linked to hypermethylation of CpG islands or aberrant acetylation in the promoters of *Per* genes, which leads to gene silencing[72,74–77]. Other core circadian genes are also frequently deregulated or silenced in human cancers. For example, the epigenetic inactivation of *Bmal1* is often linked to hematologic malignancies including NHL, diffuse large B-cell lymphoma, acute lymphocytic leukemia (ALL) and AML, whereas polymorphisms in *Clock*, *Cry1*, *Cry2* and *Npas2* gene are frequently found associated with increased risk or recurrence of NHL, AML, endometrial ovarian, colorectal and breast cancers[76,78–82]. In most studies examining the role of the molecular clock in human cancers, deregulation or polymorphism of multiple or all core circadian genes is observed. For example, deregulation or polymorphism of *Per1*, *Per2* and *Per3*, *Clock*, *Bmal1*, *Cry1*, *Cry2*, *Clock*, *Npas2*, and/or *CK1ε* are frequently found in human CML, prostate, pancreatic and epithelial ovarian cancers, leukemia, pleural mesothelioma, hepatocellular carcinoma, glioma and neck squamous cell carcinoma[69,75,81,83–90]. Based on these discoveries, a combined deregulation of *Cry1* and *Bmal1*, *or Cry1 and Per2*, has been suggested as a negative prognostic marker for epithelial ovarian cancer and CML, respectively[84,86,91].

Deregulation of the core circadian genes in human cancers is closely associated with a constitutive activation of intracellular inflammatory and oncogenic signaling pathways including constitutive activation of p38, c-Myc, NF-kB, Bcl-XL, and protein kinase A (PKA)[68,78,92–94], aberrant chromatin remodeling, deregulation of inflammatory cytokines, catalase, Tip60, telomerase, PARP [poly (ADP-ribose) polymerase], Sirt1 and p300[78,92,93,95–97], over-expression of ERα, G1 and S-phase cyclins and suppression of tumor suppressors ATM, p53, p21 and Wee1[83,94,98–100]. Deregulation of the molecular clock is correlated with the loss of control in cell proliferation, metabolism, DNA replication and repair, senescence, apoptosis, DNA damage response and increased drug resistance in all types of human cancer cells studied (Table 1)[68,78,83,88,94,96,98,99,101–107].

Central clock dysfunction increases cancer risk in humans

In the hierarchical organization of the mammalian circadian clock, the peripheral clock can only sense changes in environmental light cues via central clock-controlled circadian output pathways. Thus, central clock dysfunction induced by frequent back-and-forth phase-shifts of environmental cues may play a key role in promoting cancer development among human night-shift workers by disrupting the homeostasis of neuroendocrine function[95,108–110]. This hypothesis is supported by the facts that visually impaired people who are insensitive to changes in environmental circadian light cues and largely or completely depend on a free-running endogenous clock to organize their daily physiology display a lower cancer risk compared to the general population[111–113].

In summary, ample evidence obtained from human studies suggests that the mammalian circadian clock plays a key role in tumor suppression. Therefore, disruption of circadian homeostasis of mammalian physiology is a novel risk factor for cancer (Table 1).

Circadian disruption promotes cancer development in animal models

The central clock suppresses tumor initiation and progression in animal models

The pioneer studies to investigate the role of circadian disruption in cancer development using experimental animal models started in late 1960s. These studies demonstrate that disruption of circadian endocrine rhythms either by constant light exposure or pinealectomy increases spontaneous and carcinogen-induced mammary gland and hepatocellular carcinogenesis in rodents[114–116]. Similar experiments conducted in recent years have also shown that disruption of circadian homeostasis by a short period of back-and-forth or consecutive phase advance shifts of environmental light cues, or by constant light exposure significantly accelerate tumor growth in animals[117–121]. Compared to sham-operated animals, mice lacking a central clock due to surgical ablation of the SCN were unable to maintain circadian rhythmicity in locomotor activity, body temperature and immune function. This loss of circadian homeostasis in SCN-lesioned mice is coupled with a significant decrease in survival time due to increased rate of tumor growth compared to control tumor bearing mice with an intact SCN[122]. Together, these studies agree with the findings from human studies in that circadian dysfunction increases the risk of cancer by demonstrating that disruption of the central circadian clock promotes cancer development and progression in rodents.

Variation in cancer phenotypes reported for circadian gene-mutant mouse models

The role for mammalian circadian genes in cancer genetics was first reported in 2002 in a study showing that mice expressing a mutant PER2 (*Per2*$^{m/m}$) defective in PER2-mediated protein/protein interactions due to a 85 amino acids in-frame deletion in the PAS domain of *Per2* gene display multiple tumor-prone phenotypes including increased spontaneous and γ-radiation-induced lymphoma, hyperplastic growth in salivary and preputial glands, resistance to radiation-induced apoptosis in thymocytes, and deregulation of key tumor suppressors, cyclins and proto-oncogenes, such as *p53*, *Gadd45*α, *Cyclin D1*, *Cyclin A*, *c-Myc* and *Mdm2*[123,124]. The same study also shows that *Per2*-null (*Per2*$^{-/-}$) mice display similar cancer prone phenotypes as *Per2*$^{m/m}$ mice (Supplemental data)[124].

In contrast, other reports indicate that mice deficient in other core circadian genes either lack neoplastic phenotypes or are tumor resistant. For example, mice lacking *Bmal1 (Bmal1*$^{-/-}$*)* show significant reduced lifespan and premature aging, but not spontaneous tumor development[125]. Hepatocytes in mice lacking both *Cry1* and *Cry2* (*Cry1*$^{-/-}$*;Cry2*$^{-/-}$) proliferated slower than wild-type (Wt) hepatocytes in the first 72 hours immediately after partial hepatectomy[126]. Ablation of both *Cry1* and *Cry2* reduced cancer risk for *p53*-null mice[127]. *Clock*-mutant (*Clock*$^{m/m}$) and *Cry1*$^{-/-}$*;Cry2*$^{-/-}$ mice did not show predisposition to cancer in response to a low dose of γ-irradiation[128,129]. Furthermore, MEFs isolated from *Cry1*$^{-/-}$*;Cry2*$^{-/-}$ mice do not show deficiencies in γ-radiation-induced cell cycle arrest, whereas *Clock*$^{m/m}$ MEFs show lower levels of DNA synthesis and cell proliferation than

wild-type controls[19,128]. Together, the studies described above led to the conclusion that the cancer-prone phenotypes discovered in *Per2*$^{m/m}$ and *Per2*$^{-/-}$ mice are the result of loss of a ”none-clock function” of the *Per2* gene but not the function of the mammalian circadian clock[6].

The molecular clock suppresses tumor development in mice

We e suggest that a more detailed analysis of the available information supports a direct role for the molecular clock in tumor suppression in mice.

First, the observation of a temporary slowdown in *Cry1*$^{-/-}$;*Cry2*$^{-/-}$ hepatocyte proliferation immediately after partial hepatectomy cannot predict whether *Cry1*$^{-/-}$;*Cry2*$^{-/-}$ mice are tumor-resistant under normal physiological conditions. Surgical stress caused by partial hepatectomy can suppress the growth of hepatocellular carcinoma in mouse livers until the third post-operative day[130]. In fact, compared to wild-type controls, most mouse models prone to spontaneous hepatocellular carcinoma show an initial delay in hepatocyte proliferation after partial hepatectomy. For example, compared to wild-type controls, mice lacking the nuclear receptor FXR display a delay in hepatocyte proliferation after partial hepatectomy until the 9th post-operative days. However, *Fxr*$^{-/-}$ mice quickly regain the ability of rapid hepatocyte proliferation and develop malignant liver tumors after 12 months of age[131,132]. Since *Cry1*$^{-/-}$;*Cry2*$^{-/-}$ mice show significantly dampened *Bmal1* expression and deregulation of the Mitogen-activated Protein Kinase/Extracellular Signal-regulated Kinase (MAPK/ERK) pathway in the liver[133–135], it would be important to examine whether the temporary delay in hepatocyte proliferation in *Cry1*$^{-/-}$;*Cry2*$^{-/-}$ mice after partial hepatectomy is caused by deficiencies in cellular signaling essential for G1 cell cycle initiation[136,137].

Second, the conclusions that *Per*-mutants are cancer-prone but *Cry*-mutants are tumor resistant are confounded by significant differences in the phenotypes of control wild-type and *p53*-null mice but not *Per*- and *Cry*-mutant mice in different studies[29,124,127,128]. For example, the conclusion that a single 4-Gy sublethal dose of γ-irradiation led to a similar rate of decline in the survival of irradiated wild-type and *Cry1*$^{-/-}$;*Cry2*$^{-/-}$ mice was based on an unusual sensitivity of wild-type mice to γ-irradiation[128], which was not observed in the earlier study indicating increased sensitivity of the *Per2*-mutant mice to the same 4 Gy sublethal γ-radiation[124].

Similarly, discrepancies on the effects of *Per* or *Cry* gene ablation on the survival and tumor developing rate of *p53*-null mice can also be attributed to a significant difference in the average and maximal lifespans of *p53*-null mice[29,127], which vary from 15 to 30 and 28 to 60 weeks of age, respectively, as reported in different studies[138–145]. In accordance with our studies demonstrating that chronic back-and-forth jet-lag significantly accelerated tumor development and reduced survival of *p53*-null mice[29], mice harboring both a mutant *p53* correspondent to the *p53*^{R175H} hotspot mutation in humans and a mutant *Per2* allele (*Per2*^{S662G})[146], which leads to a short and phase-advanced behavior rhythm among human patients suffering from familial advanced sleep phase syndrome due to a single serine to glycine mutation within the CKIε binding region in PER2[147], also display increased tumor incidence and decreased survival compared to *p53*^{R175H} mice[148]. These findings suggest

strongly that circadian dysfunction cooperates with loss of *p53* to promote tumor development.

Different research teams have also independently reached the same conclusion that *Per- and Cry*-mutant mice display a similar neoplastic growth of osteoblasts in bone[149,150], and that disruption of *Period* genes increases cancer risk in mice[29,124,148,151–153]. Therefore, it would be important to verify the role of *Per* and *Cry* genes in cancer risk since *Per* and *Cry* genes are both indispensable for operating the same negative loop in the molecular clock and display the same deregulated behavioral phenotypes[123,154,155]. In addition, despite of a high *Per2* mRNA expression, PER2 protein is not detected in peripheral tissues of $Cry1^{-/-};Cry2^{-/-}$ mice[156]. Indeed, when *Per*- and *Cry*-mutant mice of the same mouse strain were studied under the exact same conditions, the two mouse models display the same increased rate of tumor development in the skeletal, immune, reproductive and digestive systems when kept in steady-state 12 hour light/12 hour dark (24 hour LD) condition, in response to a sub-lethal dose of γ-radiation, or treated with chronic jet-lag after γ-radiation[29]. Together, the evidence obtained from studying mice lacking *Per* or *Cry* under the same conditions strongly argues that as found in human studies, the *Cryptochrome* genes also function in tumor suppression in rodents.

Third, $Clock^{m/m}$ mice show a significant decrease in survival compared to wild-type controls at 80 weeks of age after a sub-lethal dose of γ-radiation. No significant difference in tumor incidence or the rate of radiation-induced apoptosis between wild-type and $Clock^{m/m}$ splenocytes was reported. The decrease in the survival of irradiated $Clock^{m/m}$ mice was attributed to accelerated aging but not tumor development[129]. Since only the apoptotic response of *in vitro* cultured $Clock^{m/m}$ splenocytes to a lethal not a sub-lethal dose of γ-radiation was studied, and that the similar aging phenotypes displayed by irradiated $Clock^{m/m}$ mice are also commonly observed in other irradiated circadian gene-mutant mouse models[29,124,128,129], a role for *Clock* in tumor suppression cannot be ruled out without examining the cancer risk of $Clock^{-/-}$ and $Clock^{-/-};Npas2^{-/-}$ mice as well as irradiated $Clock^{m/m}$ mice after 80 weeks of age. This is because aging is considered a primary risk factor for cancer[157], and the mammalian CLOCK may play a direct role in DNA damage repair after γ-radiation[158]. In addition, CLOCK and NPAS2 play overlapping roles in the molecular clock[159,160]. Unlike $Per2^{m/m}$ and $Per2^{-/-}$ mice that show a similar deregulated circadian phenotype[123,124,155,161], $Clock^{m/m}$ and $Clock^{-/-}$ mice display different circadian behavioral phenotypes and patterns of deregulation of gene expression in somatic cells[162–165].

Fourth, the observations of aggressive aging phenotypes and lack of tumor incidence among *Bmal1*-null mice are not sufficient to exclude a role for *Bmal1* in tumor suppression. When kept in stable 24 hour LD cycles, most spontaneous tumors are identified after 50 weeks of age in circadian gene-mutant mice[29], which is an age most $Bmal1^{-/-}$ mice would not live to[125]. After being treated with a sublethal dose of γ-radiation, although the maximal life-span of $Bmal1^{-/-}$ mice was further decreased, about 6–7% of them developed malignant lymphomas before or at about 40 weeks of age. This rate of tumor development in irradiated $Bmal1^{-/-}$ mice is very similar to the reported rate of tumor development among irradiated *Per*- and *Cry*-mutant mice[29,124,128]. In addition, $Bmal1^{+/-}$ mice that have a similar life-span

as *Per*- and *Cry*-mutants display the same rate of spontaneous and radiation-induced tumor development in the same organ systems as *Per*- and *Cry*-mutant mice[29].

Bmal1-null mice also display a delay in anagen progression and decreased cell proliferation in secondary hair germ cells, which is coupled with increased G1 cell cycle block as shown by decreased levels of RB phosphorylation, increased expression of cyclin-dependent kinase inhibitors $p21^{WAF1/CIP1}$ and $p16^{Ink4A}$, and accelerated epidermal aging[166]. In contrast, mice lacking *Bmal1* only in keratinocytes show constitutive elevation of cell proliferation and intracellular redox levels as well as deregulated UVB-induced DNA damage in the epidermis at linear growth age after wean[22]. However, in a different study, the same keratinocyte-specific $Bmal1^{-/-}$ mouse model was reported to display aging phenotypes in the skin starting from 10 months of age, an age most *Bmal1*-null mice could not survive to[125]. The decreased regeneration of keratinocyte-specific $Bmal1^{-/-}$ hair germ cells reported in this study cannot be rescued by overexpressing oncogenic Sos, a Ras activator[167], suggesting an early onset of replicative or cellular senescence (explained later in this review). Together with the findings that *Bmal1*-null mice display normal skin regeneration and aggressive hyperplastic growth in bone at a young age as well as increased lymphoma development after γ-radiation, and that targeted silencing of *Bmal1* in tumors induces immune suppression and accelerated tumor growth in mice[29,125,149,168], the studies described above suggest that cellular senescence resulted from hyperplastic growth, oncogenic activation and accumulated free radical-induced DNA damage is intrinsic to $Bmal1^{-/-}$ somatic cells. However, in tumors and somatic tissues that can overcome the barriers of cellular senescence and ROS-induced apoptosis, loss of *Bmal1* only accelerates tumor initiation and growth[22,29,166,168]. $Bmal1^{-/-}$ mice are specially distinct from other circadian gene-mutant mouse models in that they lack circadian homeostasis even when kept in 24 hour LD conditions[169]. This severe disruption of endogenous homeostasis at the organismal level may also contribute to increased senescence at the organismal level. However, if *Bmal1*-null mice can overcome aggressive aging, they are likely cancer prone.

Cellular based studies using mouse primary cells lacking core circadian genes

The role of core circadian genes in controlling cell proliferation and DNA damage response has also been studied using various types of primary cells isolated from different circadian gene mouse models *in vitro*[19,29,124,128,129,149,170]. The results obtained from these studies should be explained with caution. For example, primary MEFs cultured *in vitro* behave very differently from somatic cells in tissues prone to tumor development. MEFs are known to be resistant to sublethal doses of γ-radiation induced apoptosis regardless of genotypes, and therefore should not display a high rate of apoptotic death after a sublethal dose of γ-radiation in the absence of aberrant oncogenic activation[128,171,172]. In addition, the cell cycle clock is different from the molecular clock in that it does not free-run (Figure 1)[173,174]. Therefore, the serum shock protocol for setting free-running status of the molecular clock in cultured MEFs is not suitable for studying the role of a core circadian gene in cell cycle control because this protocol requires confluent cell culture condition and only provides growth factor-containing serum for a few hours at the initial serum shocking stage, which leads to uncoupling of the cell cycle clock from the molecular clock due to growth arrest induced by contact inhibition and lack of proper extracellular signals to induce

immediate early genes essential for G1 cell cycle progression after the first day of the experiment[19,175,176].

The choice of cell types and *in vitro* cell culture conditions used in a study may lead to different conclusions on the role of a gene in cell cycle control. For example, under confluent culture condition, serum-shocked differentiated skeletal muscle cells and hepatocytes from *Bmal1*$^{-/-}$ mice show high level expression of *p21*$^{WAF1/CIP1}$, leading to the conclusion that loss of *Bmal1* decreases the rate of cell proliferation[177]. However, when a human RNAi library targeting 8,000 human genes was studied to identify modulators of p53 function using the BJ-TERT-tsLT cells under subconfluent condition, which were originally isolated from normal human diploid foreskin fibroblasts, *Bmal1* was identified as a novel positive regulator of the tumor suppressor p53. Inhibition of *Bmal1* expression in this system led to loss of p53-mediated G1 cell cycle arrest at least in part due to an inability to activate the p53 target *p21*$^{WAF1/CIP1}$ [100].

In summary, genetic studies using various circadian gene-mutant mouse models strongly suggest that as found in human studies, both positive and negative loops of the molecular clock function in tumor suppression in rodents (Table 2).

The role of the mammalian circadian clock in tumor suppression

Cancer is a multifactorial disease *in vivo*. Its initiation and progression need various manifestations of abnormal physiological conditions *in vivo*. As the master regulator of mammalian physiology, the circadian clock acts at the molecular, cellular, tissue/organ and organismal levels to suppress tumor development by maintaining homeostasis of physiology.

The role of peripheral clock in tumor suppression

In cells of peripheral tissues, the clock orchestrates diverse cellular functions in a diurnal oscillating pattern via generation of a network of gene expression at the transcriptional and post-transcriptional levels[9,178–180]. Disruption of the circadian profiles of this gene expression network leads to loss of homeostasis in cell/tissue function, a key mechanism in circadian dysfunction-induced diseases. Recent studies have revealed that in both human and experimental animal models, circadian disruption specially increases the risk of cancers in the immune, digestive and reproductive systems that need daily cell proliferation to support their functions. These findings highlight the importance of circadian control of cell cycle progression in both homeostasis of tissue function and tumor suppression *in vivo*. In peripheral tissues, the molecular clock suppresses neoplastic growth by controlling cell proliferation, metabolism, senescence and DNA damage response.

Control of cell proliferation by the molecular clock—Both cell cycle and molecular clocks are operated by interlocked feedback loops of genes that display periodic and sequential phases of activation and repression at the transcription, post-transcription and post-translational levels[181]. However, although both are considered as “intracellular clocks”, a cell cycle clock is fundamentally different from the molecular clock. First, unlike the molecular clock, the cell cycle clock does not free-run in normal somatic cells. Therefore,

the activities of the peripheral clock and cell cycle clock can be separated in peripheral tissues in the absence of proper extracellular mitogenic signals[174,182–184]. Second, the period of a cell cycle clock is not always fixed as 24 hours throughout one's lifespan. It can vary from only a few hours in early embryogenesis to 24 hours in rapid renewing somatic tissues in adult life or indefinitely long due to cellular senescence[185–188]. Since tumor cells often display the properties of de-differentiation and rapid self-renewal with a cell cycle period shorter than 24 hours, loss of circadian coupling of cell cycle progression in adult life may play a key role in the initiation of neoplastic growth *in vivo*.

Circadian variation of mitotic activity in normal human tissues has been described since 1938[189]. The uncoupling of mitotic rhythm between normal host tissue and metastasizing cancer was first reported in 1940[190]. It is now well-known that cell proliferation in all rapidly renewing mammalian tissues studied follow a diurnal oscillating rhythm under normal physiological conditions but is altered in tumors[78,101,191–197]. The coupling of cell proliferation rhythm between host and tumor has been observed in slow-growing tumors that show considerably higher levels of DNA synthesis and mitotic indices than host tissues throughout a 24 hour period[197–199]. Whereas an ultradian rhythm less than 24 hour in cell proliferation is often found in metastasizing cancers[199–202].

Genome-wide studies have identified a number of genes controlling the key steps of initiation, progression and checkpoint functions of the cell cycle clock as clock-controlled genes[7,11–14]. These genes encode proto-oncogenes, tumor suppressors, caspases, cyclins, transcription factors and ubiquitin-associated factors essential for regulating cell proliferation and death[16–23]. Clock-controlled cell cycle regulators are also expressed in all circadian gene-mutant mouse models studied except that they display significant changes in expression profiles and amplitudes over a 24 hour period, which is coupled with loss of cell cycle control in adult tissues of mutant mice[22,124,126,149,166,167]. Thus, cell cycle clock can function independent of the molecular clock. However, the control of the expression of key cell cycle genes by an intact molecular clock is indispensable for coupling the rate of cell proliferation to diurnal changes in mammalian physiology *in vivo*.

Both positive and negative loops of the molecular clock are involved in circadian control of cell cycle gene expression in peripheral tissues. The best studied clock-controlled cell cycle regulators include oncogenes *c-Myc*, *Mdm2* and β-*catenin*, *Cyclins D1*, *B and A*, and tumor suppressors *p53*, *Wee1* and *p21*$^{WAF1/CIP1}$[98,124,126,149,166,177]. *c-Myc* is an immediate early responsive gene to diverse cell proliferation stimuli. It plays a key role in G1 cell cycle initiation as well as cell growth and death (Figure 1)[203]. The expression of *c-Myc* is tightly controlled in somatic cells in response to diverse stimuli at the transcriptional level via multiple cis-acting sequences in its proximal promoter region[204]. Deregulation of *c-Myc* in cooperation with loss of function in p53 promotes neoplastic transformation, tumor initiation, maintenance and metastasis[205]. In addition to clock-controlled chromatin remodeling, BMAL1/CLOCK and BMAL1/NPAS2 directly regulate *c-Myc* transcription via the two E-boxes in the *P1* promoter of *c-Myc*[124,149,206]. Disruption of circadian rhythm leads to deregulation of *c-Myc* which is coupled with increased neoplastic growth in mice, suggesting that the control of G1 cell cycle initiation is one of the key mechanisms for circadian control of tumor suppression[29,124,149]. Many key cell cycle regulators, such as

Cdk4, *Itga6*, *Wnt3*, *LHx2*, *Tcf4*, *Sox 9*, *Smad7* and *Wee1* are also directly regulated at the transcriptional level by BMAL1/CLOCK heterodimer via E-box-mediated interaction in the gene promoters[126,167,206]. p53 and MDM2 are controlled indirectly by the *Per* genes via the tumor suppressor ataxia-telangiectasia mutated (ATM) at the post-transcriptional level[29,98]. *Bmal1* has also been reported to regulate p53-*p21*$^{WAF1/CIP1}$ signaling, although the molecular mechanism of this regulation is still not clear[83,100,177]. The rhythmic expression of cell cycle genes and tumor suppressor p53 is synchronized with the oscillation patterns of the core circadian genes in normal somatic tissues in both humans and mouse models[29,124,126,207–209].

The core circadian regulators also regulate the activity of β-Catenin via directly controlling intracellular signaling pathways. Constitutive activation of the core circadian regulator CKIε mimics the effect of WNT signaling, resulting in cytoplasmic accumulation of β-Catenin and its subsequent nuclear localization[210,211]. In the nucleus, β-Catenin interacts with transcription factors of the T-cell-specific transcription factor/lymphoid enhancer factor-1 (TCF/LEF) family to regulate transcription and promote tumorigenesis[212,213]. Genes activated by β-Catenin/TCF/LEF include members of the AP1 transcription family, *c-Myc* and *Cyclin D1*[214–219]. Interestingly, the molecular clock itself also responds to β-Catenin nuclear localization to regulate the expression of genes via BMAL1/CLOCK-mediated transcriptional regulation[167]. Aberrant activation of β-Catenin also disrupts the molecular clock to promote neoplastic transformation by inducing β-transducin repeat-containing protein (β-TrCP)-mediated PER2 degradation[151].

In the absence of WNT signaling, β-Catenin is destabilized by glycogen synthase kinase-3β (GSK3β), a functional homologue of the core circadian gene *Shaggy* in the fruit fly, which functions in regulating the period length of circadian cycles by indirectly controlling PER stability and nuclear entry[220,221]. Recent studies have revealed that deregulation of GSK3β promotes tumor cell survival, proliferation, invasion and resistance to chemo- and radiation therapy in humans by inhibiting p53 and RB tumor suppressors, inducing intracellular NF-κB signaling, *Cyclin D1* over-expression and local chronic inflammation[222,223]. The activity of GSK3β exhibits robust circadian rhythm in both SCN and peripheral tissues, suggesting that GSK3β may also indirectly target PER2 in the mammalian molecular clock[224]. Together, the evidence discussed above suggests that the molecular clock couples cell proliferation with mammalian daily physiology by rhythmically pacing the key cell proliferation and tumor suppression pathways at the cellular level. Since the molecular clockworks operate as interlocked feedback loops, disruption of either a positive or negative loop would disrupt the stability of the molecular clock leading to loss of control in the circadian homeostasis of cell cycle progression[29,135,156,225,226]. Indeed, deregulation of both positive and negative loops of molecular clock frequently occurs in the same type of tumor in humans[76,78–81,83,84,86,88,94,227,228].

Control of DNA-damage response by the molecular clock—An average human being contains about 10^{14} cells, each receives tens of thousands DNA lesions every day. If not repaired, these lesions induce harmful mutations that could affect the survival of cells or even an organism[229]. DNA damage activates genes encoding key enzymes in DNA repair machinery and cell cycle checkpoints that pause cell cycle progression to give the cell time

to repair damaged DNA before continuing to divide[230]. When DNA damage exceeds the capacity of the cell to repair, efficient elimination of damaged cells by apoptosis or necrosis plays a key role in suppressing tumor development[231].

DNA damage response in mammals is mainly controlled by two master kinases, ATM and ataxia telangiectasia and Rad3-related (ATR)[232,233]. ATM/ATR targets the protein kinases CHK1 and CHK2, which together with ATM and ATR suppress cyclin-dependent kinase (CDK) activity and activate CKIs such as $p21^{WAF1/CIP1}$ in a p53-dependent manner[205,234]. Inhibition of CDKs and activation of CKIs lead to arrest of cell cycle progression at the G1/S, intra-S or G2/M checkpoints to allow DNA damage repair[235,236]. ATM/ATR signaling also enhances DNA repair by transcriptionally and post-transcriptionally activating DNA-repair genes and by recruiting repair factors to the sites of damage. Activation of p53 by ATM/ATR signaling in response to genomic DNA damage often leads to p53-mediated apoptosis (Figure 1)[237].

A large number of key players in DNA replication, recombination and repair has been identified as clock-controlled genes in mice[7,11–14]. Some of these genes, such as Xeroderma pigmentosum A (XPA) that plays an essential role in nucleotide excision repair, are deregulated in $Cry1^{-/-};Cry2^{-/-}$ mice, which correlates with a dampened circadian rhythm in nucleotide excision repair after UVB irradiation in $Cry1^{-/-};Cry2^{-/-}$ epidermis[238,239]. The evidence of direct involvement of *Cryptochromes* in DNA damage repair in mammals is still missing, although *Cryptochromes* are structurally related to evolutionarily conserved DNA photolyases that catalyze light-dependent DNA repair in plants[240]. However, mammalian CLOCK may play a direct role in DNA damage repair because it directly locates to the sites of γ-radiation-induced DNA double-strand breaks[158]. PER1 was found directly interacting with ATM and CHK2 in response to γ-radiation-induced DNA damage. Overexpression of PER1 in human cancer cells sensitizes cells to radiation-induced apoptosis by activation of *Myc*-mediated pro-apoptotic pathways[98]. The human CRY2 has been reported to interact with ATR and CHK1 to regulate intra-S checkpoint function in UV-induced DNA damage response via Timeless (TIM), a natural partner of PER in *Drosophila* and is necessary for maintaining the robustness of the mammalian central clock[241,242]. The role for BMAL1 in DNA damage response is shown by a recent study in which knock-down *Bmal1* expression abolishes γ-radiation-induced p53 activation as well as p53-dependent $p21^{WAF1/CIP1}$ induction in human colorectal carcinoma cells[100]. All core circadian genes studied are activated by exogenous DNA damage agents such as γ-radiation in peripheral tissues following a time-dependent profile over a 24 hour period in mice. Wild-type mouse thymocytes display a time-dependent response to γ-radiation-induced apoptosis *in vivo*, while loss of function in *Per2* leads to resistance to radiation-induced apoptosis in thymocytes throughout a 24 hour period and increased risk of radiation-induced lymphoma in $Per2^{m/m}$ *and* $Per2^{-/-}$ mice[29,124,243,244]. Thus, the potentiation of the molecular clock to respond to DNA damage agents varies at different times during a day and plays a key role in determining the outcomes of DNA damage response.

Control of cell metabolism by the molecular clock—Cancer is classically considered as a disease originated from genetic and epigenetic abnormalities that lead to uncontrolled cell growth and division, and formation of metastasizing tumors. The

prevalence of metabolic syndromes worldwide and its coherence to cancer has led to a renewed interest in the Warburg effect, which describes an essential role of deregulation of cell metabolism in cancer initiation. In 1956, Otto Warburg observed that normal quiescent somatic cells metabolize glucose to CO2 and H2O via a low rate of glycolysis followed by oxidation of pyruvate in TCA cycle in mitochondria. However, cancer cells predominantly use glucose to produce energy through a high rate of glycolysis followed by lactic acid fermentation in the cytosol even in the presence of abundance oxygen. Warburg predicted that this metabolic reprogram is a fundamental cause of cancer[245]. Studies in the past decade have revealed that cancer cells display an array of metabolic abnormalities and that both oncoproteins and tumor suppressors can influence the switch between aerobic glycolysis and the use of TCA cycle to generate ATP[246–251]. The predominant use of the aerobic glycolysis pathway in cancer cells not only leads to a high level of intracellular reactive oxygen species (ROS), a major source of endogenous DNA damage agents promoting cancer and aging, but also the accumulation of intermediate products including purines, pyrimidines, nonessential amino acids and free fatty acids that can be used for anabolic synthesis, cell growth and division[249,252–254].

The mammalian circadian clock is a master regulator of metabolic homeostasis both at the organismal and peripheral tissue levels[6,255–258]. In peripheral tissues, the molecular clock regulates nutrient uptake, metabolism, energy storage, mitochondria biosynthesis and intracellular redox levels by targeting key metabolic genes including those controlling the Warburg effect, such as glucose-6-phosphatase, pyruvate kinase and glucose transporter 2 (GLUT)[17,20,179,259,260]. It also responds to food cues and nutrient sensors to shift metabolic balance independent of SCN clock function[12,261–266]. The peripheral clock also indirectly controls Warburg switch by regulating the expression of oncoproteins and tumor suppressors. For example, p53 inhibits aerobic glycolysis and decreases intracellular ROS levels by suppressing GLUT1–4 and fructose-2,6-bisphosphate, a critical substrate of aerobic glycolysis, via the tumor suppressor p53-induced glycolysis and apoptosis regulator (TIGAR)[267,268], and promotes the use of TCA cycle by inhibiting glycolic enzyme phosphoglycerol mutatase[269]. Whereas c-MYC stimulates biosynthesis to support cell growth and proliferation via upregulating lipogenetic, glycolytic and mitochondrial genes[270–273], and increases glutamine uptake to compensate for the progressive loss of glucose as a mitochondrial substrate in cancers cells due to Warburg effect[274]. Myc also upregulates mitochondrial biosynthesis by regulating genes including nuclear respiratory factor 1 (NRF1) and the transcription factor A, mitochondrial (TFAM) as well as *cytochrome C* to stimulate the production of ROS[275–279]. Although elevated ROS leads to *Myc*-mediated apoptosis in normal somatic cells[280], loss of function or deregulation of p53 in combination of *Myc* oncogenic activation results in the metabolic switch to support cell proliferation, apoptotic resistance and neoplastic transformation[254,281–285].

The molecular clock not only controls metabolic homeostasis by regulating nuclear receptors and their co-activators and suppressors as well as chromatin remodeling in metabolically active peripheral tissues[6,255–258,286], but is also regulated by nuclear receptors REV-ERBα/β, RORα and PPARγ coactivator PGC-1α that play an active role in energy metabolism, adipogenesis and lipid storage in peripheral tissues, and by nutrient sensors

such as adenosine monophosphate-activated protein kinase (AMPK)[8–10,265,287]. Therefore, disruption of the molecular clockworks would inevitably shift the homeostasis of metabolism and energy balance in peripheral tissues to provide an intracellular environment that favors tumor initiation and progression.

Control of cell senescence by the molecular clock—Aging is frequently associated with disruption of circadian rhythmicity in humans and animal models[288–290]. Premature aging is commonly observed among circadian gene-mutant mouse models. Among them, *Bmal1*$^{-/-}$ mice display the most aggressive aging phenotypes leading to a significantly reduced lifespan[125]. Other circadian gene-mutant mouse models including mice carrying a mutated *Clock* (*Clock*$^{m/m}$) or lacking *Per* or *Cry* genes (*Cry1*$^{-/-}$;*Cry2*$^{-/-}$, *Per1*$^{-/-}$;*Per2*$^{-/-}$, *Per2*$^{m/m}$ or *Per2*$^{-/-}$) also display premature aging phenotypes which become more evident in response to DNA damage agents such as γ-radiation[29,124,128,129]. These premature aging phenotypes of circadian gene-mutant mouse models are closely related to deregulation of cell proliferation and DNA damage response *in vivo*.

Aging is an universal process for all multi-cell organisms on earth, which is measured chronologically by biological changes over time and is accompanied with a dramatic increase in the risk of various diseases at the mid-point of the life span[291]. Although aging is marked by progressive degeneration of tissue and cell function *in vivo*, it is also coupled with increased risk of neoplastic growth in renewable tissues in mammals, leading to the conclusion that aging is a primary risk factor of cancer[292,293]. The mechanisms linking aging to cancer including immunosenescence and age-related endocrine dysfunction at the organismal level as well as telomere shortening, reproductive cell cycle and accumulation of DNA damage over a lifetime[294–299]. These adverse age-related pathological changes have led to the conclusions that if humans live long enough, they would all eventually develop cancer[300,301].

Throughout the life span, mammals need continuous cell proliferation to support their daily physiology. However, the inherent limitations in DNA repair mechanisms inevitably lead to accumulation of errors in genomic DNA, which often results in replicative or cellular senescence, a direct cause of aging[302–306]. Senescence refers to a state of permanent and irreversible withdrawal from cell cycle resulted from accumulation of cellular damages including DNA lesions, oncogenic activation, and/or over-expression of tumor suppressors[157]. Since cancer cells do not have a limited replicative life span, cellular senescence is often used to enforce the idea that it suppresses cancer development[307]. However, mounting evidence suggests that cellular senescence also promotes cancer initiation and progression. Senescent cells are still metabolically active and often show changes in chromatin organization and gene expression, leading to secretion of proinflammatory cytokines, proteases and growth factors. The paracrine activities of senescent cells have been found to stimulate proliferation and migration of neighboring cells and promote the development of metastatic tumors[308–311]. The activation of *Myc*, Ras/MAPK oncogenic signaling and/or p53/*p21*$^{WAF1/CIP1}$ and pRB/p16^{INK4a} tumor suppressing pathways are established molecular mechanisms for cellular senescence[312–315]. Under certain conditions, suppression or even a subtle change in the expression of these tumor suppressors could lead to senescent cells to rapidly regain the ability to proliferate[316].

Increased oxidative stress in circadian gene mutant mice may lead to a higher level accumulation of DNA damage which induces early cellular senescence to promote aging[125,289,317]. The modulators of the molecular clock, such as NAD-dependent deacetylase sirtuin-1 (SIRT1) may play a role in bridging aging and cancer-prone phenotypes found in circadian gene-mutant mice[6]. SIRT1 is a class III histone deacetylase that promotes cell survival by inhibiting apoptosis and cellular senescence in mammals[318]. SIRT1 expression follows a robust circadian expression *in vivo*. It directly interacts with CLOCK and deacetylates BMAL1 to regulate the activity of the molecular clock[12,13], and also plays a role in regulating cell proliferation and apoptosis by deacetylating key tumor suppressors and oncoproteins including p53, β-Catenin and DNA repair protein KU70[319–321]. Both *Bmal1* and *Per2* are found to inhibit cellular senescence *in vivo* possibly by distinct mechanisms. *Per2*-mutation leads to AKT-dependent vascular senescence that impairs endothelial progenitor cell function, while loss of *Bmal1* promotes senescence *in vivo* via a p53-independent mechanism[23,322]. The increased cellular senescence found in circadian gene-mutant mice may be explained by their inherent high risk of deregulation of oncogenic and tumor suppression pathways, high intracellular levels of redox and its associated accumulation of genomic DNA damage, and abnormal internal physiological environments that promote oncogenic extracellular signaling. These abnormalities together with lack of proper control of gene expression could increase paracrine activities and loss of senescence surveillance, which not only leads to increased local tissue damage and inflammation that stimulate cell regeneration but also the possibility of re-entering cell cycle of senescent cells. Since cancer is a clonogenic disease *in vivo*, one or a few premalignant cells that successfully escape senescence surveillance would be sufficient enough to promote cancer development *in vivo*[205,323].

Tumor suppression *in vivo* is a clock-controlled physiological function

Although an intact molecular clock can provide self-sustained circadian oscillations in peripheral tissues, peripheral organs rely on daily entrainment signals from the central pacemaker to maintain the synchrony of the internal physiology. Disruption of central clock function leads to phase desynchrony among peripheral tissues[182]. Such desynchronization of the internal circadian homeostasis is closely related to increased risk of tumor development and accelerates tumor progression in both humans and experimental animal models[34–49,54–59,117–122]. The key entrainment signals from the central clock include extracellular signaling controlled by the autonomic nervous and neuroendocrine systems (ANS and NES)[24]. Loss of homeostasis of ANS and NES disrupts circadian homeostasis of cancer immune surveillance and energy balance as well as G1 cell cycle progression in renewable peripheral tissues, which synergistically promote tumor development.

The mechanisms of SCN control of peripheral tissues have been discussed in detail in several recent reviews[24,30–33,258,324]. Briefly, via direct and indirect targeting, the SCN clock controls brain centers especially those in the hypothalamus including the paraventricular nucleus (PVN), arcuate nucleus (ARC), dorsomedial hypothalamus (DMH), lateral hypothalamus (LHA) and endocrine neurons producing corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH). The CRH, TRH and GnRH control the activity of NES via the

hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axes, while ARC, DMH, LHA and PVN control energy expenditure and food-intake in response to both central and peripheral signals. The autonomic paraventricular neurons (aPVN) directly project to the preganglionic parasympathatic and sympathetic neurons in the brainstem nuclei, dorsal motor nucleus of the vagus (DMV), and intermediolateral cell columns (IML) of the spinal cord to control parasympathatic and sympathetic nervous systems. The SCN control of aPVN neurons leads to a robust circadian oscillation in the function of the autonomic nervous system (ANS) *in vivo*. The example of SCN control of NES is demonstrated by the rhythmic activity of HPA axis. The SCN pacemaker indirectly generates circadian oscillation of Adrenocorticotropic hormone (ACTH)-controlled corticosterone production from the adrenal gland into the blood via controlling hypothalamic CRH endocrine neurons[324]. *In vivo*, the ANS innervates all peripheral tissues except skeletal muscle through G-protein-coupled transmembrane-receptor (GPCR) in a tissue and/or cell type-specific manner[325–327]. Hormones produced by the pineal gland, HPA and HPG axes, such as melatonin, glucocorticoids, and oestrogen target a wide range of peripheral tissues especially the immune, metabolically active and reproductive organs[328–335]. The rhythmic intracellular signaling generated by neurotransmitters and hormones plays an essential role in maintaining homeostasis of tissue microenvironment (Figure 2).

Control of G1 cell cycle progression in peripheral tissues by the central pacemaker—In the central pacemaker, light stimuli activates a cascade of intracellular signal transduction pathways in the SCN neurons to phase-shift the center pacemaker including the MAPK, ERK, Protein Kinase C alpha (PKCα), Calcium/Calmodulin-dependent Protein Kinases II (CaM kinases II), c-Jun N-terminal kinase (JNK), c-AMP-Protein Kinase A (PKA) and Nitric Oxide (NO)/c-GMP pathways that differentially regulate the expression of the immediate early genes c-*Fos* and *JunB* and the core circadian genes *Per1* and *Per2* in a time-dependent manner[336–345]. The peripheral clocks do not directly respond to light stimuli, but are instead synchronized by cyclic changes in the levels of neurotransmitters, growth factors, cytokines and hormones in tissue microenvironment[324,346,347]. Despite the sensitivity of the peripheral clock to non-SCN cues such as food cues, metabolites, or fluctuation in body temperature, the central pacemaker plays a dominant role in peripheral clock control to maintain the integrity of the internal physiology[24].

The best understood intracellular signaling pathways for entraining the peripheral clock by ANS and NES include glucocorticoid and beta-adrenergic receptor (ADRβ)-mediated activation of the molecular clock. The interaction of glucocorticoid with glucocorticoid receptor (GR) in the cytoplasm stimulates GR nuclear localization and activation of GR-mediated transcription via Glucocorticoid-Responsive Elements (GREs) in gene promoters[348,349]. GREs are found in the regulatory regions of *Per1, Per2, Bmal1* and *Cry1* genes[350–352], and both CRY1 and 2 directly interact with GR in a ligand-dependent fashion to modulate the transcriptional activity of GR[353]. Administration of dexamethasone, a glucocorticoid analog, phase-shifts the molecular clock in cultured rat-1 fibroblasts as well as in mouse livers. Although unable to phase-shift the SCN clock, dexamethasone can resynchronize about 60% of the circadian transcriptome in the livers of SCN-lesioned mice

via at least in part directly phase-shifting the molecular clock[31,350]. Adrenalectomy results in deregulation of the core clock genes, desynchronization and dampening of the molecular clock in multiple peripheral tissues[354].

The SNS directly innervates all peripheral tissues by releasing norepinephrine (NE) to target adrenergic receptors (ADRs) on cell membranes. It also controls the production and secretion of epinephrine (EPI) from the adrenal medulla, which then target all cells expressing ADRs in the body via blood circulation[355]. ADRβ2 is the best studied ADR that responds to ligand binding by activating cAMP Response Element-Binding Protein (CREB) which then interacts with the cAMP Response Element (CRE) in promoters to regulate gene transcription. *Per1* and *Per2* both contain CREs in the promoters and are among the immediate early genes activated by CREB in cultured primary osteoblasts, NIH3T3 cells and mouse liver slides in response to administration of isoproterenol, a synthetic agonist of ADRβ2, EPI or NE *in vitro* and in mouse livers after intraperitoneal injection of adrenalines *in vivo*[29,149,356]. Loss of function in *Per1* and *Per2* or sympathectomy abolishes SNS-induced peripheral clock activation in affected tissues in rodents[29,149,357–360].

The activation of ADRβ is followed by β-arrestin-mediated receptor desensitization. As multifunctional scaffold proteins, the interaction of β-arrestins with ADRβ leads to activation of other signal transduction pathways including the MAPK, Ras/ERK, JNK, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), β-Catenin, CaM kinases II, Phosphatidylinositide 3-Kinases/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/AKT/mTOR), Janus kinase 3/Signal Transducer and Activator of Transcription (JAK3/STAT), insulin-like growth factor 1 (IGF-1) and MDM2-p53 pathways[134,361–365]. Glucocorticoid signaling also crosstalks with pathways controlled by NF-κB, β-Catenin, PI3K and epidermal growth factor receptor (EGFR)[366–370]. The pathways stimulated by glucocorticoid and ADRβ signaling not only modulate the molecular clock at transcriptional and post-translational levels but also cell proliferation, apoptosis and metabolism in a tissue and cell type-specific manner, leading to coupling of peripheral clock activity with tissue-specific functions *in vivo* (Figure 3)[246,252,254,316,371–374].

The initiation of G1 cell cycle progression *in vivo* is strictly controlled by extracellular signals that activate proto-oncogenes *c-Myc* and/or *E2f* via intracellular signaling include c-AMP-PKA, MAPK, Ras/ERK, JNK, β-Catenin, and/or PI3K pathways in a cell type-specific manner[174]. Loss of homeostasis in HPA axis and ANS signaling is frequently associated with increased risk of cancer[375,376]. The role of central clock in controlling cell cycle progression in peripheral tissues can be explained by a model obtained from studying circadian control of *Myc* transcriptional activation. In cultured primary osteoblasts, isoproterenol-mediated ADRβ signaling stimulates cell cycle progression via a coupled activation of peripheral clock, cell cycle clock and p53 controlled by immediate early genes including *Per1* and *Per2, Ap1 and Myc*, and ATM, respectively. Activation of *Myc* leads to cell cycle progression, while activation of peripheral clock prevents *Myc* overexpression and also stimulates ATM-mediated p53 induction. Loss of function in the *Per* genes, or elevated concentration of isoproterenol, prevents the activation of peripheral clock and ATM but not AP1-controlled *Myc* activation, leading to suppression of p53 induction and uncontrolled osteoblast proliferation due to *Myc* overexpression. The PER proteins may be directly

involved in SNS-stimulated ATM activation since PER1 has been found to interact with ATM in response to γ-radiation[98], whereas CRY proteins may prevent uncontrolled c-AMP-PKA-CREB-*AP1-c-Myc* signaling in response to ADRβ activation by directly inhibiting the G_s alpha subunit (Gsα) essential for activating adenylate cyclase[377]. *In vivo*, *Per*- and *Cry*-mutant mice both show uncontrolled SNS signaling and display a phenotype of neoplastic growth of osteoblasts in bone[29,149,150,377,378]. Disruption of homeostasis of SNS signaling by chronic jetlag is associated with the disruption of peripheral clock function, suppression of p53 and *Myc* oncogenic activation, which is coupled with increased tumor development in all mouse models studied[29]. Together with previous reports on increased tumor development and progression in rodent models treated with constant light exposure, pinealectomy, chronic jet-lag, or SCN-lesion, these findings provide an explanation on how circadian dysfunction induces tumor development in the absence of gene mutations[117–122], which is especially relevant for developing novel strategies for cancer prevention in the modern world in which frequent disruption of endogenous circadian homeostasis due to lifestyle change is associated with a dramatic increase in the risk of sporadic cancers (Figure 4)[379].

Circadian control of cancer immune surveillance—The current concept of cancer immunoediting is based on the evidence of sequential steps of elimination of transformed cells *in vivo* by the immune system[380]. When transformed cells accumulated above a threshold, they are recognized by lymphocytes including Nature Killing T (NKT), Nature Killing (NK) and gamma deltaT (γδT) cells that are stimulated by transformed cells to produce interferon γ (IFN-γ). This triggers a cascade of innate immunity including the induction of chemokines CXCL9, 10 and 11 to block neovascularization in the tumor and the recruitment of NK cells, dendritic cells, macrophages and other immune effector cells to the tumor site. The anti-proliferative effects of IFN-γ on transformed cells and the cytocidal activities of macrophages and NK cells result in the death of tumor cells which are ingested by dendritic cells and trafficked to the draining lymph node, where the tumor specific $CD4^+$ and $CD8^+$ T-lymphocytes are developed. These tumor-specific T-lymphocytes are then directed to the tumor site along a chemokine gradient, where they act together with NK cells and activated macrophages to recognize and destroy tumor cells[380,381]. Mice deficient in cancer immunoediting display a significantly higher risk of spontaneous tumor development in the immune, digestive, respiration and reproductive organs[382–386]. Cancer immunoediting is usually abolished by cancer-induced immunosuppression in human cancer patients[380,381].

The mechanisms of cancer immunosuppression include deregulation or loss of expression of cancer cell surface markers leading to lack of recognition of transformed cells by cytotoxic T lymphocytes, resistance to cell death induced by cytotoxic T lymphocytes due to deregulation of apoptotic factors and death receptors, production of immunosuppressive factors including free radicals, cytokines and growth factors that negatively affect cancer immunoediting by impeding the proliferation and/or function of $CD4^+$ and $CD8^+$ T cells. The immunosuppressive microenvironment in tumors also stimulates the generation and/or promotion of immunosuppressive cells such as type 2 macrophages, myeloid-derived suppressor cells, immature dendritic cells and regulatory T lymphocytes[380,381,387,388].

Both primary and secondary lymphoid organs including thymus, spleen and lymph nodes are intensively innervated by ANS and NES[389–394]. Under normal physiological conditions, the production of cytokines and cytolytic factors, proliferation of leukocytes, activities of NK cells, and redistribution of T and B lymphocytes, dendritic cells, leukocytes and macrophages to lymphoid organs all follow a robust circadian rhythm *in vivo*[395–403]. Disruption of circadian homeostasis is closely related to immune suppression[404]. Ablation or deregulation of the core circadian genes *Per1*, *Per2*, *Bmal1*, *Rev-erbα*, or *Clock* in mice induces an array of abnormalities in the immune system, including deregulation of proinflammatory cytokines, cytotoxic receptors, immunoregulatory genes and NK and mast cell activities, and inhibition of B lymphocyte differentiation[164,397,405–411]. Mice lacking both *Cry1* and *Cry2* display constitutive elevation of proinflammatory cytokines and are prone to chronic inflammation, a common underlying mechanism for cancer[93]. Importantly, the immune function is not controlled at the cell autonomous level *in vivo*. Consecutive phase advance shifts of environmental light cues disrupt the molecular clock and circadian homeostasis of NK cell function in rats[412]. Ablation of sympathetic innervation abolishes the circadian oscillation of cytokines and cytolytic factors in splenocytes and NK cells[359], haematopoietic stem cell trafficking and the expression of chemokine CXCL12[360]. Adoptive transfer of *Bmal1*$^{-/-}$ bone marrow deficient in B lymphocyte differentiation to lethally irradiated BALB/c*Rag2*$^{-/-}$ recipients that are unable to generate mature B lymphocytes due to lack of V(D)J recombination activating gene 2 (*Rag2*) resulted in normal T and B lymphocyte differentiation from *Bmal1*$^{-/-}$ bone marrow. However, reciprocal transfer of BALB/c *Rag2*$^{-/-}$ bone marrow to lethally irradiated *Bmal1*$^{-/-}$ mice did not lead to normal B lymphocyte development, suggesting that the SCN control of tissue microenvironment in bone marrow plays a dominant role in lymphocyte precursor proliferation and differentiation *in vivo*[410].

The central pacemaker not only controls the function of immune system but can also be modulated by immune products such as proinflammatory cytokines Interleukin 1 and 6 (IL-1 and IL-6), Tumor Necrosis Factor-α (TNF-α) and anti-inflammatory drugs, which alter intracellular expression of *Bmal1*, *Npas2*, *Cry1* and/or *Per2*[413–415] and the activity of the SCN clock and HPA axis at the organismal level[416,417]. Such modulation provides a circadian-paced immune-regulatory feedback loop that acts as an internal cue to the central clock to control the homeostasis of internal physiology.

Circadian homeostasis of energy balance suppresses tumor development— Human nightshift workers show a coupled increase in the risk of metabolic syndromes and cancers[29,46,418–422]. Disruption of circadian rhythm in mouse models also induces metabolic syndromes and whole body, local and/or organ-specific adiposity[6,255–258,423–425], which is coupled with a significantly higher risk of tumor development in the digestive system[29]. As discovered from cancer epidemiological studies, deregulation, epigenetic silencing and/or polymorphisms of core circadian genes including *Per2*, *Bmal1*, *Cry2* and *Clock* are frequently associated with increased risk of obesity and metabolic syndromes in humans[426–431]. Together, these findings strongly argue that disruption of circadian homeostasis of energy balance is an important cancer risk factor.

Energy homeostasis *in vivo* is maintained by the reciprocal interaction of peripheral adiposity signals and the central nervous system[432,433], which are both under close surveillance of the circadian clock[258,434]. Although beyond the scope of this review, the evidence of direct and indirect interactions between the SCN pacemaker and the brain energy homeostasis center ARC, feeding and satiety center LHA and catabolic center PVN suggest that although the central circadian clock does not directly respond to food cues[435], it plays an active role in the brain circuits of energy balance[436–441]. Together with its role in modulating daily activity of NES and ANS that controls the production and circulating levels of most if not all peripheral adiposity signals as well as metabolic balance in peripheral tissues[33,442–448], the central pacemaker acts as a master regulator of energy homeostasis *in vivo* (Figure 2).

Although the biological mechanisms linking obesity and cancer are still not well-understood, obesity-induced deregulation of extracellular signaling, angiogenesis and chronic inflammation are considered as the major pathways promoting cancer development[449–451]. Obesity leads to increased production of metabolic hormones from the fat and livers of obese subjects, such as Leptin and bioavailable IGF-1, which stimulate biosynthesis, cell growth, proliferation and survival via activation of intracellular signaling pathways including the PI3K/AKT/mTOR, MAPK and JAK3/STAT pathways that are often abrrantly activated in tumors[452–454]. Obesity also promotes chronic inflammation by increasing circulating free fatty acids, proinflammatory cytokines IL-1β, IL-6, TNF-α and monocyte chemoattractant protein (MCP)-1, stimulating type 2 macrophages polarization, and activating NF-κB-mediated proinflammatory and pro-proliferation pathways[450,455–457]. Such changes in tissue microenvironment lead to tissue damage due to increased cell necrosis induced by constant stress of increasing in biosynthesis, oxidative stress and DNA damage, which in turn stimulates tissue regeneration that needs active cell proliferation to support. However, the deregulation of multiple oncogenic and tumor suppression pathways as well as immunosuppression due to circadian disruption would result in increased risk of neoplastic growth that accelerate cancer development in obese subjects[458–460].

Anticancer chronotherapy

Chemotherapy using one or more cytotoxic drugs in conjunction with radiation therapy or surgery is one of the most common procedures for anticancer therapy. Since chemotherapeutic drugs indiscriminately target both cancerous cells and normal host cells in renewable tissues, these drugs often generate intolerable side effects that impair the treatment[461]. The “targeted” anticancer therapy developed in recent years is aimed at blocking the growth of cancer cells via monoclonal antibodies recognizing tumor-specific antigens on tumor cell surface or small molecules that block intracellular tyrosine-kinase signaling including MARK/ERK, JAK, PI3K, CDKs, estrogen receptor (ER), epithelial growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) controlled pathways[462]. However, since these signaling pathways are also important for mediating neuroendocrine functions in host tissues, these small inhibitors also potentially increase the risk of fatal side effects among cancer patients[463]. Thus, to maximally increase tumor targeting efficiency and protect normal host tissues are the biggest challenges for successful anticancer treatments.

Tumors are derived from host tissues after regaining the properties of rapid self-renewing and de-differentiation phenotypes. Most biological processes supporting tumor growth are also essential for normal physiological functions of the host except that the biological processes in normal host tissues are properly controlled and integrated with the daily physiology. Thus, anticancer treatments would inevitably have adverse effect on patients. Biological processes determining the efficiency of anticancer drugs including drug absorption, distribution, intracellular metabolism and elimination all follow circadian rhythms in the host[464]. In addition, once inside the tumor cells, the function of a cytotoxic drug is largely determined by the circadian phase of cell proliferation in the tumors, which even in the advanced stage tumors is not temporally disorganized[192,197–201,465]. Therefore, to apply anticancer treatment at a selected time during the day based on circadian variation in host internal physiology and the asynchronies in cell proliferation and drug metabolic rhythms between normal and malignant tissues could maximize drug toxicity to tumors and increase the efficiency of anti-cancer treatment[466].

Studies using mouse models have revealed that both host tolerability and drug efficacy are affected by circadian timing, and that the best therapeutic index is achieved by coupling the time for drug delivery with host endogenous circadian rhythms[467]. These results have been extrapolated to randomized clinic trials of patients undergoing treatment for advanced-stage cancers including metastatic ovarian, lung, colorectal, and breast cancers using conventional chemotherapeutic drugs[58,468,469]. The results of these studies have revealed that current procedures of anticancer chronotherapy indeed leads to better therapeutic outcomes and is especially more beneficial to patients who still maintain the endogenous circadian rhythmicity. The improved therapeutic index is shown by reduced drug toxicity, improved tumor response rate and the duration of the response, and decreased frequency of tumor metastasis. However, although chronotherapy has been shown to significantly increase the survival time for children with ALL[470], it does not increase the long-term survival of patients with metastasizing cancers[471], suggesting that anti-cancer chronotherapy is still at its initial stage of practice and needs further improvement. The facts that the molecular clock directly responds to genotoxic insults and that mice deficient in the *Clock*, *Bmal1* and *Cry* genes all respond differently to anti-cancer drugs compared to wild-type controls suggest that the response to anticancer treatment is a complicated clock-controlled physiological function *in vivo*[124,243,244,472]. Further investigation of the mechanisms of cancer chronotherapy, especially the mechanisms controlling the response of the circadian clock to anticancer treatment, the consequence of such response to host physiology and tumor biology, the effect of tumor development on host circadian homeostasis and the ability of the clock to respond to anticancer treatment would contribute greatly to improve the current anticancer chronotherapy.

Conclusions

The rate of cancer continues to rise as more people live to an old age and changes in lifestyle affect more developing countries[473]. Cancer is usually not detected at the early stage due to lack of obvious symptoms[474,475]. However, the fact that only 5–10% of all cancers diagnosed are caused by inheritated genetic mutations suggests that an unhealthy lifestyle is the major risk factor for cancer. Therefore, cancer is preventable[379]. Mounting evidence

obtained from recent studies suggests that disruption of endogenous circadian homeostasis is a novel and independent risk factor for cancer. In addition, as a master regulator of mammalian physiology, disruption of the clock likely manifests cancer development and progression induced by previously identified exogenous and endogenous cancer risk factors including diet choices, tobacoo and alcohol usage, viral infection, air polutions, aging, endocrine dysfunction, metabolic syndormes and immnue deficiencies[476,477]. Although still at the initial stage, recent advancements strongly suggest that both tumor suppression and response to anticancer treatments are clock-controlled physiological functions *in vivo*. Therefore, the mammalian circadian clock provides an invaluable and exciting system to study the mechanism of cancer and anticancer chronotherapy at the molecular, cellular, tissue organ and organismal levels *in vivo*. Such studies will have a significant impact on human health in the future by improving both cancer prevention and treament.

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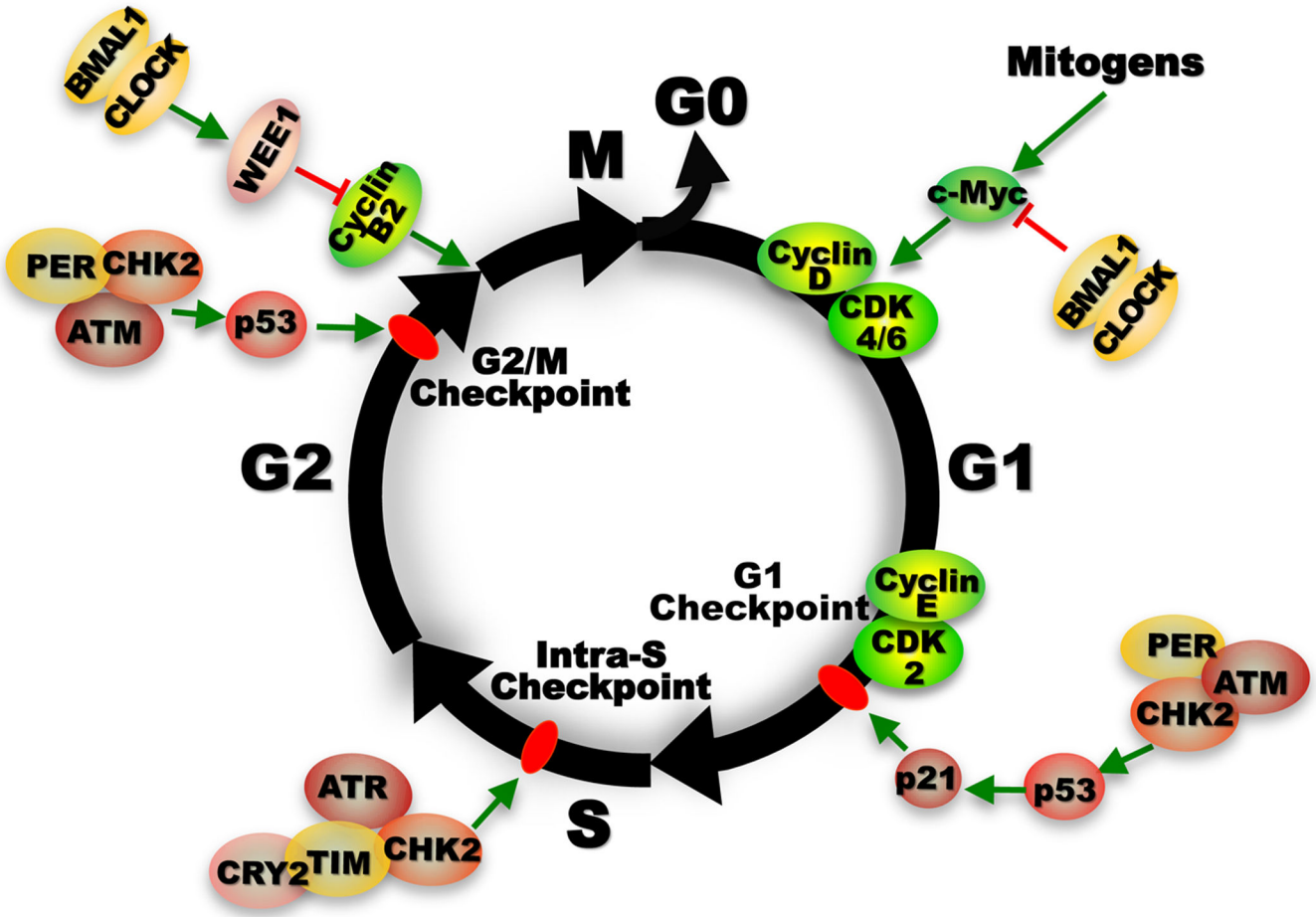

Figure 1. Control of cell proliferation by the molecular clock

Unlike the molecular clock, the cell cycle does not free run before passing the G1/S phase transition. The initiation of cell cycle progression is strictly controlled by extracellular mitogenic signals that transiently activate immediate early genes such as *c-Myc*, which then induces Cyclin D leading to activation of CyclinD/CDK4/6 complex that in turn activates E2F-dependent Cyclin E expression by suppressing tumor suppressor RB (not shown). The interaction of Cyclin E with CDK2 allows G1 to S phase transition. G1 is the longest phase in the cell cycle during which most biosynthesis essential for supporting cell cycle progression occurs. c-MYC or E2F oncogenic activation induced elevation of G1 Cyclin expression or genomic DNA damage leads to activation of G1 checkpoint mediated by $p16^{Ink4A}$ and $p21^{WAF1/CIP1}$, controlled by RB and p53 respectively. $P16^{Ink4A}$ disrupts Cyclin D/CDK4/6 complex (not shown), whereas $p21^{WAF1/CIP1}$ disrupts Cyclin E/CDK2 interaction. The activation G1 checkpoint leads cells to pause before entering S-phase to repair damaged DNA or exit cell cycle to enter G0 phase (non-dividing status). Under certain conditions, excessive DNA damage or uncontrolled oncogenic signaling can both activate RB and/or p53 tumor suppression pathways leading to cellular senescence. DNA damage induced by UV radiation leads to activation of ATR/CHK1-mediated intra-S checkpoint that couples DNA damage repair with replication. Whereas double-stranded DNA damage induced by γ-radiation activates ATM/CHK2-mediated G1/S and G2/M

checkpoints to prevent damaged cells to enter S or mitotic (M) phase. Prolonged G2/M checkpoint arrest is also often associated with p53-mediated apoptosis. G2/M transition is also regulated by WEE1, a kinase that phosphorylates and inactivates the Cyclin B1/Cell Division Cycle 2 (CDC2) complex essential for G2/M transition. Upon the completion of mitosis, cells either enter the next cell cycle stimulated by extracellular mitogen, or withdraw from cell cycle to enter the G0 phase in the absence of mitogenic signals[174,234]. The molecular clock functions in all phases of the cell cycle to prevent neoplastic growth. At the early G1 phase, the BMAL1/CLOCK heterodimer down regulates *Myc* transcription to prevent its overexpression[29,124,149]. PER1 directly interacts with ATM and CHK2 to control G1 checkpoint in response to double-strand DNA damage[98]. In the S phase, CRY2/TIM complex directly interacts with ATR/CHK1 to control intra-S checkpoint[242]. In the G2 phase, PER-mediated ATM/CHK2/p53 signaling in response to DNA double-strand breaks and BMAL1/CLOCK activated *Wee1* expression both lead to activation of G2/M checkpoint to prevent inappropriate M phase entry[98,126].

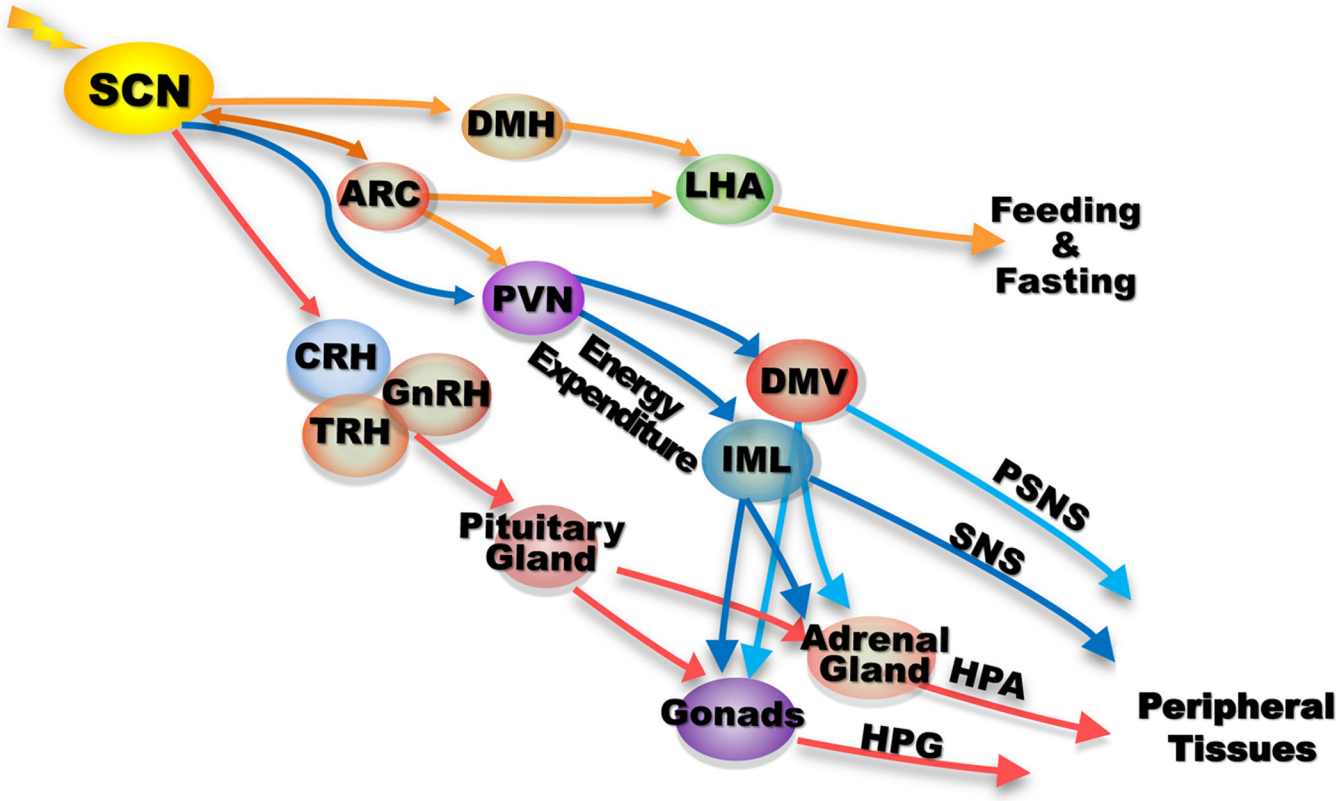

Figure 2. Peripheral control by the SCN pacemaker

The SCN clock targets a variety of brain centers within the hypothalamus to control homeostasis of endogenous physiology. It controls nutrient intake and energy expenditure by targeting the brain energy homeostasis center arcuate nucleus (ARC) and catabolic center paraventricular nucleus (PVN) directly, and feeding and satiety center LHA indirectly via ARC and dorsomedial hypothalamus (DMH). It also controls the neuroendocrine system (NES) by directly targeting the corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH) neurons that control the adrenal and gonadal glands via pituitary glands. The SCN pacemaker directly targets the autonomic paraventricular (aPVN) neurons that project to the preganglionic parasympathetic and sympathetic neurons in the dorsal motor nucleus of the vagus (DMV) and intermediolateral cell columns (IML) of the spinal cord to control parasympathetic and sympathetic nervous systems (PSNS and SNS). Both PSNS and SNS also crosstalk with the HPA and HPG axes by directly innervating the adrenal and gonadal glands. The NES and ANS innervate all peripheral tissues *in vivo* to generate circadian rhythm of internal physiology by controlling extracellular signaling and peripheral clock activity[24,30–33,258,324].

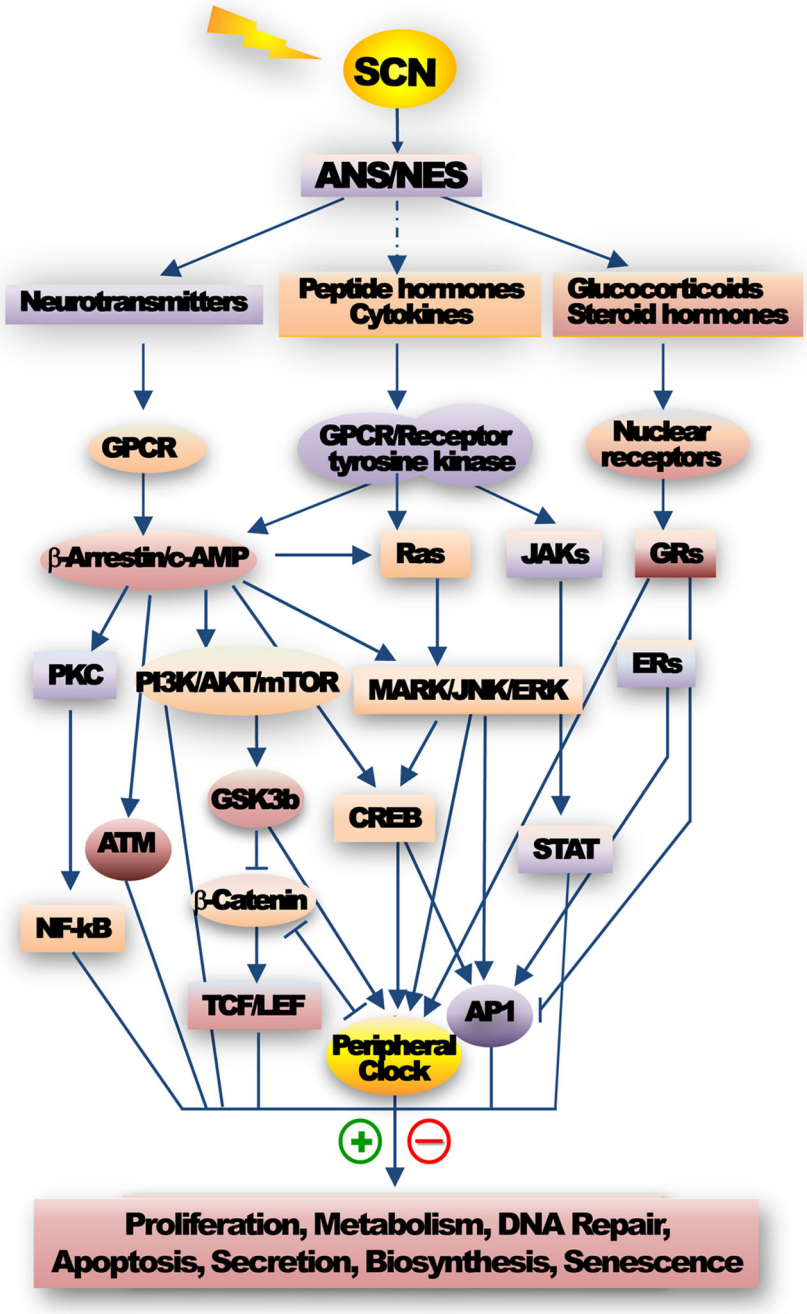

Figure 3. Circadian control of intracellular signaling

The central pacemaker controlled autonomic nervous and neuroendocrine systems (ANS and NES) rhythmically signal to all of their target tissues. The resulting circadian rhythm in peripheral tissue function also generates local and/or circulating signaling molecules that rhythmically act on their targets. Together, these extracellular signals including neurotransmitters, steroid hormones, peptide hormones, chemokines, growth factors and cytokines activate intracellular signaling mediated by G-protein coupled receptors (GPCRs), tyrosine kinase receptors, integrins (not shown), and nuclear receptors in a tissue and cell-

type specific manner. These same intracellular signaling pathways also activate the peripheral clock. The coordinated activities of the central and peripheral clocks orchestrate the complicated extracellular and intracellular signaling to maintain tissue homeostasis by controlling a network of gene expression. Disruption of the central clock-controlled extracellular signaling or mutations in core circadian genes both abolish peripheral clock activity leading to loss of circadian homeostasis in peripheral tissues. The representative intracellular signaling pathways directly or indirectly controlled by the central clock shown in the figure include the c-AMP/PKA/CREB/AP1, Ras/MARK/JNK/ERK and PI3K/AKT/β-Catenin/TCF/LEF pathways essential for *c-Myc* activation and cell cycle progression[478–480], the PI3K/AKT/mTOR signaling controlling biosynthesis and drug resistance[451,481], the GPCR/ATM signaling for p53 activation[29], the GPCR/PKC/NF-κB pathway that regulates stress and immune response[482], the JAK/STAT pathway controlling apoptotic response[483], and the GR and ERα signaling pathways cross-talking with the AP1 signaling[484,485]. These signaling pathways also control the expression and function of circadian genes leading to a coupled activation of the molecular clock with tissue-specific function *in vivo* including cell proliferation, metabolism, apoptosis, DNA repair, biosynthesis, secretion and senescence[371–374].

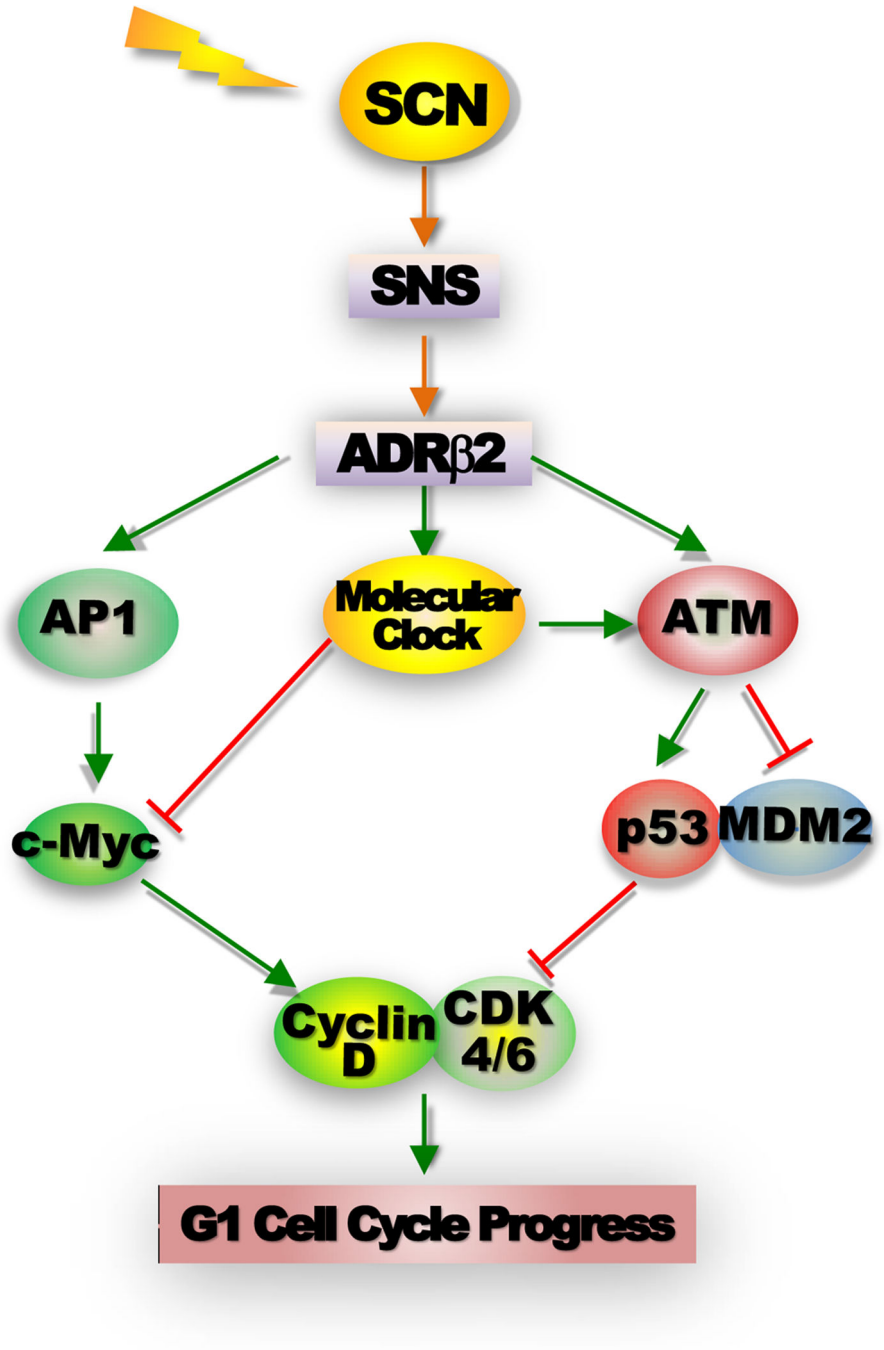

Figure 4. Control of G1 cell cycle progression by the peripheral clock and the SNS

The activation of the β-adrenergic receptor 2 (ADRβ2) by SNS signaling leads a coupled induction of *Ap1* and *Period* genes via CREB-mediated transcriptional regulation, which in turn activates AP1-controlled *Myc* induction and *Myc*-dependent G1 cell cycle progression as well as peripheral clock that prevents *Myc* overexpression via BMAL1/CLOCK-mediated transcriptional regulation. The activation of ADRβ2 intracellular signaling and the peripheral clock also synergistically activate ATM, which induces p53 by blocking p53-MDM2 interaction to provide an additional mechanism for preventing MYC oncogenic

activation. Disruption of the central clock-SNS-peripheral clock axis in mice by chronic jet-lag or ablation of *Per* genes suppresses peripheral clock activation in response to ADRβ2 activation and abolishes ATM-mediated p53 induction but had no effect on *Ap1-Myc* signaling. Together these events lead to uncontrolled G1 cell cycle progression and neoplastic growth of osteoblasts both *in vitro* and *in vivo*[29,149].

Table 1

Deregulation of the Core Clock Genes in Human Cancers

Cancer Type	Circadian genes Deregulated	Deregulated Targets	Cellular Functions Affected	References
Breast cancer	*Bmal1, Clock, Cry1, Cry2, Per1, Per2, Per3,* and *Npas2*	BCCIP, BCL2, BRAC1, ERα, Estrogen, EXO1, cAMP, CDKN1A, Cortisol, CyclinD1, c-ERBB2, GADD45A, HERC5, Melatonin, MCM5, MSH2, p21, p38, p53, PARP, PKA, PPP1R15A, SIRT1, SUMO1, TERT, TIP60, and UBA1	Apoptosis, cell cycle control, chromatin remodeling, DNA damage repair, and teleomere length	38, 39, 42, 44,45, 48–50, 53, 55, 63, 66, 74, 80, 92, 96, 99, 100, 102, 104–107
Acute Lymphocytic Leukemia (ALL)	*Bmal1* and *Clock*	Catalase, c-MYC, and p300	Cell cycle control and chromatin remodeling	78
Acute Myeloid Leukemia (AML)	*Bmal1, Per1, Per2,* and *Per3*	Catalase, c-MYC, and p300	Cell cycle control and chromatin remodeling	78
Chronic Lymphocytic Leukemia (CLL)	*Cry1 and Per2*	ZAP70	Cell cycle control, chromatin remodeling, and DNA damage repair	86, 91
Chronic Myeloid Leukemia (CML)	*Bmal1, Cry1, Cry2, Per1, Per2,* and *Per3*	c-MYC, CyclinB1, and p53	Apoptosis, cell cycle control, and chromatin remodeling	75,94
Colorectal cancer	*Clock, Per1, Per2,* and *Per3*	Cortisol, ATM, EGFR, ER-β, EXO1, IL-6, MSH2, p53, PARP, TGFα, and TNFα	Chromatin remodeling and DNA damage repair	34, 43, 54, 58, 62, 82, 98, 101, 102
Endometrial cancer	*Cry1, Per1, Per2,* and *Per3*	Melatonin	Chromatin remodeling	36, 42, 76
Glioma	*Cry1,Cry2, Per1, Per2,* and *Per3*	N/A	Apoptosis and cell cycle control	64, 65, 90
Head and neck squamous cell carcinoma	*Bmal1, CKIε, Cry1, Cry2, Per1, Per2, Per3,* and *Tim*	TIP60	N/A	52, 70, 85, 104
Hepatocellular carcinoma	*Cry2, Per1, Per2, Per3,* and *Tim*	CDC2, CyclinB1, EZH2, GR, IGF-1, and WEE1	Cell cycle control, chromatin remodeling	47, 71
Lung cancer	*Clock, Per1, Per2,* and *Per3*	Cortisol and TIP60	Cell cycle control, chromatin remodeling, DNA damage repair	43, 56, 57, 72, 98, 104
Malignant pleural mesothelioma	*Bmal1, Cry2, Per1, Per3, Npas2, Rev-erb*α, *Rev-erb*β and *Tim*	CASP3, CyclinB, CyclinE, $p21^{WAF1/CIP1}$, and WEE1	Apoptosis, cell cycle control, chromatin remodeling, and deregulated chemotherapy drug response	83, 87
Non-Hodgkin's Lymphoma (NHL)	*Npas2*	DMC1, EXO1, and MSH2	Cell cycle control, DNA damage repair, and immune deficiency	37, 79, 102
Diffuse large B-cell Lymphoma	*Bmal1* and *Clock*	Catalase, c-MYC, and p300	Chromatin remodeling	78
Osteosarcoma	*CK1ε* and *Per2*	CASP3, CyclinB, and CyclinA2	Apoptosis and cell cycle control	40, 88
Ovarian cancer	*Bmal1, CK1ε, Clock, Cry1, Cry2, Per1, Per2,* and *Per3*	Cortisol	Apoptosis, cell cycle control and deregulated chemotherapy drug response	39, 84, 103

Cancer Type	Circadian genes Deregulated	Deregulated Targets	Cellular Functions Affected	References
Pancreatic cancer	*Bmal1*, *CK1ε*, *Clock*, *Cry1*, *Cry2*, *DEC1*, *Per1*, *Per2*, *Per3*, *Tim*, and *Tipin*	BCL-XL, CDC2, CyclinB1, TNF-α, and USP30	Apoptosis, cell cycle control and chromatin remodeling	68, 69, 77, 89
Prostate cancer	*Bmal1*, *CK1ε*, *Clock*, *Cry1*, *Cry2*, *Npas2*, *Per1*, *Per2*, and *Per3*	Melatonin, SIRT1, and TIP60	Apoptosis, cell cycle control, DNA damage repair and transactivation of AR	35, 43, 45, 67, 73, 81, 97, 104

Table 2

Phenotypes of Circadian Gene-mutant mouse models

Circadian Genes	Mouse Models	Circadian Behavior Phenotypes	Disease Phenotype	Key Targets Affected	References
Bmal1	*Bmal1*-heterozygous	Normal	Premature aging and cancer prone	N/A	29
	Bmal1-null	Arrhythmic	Premature aging, metabolic syndrome, immune deficiency, caner prone, deregulated drug response	CDC2, CyclinB1, CyclinD1, CyclinE, $p21^{WAF1/CIP1}$, $p16^{Ink4a}$, p53, RB, and WEE1	23, 29,124,125, 149,166,168, 169, 410, 424, 472
	Keratinocyte-specific *Bmal1*-null	Normal	Hyperproliferation and deregulated UVB DNA damage of hair cells at a young age	DAB2, DKK3, LEF1, p16, SMAD3, TGFBR2, and WNT10a	22
	Keratinocyte-specific *Bmal1*/oncogenic *Sos*	Normal	Resistance to cutaneous squamous tumors, senescence of hair cells at 10 months of age	$CD34^+$ and Integrin-α6	167
	Macrophage-specific *Bmal1*-null	Normal	Immune deficiency	IL-6	405
Clock	*Clock*-mutant (*Clock* Δ19)	Lengthened period & arrhythmic in constant darkness	Metabolic syndrome, premature aging, and deregulated drug response	AKT1, ATR1, Cdk2, Chk1, Chk2, CyclinD3, CyclinE1, EGF, ERα, JAK2, p21, p27, PBEF, TGFβ, and WEE1	19,129, 163, 166, 407, 423–425, 471
	Clock-null	Shortened period & failure of phase delay/advance	Premature aging and immune deficiency	NF-κB and WEE1	162, 164
Cry	*Cry1*-null	Shortened period	Cancer prone	N/A	29, 154,
	Cry2-null	Lengthened period	Cancer prone	N/A	29, 150, 154
	Cry1; *Cry2* double knockout	Arrhythmic	Cancer prone, immune deficiency, premature aging, metabolic syndrome, cell cycle control, neuroendocrine deficiency, and deregulated drug and DNA damage response	IL-6, MAPK/ERK, TNFα, WEE1, and XPA, GR and Gsα	29, 93, 126,134, 149, 154, 170, 353, 377–378, 474
			Tumor resistant		127,128
Per	*Per1*-null	Unstable period length	Immune deficiency	IFNγ, Perforin, Granzyme B	155,406
	Per2-null	Shortened period & arrhythmic in constant darkness	Cancer prone, premature aging, immune deficiency, and deregulated drug response	c-MYC, CyclinD1, CyclinA, GADD45α, IFNγ, IL-1β, LY49C, MDM2, and p53	29, 124,161, 409,
	Per2 mutant ($Per2^{Brdm1}$)	Shortened period & arrhythmic in constant darkness	Cancer prone, vascular senescence, premature aging, immune and neuroendocrine deficiency, and metabolic syndrome	AKT, β-catenin, CAR, c-MYC, CyclinD1, CyclinA, GADD45α, IFNγ, IL-1, IL-6, IL-10, MDM2, p53, and NKG2D,	29,123,124,149–153, 155, 322, 395, 405, 409, 411
	Per2 mutant ($Per2^{S662G}$)	Shortened period & phase-advance rhythm	Cancer prone	CyclinD and p21	146, 148

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Circadian Genes	Mouse Models	Circadian Behavior Phenotypes	Disease Phenotype	Key Targets Affected	References
	Per1; *Per2* double knockout	Arrhythmic	Premature aging, cancer prone and metabolic syndrome	AP1, ATM, c-MYC, CyclinD1, CyclinE, MDM2, and p53	29, 149, 167
Rev-erb	*Rev-Erb*α-null	Shortened period	Metabolic syndrome and immune deficiency	CCL2, CXCL6, CXCL11, IL-6, IL-19, and IL-10	9, 407
	*Rev-Erb*α; *Rev-erb*β double knockout	Arrhythmic	Metabolic syndrome	POR, PPARα and SCO2	9
Rorα	*Ror*α-null	Shortened period	Metabolic syndrome and cerebellar ataxia	TUBα8 and RASD1	10