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Circadian Rhythm Disruption in Cancer Biology

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Circadian rhythms show universally a 24-h oscillation pattern in metabolic, physiological and behavioral functions of almost all species. This pattern is due to a fundamental adaptation to the rotation of Earth around its own axis. Molecular mechanisms of generation of circadian rhythms organize a biochemical network in suprachiasmatic nucleus and peripheral tissues, building cell autonomous clock pacemakers. Rhythmicity is observed in transcriptional expression of a wide range of clock-controlled genes that regulate a variety of normal cell functions, such as cell division and proliferation. Desynchrony of this rhythmicity seems to be implicated in several pathologic conditions, including tumorigenesis and progression of cancer. In 2007, the International Agency for Research on Cancer (IARC) categorized "shiftwork that involves circadian disruption (as) *probably carcinogenic to humans*" (Group 2A in the IARC classification system of carcinogenic potency of an agentagent) (*Painting, Firefighting, and Shiftwork*; IARC; 2007). This review discusses the potential relation between disruptions of normal circadian rhythms with genetic driving machinery of cancer. Elucidation of the role of clockwork disruption, such as exposure to light at night and sleep disruption, in cancer biology could be important in developing new targeted anticancer therapies, optimizing individualized chronotherapy and modifying lighting environment in workplaces or homes.

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INTRODUCTION

The term "circadian" is derived from the Latin phrase *circa diem*, which means "about a day." The suprachiasmatic nucleus (SCN) in the anterior hypothalamus serves as a circadian master clock, or an endogenous biological oscillator, that controls biochemical, physiological and behavioral rhythms, entrained by light and other external signals (1). The first reference of periodicity in medicine was made by Hippocrates when describing the fever's course: "The quotidian, tertian, and quartan fevers. . . ." (2). SCN also has the unique ability to provide critical stimulus for resetting its clock phase in direct response to a light signal, which is relayed from the retina via the retinohypothalamic tract (3).

Circadian rhythms are generated by a set of clock genes and proteins (4) regulating many functions, including the ability to fall asleep or to snap out of sleep into wakefulness (5), body temperature (6), blood pressure (7), hormone biosynthesis (8), digestive secretion (9) and immune responses (10). Further to the central nervous system, circadian rhythmicity is present in peripheral tissues, too. Individual normal cells and even cancer cells keep circadian time by expressing similar clock genes (11). Circadian clocks in peripheral tissues regulate the expression of specific genes and synthesis of products, such as thymidylate synthase, p21 and Wee-1, which control DNA synthesis, cell division cycle and cell proliferation, coordinating physiological processes in a circadian manner (12–14). It is noteworthy that, in the industrialized world, there is a change in the lighted environment from a sun-based system to an electricity-based system. Modern lifestyle forces more people to work late shifts, to change shifts regularly or to spend more time doing other activities, prolonging the exposure to light. Epidemiological studies correlate disruption of circadian rhythms with incidence of breast cancer and poorer prognosis of the disease (15,16). In mouse models, data show that disturbed circadian clock gene expression and disruption of circadian rhythms correlate with tumor development and tumor progression (17).

REGULATION OF CIRCADIAN CLOCK GENES

Timing of circadian clocks is established in a cell-autonomous manner by a self-sustaining molecular oscillator that consists of intertwined negative and positive transcription/translation-based feedback loops in SCN (18) and peripheral tissues (19,20). Human period (*hPer1*, *-2* and *-3*) and cryptochrome (*Cry1* and *-2*) clock genes are components of the SCN circadian clockwork (21–23). Protein products of these genes (PER and CRY) inhibit their own transcriptional activators: circadian

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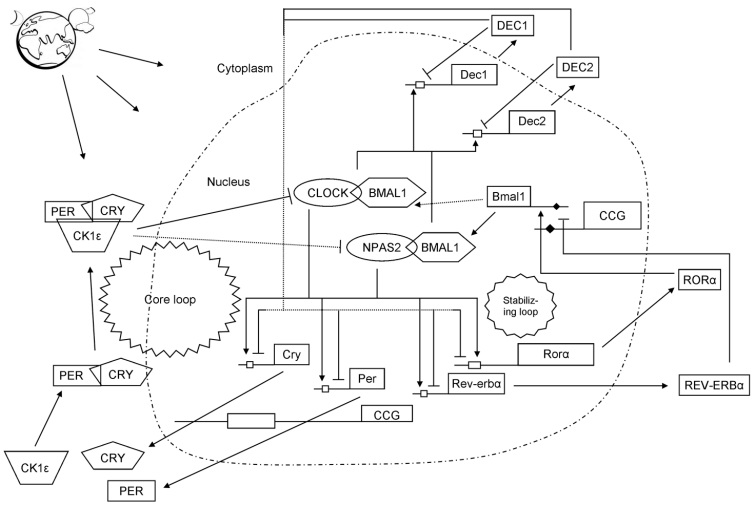

Figure 1. A simplified depiction of the mammalian molecular circadian clock machinery. Light perceived by the retina is the most potent synchronizer of the SCN clock. The circadian clock consists of positive and negative autoregulatory feedback loops. The oscillator is composed of interlocking transcription/translational feedback loops, controlling circadian timing. The CLOCK:BMAL1 or CLOCK:NPAS2 heterodimer (positive elements) is the "core loop" and induces E-box–mediated transcription of *Per, Cry* and *Dec*; their products are cyclically released in the cytoplasm. When PER and CRY proteins reach a critical concentration, they form heterodimers PER:CRY (negative elements), phosphorylate and translocate into the nucleus, where they inactivate the BMAL1:CLOCK or BMAL1:NPAS2 E-box–mediated transcription, including transcription of their own genes, which reduces their levels sufficiently to allow for the new transcription cycle. In addition, DECs bind to the E-box element of their promoter and inhibit their own transcription directly. CLOCK:BMAL1 also controls the levels of the nuclear receptors retinoid-related orphan receptor α (RORα) and Rev-erbα (known as nuclear receptor subfamily 1, group D, member 1 (NR1D1)), which constitute the "stabilizing/auxiliary loop" by repressing BMAL1 concentration via competitive actions on the retinoic acid–related orphan receptor response element (RORE) (black diamond shape) in the *Bmal1* promoter. Cycling of clock components by the core and stabilizing/auxiliary loops also promotes cyclic accumulations of clock-controlled gene (CCG) mRNA species, thus achieving an oscillating pattern and generating rhythmic physiological outputs in a cell type–specific fashion (steroid biosynthesis, cell cycle progression/arrest, cell proliferation, apoptotic pathways, immune function, hormonal oscillations, body temperature, metabolism, DNA repair, response to anticancer drugs and so on). E-boxes (white rectangle shape): regulatory enhancer sequences present in the promoter regions of the genes to which CLOCK:BMAL1 heterodimer binds. Casein kinase (CK) isoforms phosphorylate PER and CRY proteins modulating the nucleocytoplasmic translocation of core clock elements and thereby their transcriptional activity.

locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) (24). For example, PER2 binds to both BMAL1 and CLOCK, whereas CRY1 and CRY2 are only able to interact with BMAL1 (25). CLOCK and BMAL1 form a heterodimer (CLOCK:BMAL1) that is involved in the rapid induction of *mPer1* during phase resetting of the clock (26). CLOCK and BMAL1 are heterodimeric transcriptional activators consisting of two Per-Arnt/AhR-Sim basic helix-loop-helix (bHLH-PAS) domain protein subunits (27–29). A delay between production and action of inhibitory clock gene products is regulated by nuclear export of the PER protein, resulting in production of stable oscillations of gene expression with a period of 24 h (30). *Dec1* and *Dec2*, basic helix-loop-helix transcription factors, are involved in the regulation of the mammalian circadian clock. CLOCK:BMAL2 heterodimer increases the expression of *Dec1* and *Dec2* genes. Deleted in esophageal cancer 1 (DEC1) and DEC2, products of *Dec* genes, suppress the expression of *Per* or *Cry* genes (31–34). As a result of these self-contained feedback loops, the circadian protein levels oscillate in a rhythmic manner (Figure 1). Light stimulus activates the expression of several genes in SCN, with different expression patterns. For example, the expression level of the circadian clock gene *Per1* peaks 30–45 min after light pulse, with *Per2* to show slower activation (35). Light also promotes binding of Cry1a to the transactivation domain of BMAL and blocks active dimerization of CLOCK and BMAL. Consequently, these actions inhibit CLOCK:BMAL function (36). Activity of the serotoninergic system possibly resets the circadian clock in SCN (37). The effect of light-at-night exposure to expression patterns of peripheral clock genes seems to be organ and time-of-day specific, in coordination with the autonomic nervous system that modifies this expression (38). However, a light pulse induces *Dec1* expression in SCN and *Per1* and *Per2* in extra-SCN clocks (39,40). The exact role of the mammalian protein TIMELESS (TIM) in the circadian clock mechanism has not been fully elucidated. TIM forms a heterodimer with PER and translocates in the nucleus, where it inhibits the activity of CLOCK:BMAL1 on the *mPer1* promoter (41). Another regulatory mechanism is controlled by microRNAs (miRNAs), small molecules that regulate gene expression, in the posttranscriptional level, via translational repression or direct destruction of their mRNA targets (42,43). miRNA-mediated translational control regulates the circadian clock, too. miR-132 is an miRNA that is induced in response to light stimulation in the murine SCN (44). The expression of miR-132 negatively regulates light-induced entrainment of the circadian clock through regulation of a number of target genes that are associated with chromatin remodeling (methyl-CpG-binding protein 2 [*MeCP2*], *p300*, JumonjiC (JmjC) and ARID domain-containing histone lysine demethylase 1a

[*JARID1A*]) and protein translation (B-cell translocation gene 2 [BTG2], poly(A) binding protein interacting protein 2 [PAIP2A]) (45). However, there are other molecules that interact with clock genes and have important coeffects on circadian oscillation processes. For example, the receptor for activated protein kinase C-1 (RACK1) is a protein that mediates or regulates functions of PER1 (46). Activation of the MAPK cascade is able to trigger the induction and resetting of the circadian oscillation of gene expression (47). Fluctuating levels of circulating ovarian steroid hormones during the estrous cycle regulate the rhythm of clock gene expression in reproductive tissues (48).

ROLE OF CIRCADIAN CLOCK GENES IN CANCER

Core circadian genes seem to be important in tissue homeostasis and tumorigenesis. Disruption of circadian rhythms is associated with various forms of cancer in humans. There is increasing evidence that links dysfunction of the clockwork with the pathogenesis of cancer. The master circadian clock in SCN is an endogenous timekeeping system and controls multiple peripheral clocks in other peripheral tissues of the body. Many studies have shown that circadian clock gene deregulation is implicated in the development of cancer and other diseases. Disruption of circadian rhythms accelerates tumor progression, and potentially restoring circadian rhythms should improve prognosis. Decreased expression levels of *Per1* and *Per2* genes are observed in sporadic and familiar breast tumors when compared with normal breast tissues. The *Per1* gene shows lower expression levels in familiar forms of breast cancer when compared with sporadic forms, suggesting that a potential deregulation of the circadian clock may contribute to the inherited form of the disease (49). Methylation of promoters of the *Per1* and *Cry1* genes may lead to survival of breast cancer cells through inactivation of expression of these genes and disruption of the circadian cell rhythm (50). Moreover, a significantly higher risk of breast cancer associated with clock genetic polymorphisms is observed in Chinese populations (51). *Bmal1* epigenetic inactivation, via cytosine-guanine (CpG) island promoter hypermethylation, contributes to the development of hematologic malignancies, non–Hodgkin lymphoma and acute lymphocytic leukemia, by disrupting cellular circadian clock, leading to loss of circadian rhythmicity of target genes such as *c-myc*, catalase and p300 (52). Genetic variations in *Cry2* and Ala394Thr functional polymorphism in the circadian gene neuronal PAS domain protein 2 (NPAS2) increase the inherited susceptibility to non–Hodgkin lymphoma (53,54). Methylation of CpG sites of the *hPer3* gene is observed in patients with chronic myeloid leukemia (55). Prostate cancer is the most common cancer, excluding skin cancer, and the second leading cause of cancer-related death in men in the United States (56). The only well-established risk factors for prostate cancer are older age, family history of the disease and race. Circadian disruption may be a novel risk factor in prostate tumorigenesis. Results from a population-based case-control study provide evidence for an association of genetic variations in circadian genes with prostate tumorigenesis (53). Clock genes and the androgen receptor are expressed with circadian oscillations in the normal prostate. *Per1* inhibits transcriptional activity of the androgen receptor, and downregulation of this clock gene seems to contribute to prostate tumorigenesis (57). Significant dysregulation of clock genes is one of the basic mechanisms driving the mesothelioma process (58). The expression of protooncogene *c-myc* is under circadian regulation, in the same phase with *Per1*, in the neuroblastoma cell line (59). Expression rates of *Per1* and *Per2* are lower in glioma cells when compared with nonmalignant cells (60,61). *Per1* and *Per2* seem to be involved in suppressing the proliferation of pancreatic cancer cells (62,63).

Circadian disruption promotes liver carcinogenesis and possibly participates in its initiation, as observed in mice exposed to the hepatic carcinogen diethylnitrosamine (64). Hepatoma has the same circadian oscillation pattern with normal cells but is less sensitive to circadian timing signals, such as mealtimes, leading to dissociation of circadian rhythms in cancer and healthy cells (65).

The expression levels of *Cry1* and *Bmal1* core clock genes are correlated with clinicopathological parameters in epithelial ovarian cancer, and combination of low expression levels of both genes is an independent prognostic factor, as are stage and histological subtype (66). Disruption of the circadian clock, after methylation of the promoter CpG in *Per1*, *Per2* or *Cry1* circadian genes, is possibly involved in the development of endometrial cancers (67). The expression level of *TIM* was higher in the tumor tissue of colorectal cancer patients (68). The possible link of peripheral clock regulation in peripheral tissues with particular cancers is further supported by the following data. Several nuclear receptors are implicated in expression of peripheral clocks and constitute molecular links between clock genes and metabolic functions (reviewed in [69]). Expression levels of *PER1–3*, *CRY1–2*, *CK1e* and *TIM* are downregulated in patients with chronic myeloid leukemia (70). Tumor suppression through the ATM-p53 signaling is a clock-controlled physiological function, and disruption of this function leads to myc oncogenic activation in mice (71). β-Catenin increases β-TrCP (β-transducin repeat–containing protein) levels and shortens PER2 protein half-life, suggesting a possible mechanism for intestinal epithelial neoplastic transformation (72). Implication of circadian genes in various forms of cancer is supported by these data, and ongoing research will provide evidence to elucidate their biological role.

CIRCADIAN RHYTHMICITY IN CANCER GENETICS

DNA Repair and Circadian Rhythmicity

The circadian clock determines the strength of cellular responses to DNA damage, including DNA repair. DNA repair pathways maintain genetic stability,

protecting DNA integrity from exogenous and/or endogenous stimuli (73,74). Several components of these pathways seem to be entrained by circadian oscillations. Nucleotide excision repair is a DNA repair mechanism that prevents genomes from damage caused by several sources, such as ultraviolet light irradiation and chemical mutagens (75). Nucleotide excision repair in the mouse brain seems to exhibit circadian periodicity, mainly mediated by xeroderma pigmentosum A, a DNA damage recognition protein (76,77). Tip60, a histone acetylase of chromatin, with DNA damage response and repair competency (78), is overexpressed in cisplatin-resistant cells and its silencing sensitizes cells to this cancer chemotherapeutic agent (79). In the same study, the expression of Tip60 is regulated by the circadian transcription factor *Clock*, providing evidence that DNA repair through histone acetylation is under circadian regulation. The high mobility group box 1 (Hmgb1) protein is involved in DNA mismatch repair (80) and shows a circadian rhythmic expression in rat retina (81). Apurinic/apyrimidinic endonuclease (APE) is an enzyme component of DNA base excision repair (82). The APE/Ref-1 gene is highly expressed in SCN, the main circadian pacemaker in mammals (83). However APE/Ref-1 mRNA levels do not show circadian patterns of expression (83).

Cell Proliferation and Cancer Cell Growth Are Under Clock Regulation

Proliferation rhythm of tumor cells follows a cyclical pattern different from that in normal tissues (84–87). Disruption of cellular circadian rhythm is associated with alterations in cancer cell proliferation. Downregulation of *Per1* or *Per2* increases cancer cell growth *in vitro* only at certain specific times of the day and enhances time-dependent tumor growth *in vivo* (88). *Per1* has tumor suppressor function (89) and inhibits breast cancer cell proliferation and tumor growth in a circadian expression pattern (90). Downregulation of *Per2* accelerates breast cancer cell proliferation and tumor growth in a circadian time-dependent manner *in vivo* (91). Mammalian *Per2* (*mPer2*)-deficient mice have tumor occurrences indicating tumor suppression function of *mPer2* (92). Clock mutation significantly inhibits cell growth and proliferation through upregulation of cell cycle inhibitory genes and reduced ability of mutant cells to respond to mitogenic signals (93). In contrast, disruption of the circadian clock, because of deficiency of the functional CLOCK protein, does not affect the rate of carcinogenesis in mice after exposure to ionizing radiation (94). These data suggest the existence of composite relations between genotoxic stress–induced carcinogenesis and the circadian clock. DNA synthesis in tumor cells seems to be modulated by several factors such as platelet-derived growth factor (PDGF) (95). PDGF signaling is activated during tumor development (96–98) and is related to tumor vascularization (99), adhesion, invasion (100) and aggressiveness (101) of cancer cells. Inhibition of this pathway synchronizes DNA synthesis in tumor cells with the rhythm of DNA synthesis in normal bone marrow cells (95). DNA synthesis and telomerase activity, which prevents cells from apoptosis (102), are expressed with a circadian pattern in hepatic cancer cells (103). Interferons (IFNs) are multifunctional cytokines that have antitumor activity, and their receptor shows a diurnal rhythm of expression in implanted-tumor cells (104), showing the importance of dosing time for IFN-β (105).

Mechanisms of Action of Circadian Genes in Cancer

Downregulation of *Per2* increases β-catenin protein levels and its target cyclin D, leading to cell proliferation in colon cancer cell lines and intestinal and colonic polyp formation. This finding suggests that the *Per2* gene product suppresses tumorigenesis in the small intestine and colon by downregulation of β-catenin and β-catenin target gene signaling pathways (106,107). Increased β-catenin affects the circadian clock and enhances PER2 clock protein degradation in colon cancer cells (107). Suppression of human β-catenin expression inhibits cellular proliferation in intestinal adenomas (108).

Disruption of the peripheral intestinal circadian clock may, in part, contribute to intestinal epithelial neoplastic transformation of human colorectal cancer. The circadian expression of dihydropyrimidine dehydrogenase (DPD), an enzyme that is implicated in the metabolism of the anticancer drug 5-fluorouracil, is possibly regulated by *Per1* in high-grade colon tumors (109). Transferrin receptor 1 (TfR1) is a cell surface receptor required for iron delivery from transferrin to cells (110). Overexpression of TfR1 is associated with an increased rate of cell proliferation and malignant progression to colorectal cancer (111,112). TfR1 shows a 24-h rhythm of expression activated by the clock-controlled gene c-Myc in colon cancer–bearing mice (113). There is also a significant decrease of both estrogen receptor beta (ER-β) and *Per1* in undifferentiated colorectal tumors (114). Casein kinase 1ε (CK1ε) phosphorylates PER2 protein, leading to degradation of PER2 by 26S proteasome (115,116). Thus, inhibition of CK1ε by IC261, a kinase domain inhibitor, exerts a growth-suppressive effect of PER2 (117). Methylation of the *Per* gene promoters causes deregulation in the expression of PER proteins, resulting in proliferation of breast cancer cells (118). *Per1* mediates inhibition of proliferation of a human pancreatic cancer cell line (MIA-PaCa2) by tumor necrosis factor (TNF)-α. The expression of *Per1* is suppressed by TNF-α, and knockdown of *Per1* decreases proliferation of MIA-PaCa2 cells (119). Chronic jetlag increases the risk of various cancers in mice, and circadian gene mutations make mutant mice more prone to cancer (71). Clock and Per2 protein levels are decreased, whereas Bmal1 protein levels are increased in prostate cancer (PCa) cells when compared with normal human prostate epithelial cells. Melatonin resynchronizes deregulated core clock genes in human PCa cells by upregulation of mRNA levels of Clock and Per2 and downregulation of Bmal1 mRNA (120),

suggesting the preventive effects of melatonin against loss of rhythmicity, that is, observed during tumor progression (121).

Epigenetic Modifications of Circadian Clock Genes

Epigenetic modifications are heritable changes that take place independently of changes in the DNA sequence and are involved in regulation of gene transcription (122). DNA methylation and histone modifications are the main epigenetic mechanisms. In mammals, DNA methylation occurs primarily through addition of a methyl group to the 5′ carbon of cytosine located next to a guanine in CpG dinucleotides (123). Changes in DNA methylation accompany tumor initiation and progression (124,125). Promoter regions of tumor suppressor genes are methylated in cancer, resulting in gene silencing in contrast to normal cells, where most CpG islands are unmethylated (126). In addition, the consequence of hypomethylation leads to genomic instability through an opening of the chromatin and subsequent chromosomal breakage (127). Acetylation is the main, but not the only, posttranslational modification of nucleosomal histones that is involved in cancer initiation and progression (128,129). Histone acetylation is controlled by the opposing action of histone acetyltransferase (HAT) and histone deacetylases (HDAC) enzyme (130). Disruption of HAT or HDAC activity may play a key role in tumor invasion and metastasis (131).

INTERACTIONS BETWEEN ENVIRONMENT AND CLOCK GENES

Activation of aryl hydrocarbon receptor (AhR) by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) inhibits *Per1* gene expression by blocking CLOCK:BMAL1 heterodimer binding to enhancer boxes (E-boxes) in the *Per1* promoter (132). This is a potential mechanism by which environmental pollutants may contribute to the development of carcinogenesis through disruption of circadian rhythm and repression of clock. Disruption of clock genes, *Per1* and/or *Per2*, modifies mammary gland (133,134) and liver (134,135) responses to the environmental toxin TCDD by altering the inductive effects of TCDD on expression of cytochrome P450 genes (136). AhR activation by TCDD changes the circadian rhythms of murine hematopoietic stem progenitor cells (137) and mouse ovary (138). *Per1* sensitizes cancer cells to activate their apoptotic machinery after DNA damage from double-strand break–causing agents, such as ionizing irradiation (89).

INTERACTIONS OF THE CLOCK WITH THE STEROID HORMONE RECEPTORS AND IMPACT ON CANCER

Glucocorticoid receptor (GR) is activated by glucocorticoids, a class of steroid hormones (139). Subsequent to, activation of GR involves (a) its nuclear translocation, (b) transactivation or binding to glucocorticoid-responsive element to regulate gene expression (140,141).

Stress has been associated with cancer progression through the glucocorticoid receptor system. GR expression is implicated in various forms of cancer such as prostate cancer and renal cell neoplasms (142,143). In human small cell lung cancer cells, GR expression is lost by DNA methylation, causing their increased survival (144). In contrast, high expression levels of GR are associated with shorter relapse-free survival in estrogen receptor–negative breast cancer (145). GR and core clock proteins (PER2 and CLOCK) are coexpressed in bronchiolar epithelial cells (146), and CLOCK-related genes regulate glucocorticoid action in all tissue through attenuation of the transcriptional activity of GR (147,148). A possible mechanism is the acetylation of several lysine residues of GR and concomitant attenuation of GR binding to glucocorticoid response elements (149). Desynchronization of circadian clock genes is possibly implicated in the role of the stress system in cancer progression through these mechanisms. As mentioned above, expression rhythms of circadian genes (*Per1/2* and *Bmal1*) are modulated by the levels of ovarian steroid hormones in both reproductive and nonreproductive tissues (48). In addition, progesterone seems to cause acute increases of *Per1*, *Per2* and *Bmal1* expression in human breast cancer MCF-7 cells (48). Single nucleotide polymorphisms (SNPs) of the Clock gene are significantly associated with estrogen receptor/progesterone receptor (ER/PR)-negative cases of breast cancer (150). SNPs of NPAS2 have been linked to the risk of prostate cancer risk and hormone-related breast cancer (53,151). The possible mechanism implicates the aryl hydrocarbon receptor nuclear translocator-like (ARNTL)/NPAS2 heterodimer that suppresses transcription of the oncogene *c-myc* (152). Increased expression of *Per2* in breast cancer cells leads to tumor apoptosis, possibly acting as an estrogen-inducible ER-α corepressor (153). CLOCK has histone acetyltransferase activity and acts as a coactivator of ERα, explaining the association between circadian rhythm disruption and breast cancer (154). Association of clock genes and proteins with various forms of cancers is summarized in Table 1.

CLOCK GENES IN CANCER PROGRESSION, METASTASIS AND ANGIOGENESIS

Circadian disruption promotes tumor growth and angio-/stromagenesis, especially growth of both fibroblasts and vascular endothelial cells, induced by overexpression of wingless-type MMTV integration site family, member 10A (*WNT10A*) in tumor stroma cells as a result of increased levels of oxidative stress (155). Elevated expression of the *mPer1* gene found in tumor stroma may affect interactions between cancer and stromal cells and is consequently involved in cancer progression and metastasis (156). The 24-h rhythm of methione aminopeptidases, which are involved in tumorigenesis (157) and tumor angiogenesis (157,158), is regulated by transcription of clock genes, enhanced by mCLOCK:mBMAL1 heterodimer and inhibited by mPER2 or mCRY1 (159). However, the effects of exogenous melatonin on tumor growth de-

Table 1. Association of clock genes and proteins with various forms of cancers.

Cancer type (and effect)	Trigger	Circadian genes/proteins	Reference
Sporadic and familiar breast tumors	Decreased expression levels	*Per1, Per2*	49
Familiar breast tumors (than sporadic)	Lower expression levels	*Per1*	49
Survival of breast cancer cells	Methylation of promoters	*Per1, Cry1*	50
Proliferation of breast cancer cells	Methylation of promoters	*Per*	118
Higher risk of breast cancer	Polymorphisms	*Clock*	51
Inhibits breast cancer cell proliferation and tumor growth	Expression	*Per1*	89
Breast cancer cell proliferation and tumor growth	Downregulation	*Per2*	91
ER/PR-negative cases of breast cancer	SNPs	*Clock*	150
Breast cancer	Histone acetyltransferase activity	CLOCK (protein)	154
Tumor apoptosis in breast cancer	Increased expression	*Per2*	153
Prostate cancer risk and hormone-related breast cancer	SNPs	*NPAS2*	53,151
Non–Hodgkin lymphoma and acute lymphocytic leukemia	Epigenetic inactivation (via CpG hypermethylation)	*Bmal1*	52
Non–Hodgkin lymphoma	Genetic variations, functional polymorphism	*Cry2, NPAS2*	53,54
Chronic myeloid leukemia	Methylation	*Per3*	55
Prostate cancer	Downregulation	*Per1*	57
Prostate cancer	Increased expression level	*Per2, Clock*	120
Prostate cancer	Decreased expression levels	*Bmal1*	120
Glioma	Lower expression rates	*Per1, Per2*	60,61
Suppression of proliferation in pancreatic cancer	Expression	*Per1, Per2*	62,63
Proliferation of human pancreatic cancer cell line	Knockdown	*Per1*	119
Epithelial ovarian cancer	Low expression levels	*Cry1, Bmal1*	66
Endometrial cancer	CpG methylation	*Per1, Per2, Cry1*	67
Colorectal cancer	Increased expression level	*Tim*	68
Colon cancer	Downregulation	*Per2*	106,107
Undifferentiated colorectal tumors	Decreased expression levels	*Per1*	114
Chronic myeloid leukemia	Downregulation	*Per1, Per2, Per3, CRY1–2, TIM*	70
Intestinal epithelial neoplastic transformation	PER2 protein degradation	*Per2*	72

pend on the timing of administration (121). The laminin receptor 1 (Lamr1) is important in several physiological and pathological processes, including cell differentiation and viability, cancer development, invasion, migration and metastasis (160–163). Lamr1 interacts with human circadian clock protein hPer1 but does not have circadian pattern of expression (164). CLOCK:BMAL1 and sirtuin 1 (SIRT1) form a chromatin regulatory complex at promoters of clock-controlled genes (165). Sirtuins (SIRT proteins) are a unique class of type III (NAD)-dependent HDACs, which are important in the regulation of gene expression and especially in gene silencing (166). However, this activity shows oscillations in a circadian manner contributing to circadian control (165). SIRT1 is involved in the development of various cancers such as prostate (167), breast (168) and colorectal (169) and in chemotherapeutic drug resistance of cancer cells (reviewed in [170]).

MELATONIN AND CANCER

In 2007, the International Agency for Research on Cancer categorized "shift-work that involves circadian disruption [as] *probably carcinogenic to humans*" (Group 2A in the IARC classification system of carcinogenic potency of an agent) (171). Light during the night can suppress melatonin, disrupting circadian rhythms (172). Melatonin (5-methoxy-N-acetyltryptamine) is a hormone of the circadian system, synthesized in the pineal gland and retina (reviewed in [173,174]). In patients with untreated non–small-cell lung cancer (NSCLC) melatonin/cortisol mean nocturnal level ratio and melatonin nocturnal levels are decreased (175,176). These results may indicate a neuro-immune-endocrine system dysfunction. Melatonin concentrations progressively decrease after standard chemotherapy in NSCLC patients (176). Melatonin can resynchronize a rhythmic pattern of gene expression, correcting defects in expression patterns of various circadian rhythm genes responsible for cancer development (120). Melatonin inhibits myeloperoxidase catalytic activity (177), which is important in the pathogenesis of cancer (178,179). Melatonin has a protective effect against the DNA-damaging action of hydrogen peroxide, by chemical inactivation of this DNA-damaging agent and stimulation of DNA repair (180). Melatonin inhibits tumor signal transduction and metabolic activity of cancer cells, leading to suppression of growth of human breast

cancer via activation of melatonin receptor MT1 (181). Disruption of nocturnal circadian melatonin signal by light at night upregulates tumor metabolism, stimulating its growth (182). Women with total visual blindness have a lower risk of breast cancer than blind women with light perception (183). The antiproliferative ability of melatonin is associated with its uptake into human androgen-dependent LNCaP and androgen-independent PC-3 prostate cancer cells, mainly mediated by an active transport (184).

Preventing low-wavelength light from reaching the retina, for example, by using optical filter goggles may protect shift workers from bright-light suppression of melatonin (185). If epidemiologic and basic science evidence leads to a "proof of causality" of adverse effects from light at night, then lighting standards and building designs should be developed with consideration of the circadian system both at night and during the day, to minimize or eliminate adverse consequences for human health (186–188).

CIRCADIAN RHYTHMS IN CANCER MANAGEMENT

The most important principle of chronomodulated therapeutics against various forms of cancer is to create a balance between effectiveness and adverse toxic effects of drugs. The circadian clock is responsible for rhythmicity of several physiological processes that in turn influence efficiency and tolerance of pharmacotherapy. Chronomodulated infusion of fluorouracil, leucovorin and oxaliplatin for 4 d achieves similar survival when compared with conventional 2-d delivery of the same drugs and acceptable tolerability, with more incidences of diarrhea with 4-d delivery and neutropenia with 2-d delivery. These results were observed in patients with metastatic colorectal cancer in a multicenter randomized phase III trial (189). However, chronomodulated hepatic arterial infusion multidrug chemotherapy shows antitumor activity and is well tolerated in patients with metastatic colorectal cancer after failure of several current standard therapeutic options (190). Combination of cetuximab, a chimeric monoclonal antibody directed against the extracellular domain of epidermal growth factor receptor, with circadian chronomodulated chemotherapy can be used effectively in initially unresectable residual metastatic colorectal cancer (191). In a phase II study, use of chronochemotherapy composed of 5-fluorouracil and leucovorin, and local hyperthermia combined with preoperative radiation therapy for locally advanced low-rectal adenocarcinoma had high antitumor activity rate and low incidence of adverse effects (192). Patients with ovarian cancer demonstrate altered diurnal cortisol rhythms, with significantly higher afternoon and nocturnal cortisol levels and lower cortisol variability when compared with patients with benign disease or healthy women (193). Dysregulation in rhythmic function of the hypothalamic-pituitary-adrenal axis is described in breast cancer survivors (194,195) or individuals with metastatic disease (196), in patients scheduled for lumbar disc surgery (197), in metastatic colorectal cancer patients (198) and in patients with cancer-related depression (193,199). Various anticancer agents are implicated in cancer therapeutics after circadian principles. Dietary methylselenocysteine (3 ppm selenium) given for 30 d significantly enhances circadian expression of circadian and growth-regulatory genes that are disrupted by nitrosomethylurea (200). Nitrosomethylurea-induced mammary carcinogenesis in rats is inhibited by methylselenocysteine, possibly through upregulation of circadian oscillations of *Per2* (201). As it mentioned above downregulation of *Per2* accelerates breast cancer (91). The *Per2* gene intratumoral delivery induces apoptosis and inhibits tumorigenesis in C57BL/6 mice transplanted with Lewis lung carcinoma (202). Antitumor effect and tolerability of Seliciclib, a cyclin-dependent kinase inhibitor in mice bearing Glasgow osteosarcoma, is found to depend on circadian rhythmicity (203). Biological parameters of a tumor, such as its growth kinetics, can affect the timing of optimal chronomodulated treatment, indicating the importance of tailoring these treatments for individual patients. The length of the cell cycle targeted by treatment and proliferation rate of cancer cells are important parameters to define the most effective time to administer cell cycle–specific drugs (204). The severity of acute gastrointestinal mucositis in patients undergoing radiotherapy is significantly increased when therapy is applied in the morning compared with the evening arm, implying that function of intestinal mucosa of the human intestine is possibly under circadian rhythmicity (205). In a retrospective review of local control, frequency of central nervous system–related cause of death and survival, in patients treated with gamma knife radiosurgery for metastatic NSCLC, had better outcomes in procedures earlier in the day versus later in the day (206). Various studies have indicated that toxicity and anticancer efficacy of anticancer drugs can be significantly modified by circadian stage of administration (reviewed in [203,207,208]). Drugs that target proliferation pathways and mimic or control rhythmicity increase susceptibility of cancer cells and thus improve their therapeutic index when given at specific times of day. Timing of any therapy targeting a cancer cell proliferation-related pathway will work substantially better if it is given at certain times within the day, when cancer cell proliferation is most active (reviewed in [209]). A way to optimize current therapies is the elucidation of links between clock genes and drug pharmacodynamic and pharmacokinetic parameters, resulting in development of new therapeutic strategies (210).

SUMMARY

Circadian genes have clock functions that regulate expression of other genes with circadian rhythmicity, resulting in daily oscillations of proteins. Therefore, disruption of clock damages organization of these gene and protein expres-

sions, leading to deregulated cell proliferation and subsequent tumorigenesis. Circadian genes also have nonclock functions, which are important in regulation of cell cycle progression, DNA damage response and genomic stability. Clock and nonclock functions constitute the association between disruption of circadian rhythmicity and cancer.

A major consequence of modern lifestyle is disruption of circadian rhythms. Circadian disruptions induced by light at night, genetic or epigenetic variations in circadian genes and interactions between genes and environment form a set of data that propose that some cancer cases could be explained by these mechanisms. Elucidation of molecular mechanisms that form a link between disruption of circadian rhythm and cancer and determination of how a disrupted circadian peripheral clock contributes to neoplastic transformation is fundamental to provide essential leads developing future novel circadian clock–based strategies for cancer prevention, control and therapeutic intervention.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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