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REVIEW

Circadian rhythm disruption and endocrine-related tumors

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Abstract

This review delved into the intricate relationship between circadian clocks and physiological processes, emphasizing their critical role in maintaining homeostasis. Orchestrated by interlocked clock genes, the circadian timekeeping system regulates fundamental processes like the sleep-wake cycle, energy metabolism, immune function, and cell proliferation. The central oscillator in the hypothalamic suprachiasmatic nucleus synchronizes with light-dark cycles, while peripheral tissue clocks are influenced by cues such as feeding times. Circadian disruption, linked to modern lifestyle factors like night shift work, correlates with adverse health outcomes, including metabolic syndrome, cardiovascular diseases, infections, and cancer. We explored the molecular mechanisms of circadian clock genes and their impact on metabolic disorders and cancer pathogenesis. Specific associations between circadian disruption and endocrine tumors, spanning breast, ovarian, testicular, prostate, thyroid, pituitary, and adrenal gland cancers, are highlighted. Shift work is associated with increased breast cancer risk, with *PER* genes influencing tumor progression and drug resistance. *CLOCK* gene expression correlates with cisplatin resistance in ovarian cancer, while factors like aging and intermittent fasting affect prostate cancer. Our review underscored the intricate interplay between circadian rhythms and cancer, involving the regulation of the cell cycle, DNA repair, metabolism, immune function, and the tumor microenvironment. We advocated for integrating biological timing into clinical considerations for personalized healthcare, proposing that understanding these connections could lead to novel therapeutic approaches. Evidence supports circadian rhythm-focused therapies, particularly chronotherapy, for treating endocrine tumors. Our review called for further research to uncover detailed connections between circadian clocks and cancer, providing essential insights for targeted treatments. We emphasized the importance of public health interventions to mitigate lifestyle-related circadian disruptions and underscored the critical role of circadian rhythms in disease mechanisms and therapeutic interventions.

Key Words: Circadian rhythm; Circadian disruption; Shift work; *CLOCK* gene; Cancer; Endocrine tumors; Chronotherapy

Core Tip: This review explored the pivotal role of circadian clocks in physiological processes and adverse health outcomes, including metabolic syndrome and cancer, linked to their disruption. Orchestrated by interlocked *CLOCK* genes, the circadian system regulates vital functions, from sleep-wake cycles to immune response. Disruptions, often from night shift work, correlate with increased risks, notably in endocrine tumors. Molecular insights highlight potential therapeutic vistas, emphasizing the need for integrating circadian considerations in personalized healthcare. Chronotherapy emerges as a promising approach for endocrine tumor treatment, urging further research into precise mechanisms and public health interventions to mitigate lifestyle-related circadian disruptions.

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INTRODUCTION

Circadian clocks are intrinsic oscillators in cells and organisms, coordinating multiple biological processes within an approximate 24-hour cycle. The circadian timekeeping system comprises a network of clock genes (CGs) interlocked in a complex of autoregulatory transcriptional-translational feedback loops that generate and synchronize circadian rhythms, primarily influenced by light-dark cycles[1]. This self-sustained internal system orchestrates fundamental physiological processes, including the sleep-wake cycle, energy metabolism, immune function, cognitive and physical performance, as well as cell proliferation and tumorigenesis[2,3]. Additionally, it contributes to the adaptation of organisms to environmental changes, thereby maintaining systematic and tissue homeostasis[3,4].

In mammals, the circadian timing system consists of a central oscillator located in the hypothalamic suprachiasmatic nucleus (SCN) and various peripheral tissue clocks. The core pacemaker of these intricate rhythms is the SCN, which is attuned to geophysical time and environmental changes[5]. This synchronization is mediated by light transmitted to the SCN, primarily *via* retinal ganglion cells, and subsequently temporal information is conveyed to peripheral tissue clocks, thereby aligning internal timing with the light-dark cycle[6].

However, it has been proposed that other environmental cues, with feeding times being the most crucial, can also synchronize peripheral oscillators[7]. Circadian homeostasis among central and peripheral clocks is well documented as integral to optimal health status and survival. In contrast, there is growing evidence of the detrimental effects of circadian rhythm disruption due to environmental or behavioral factors, which are often concomitants of modern society. These factors include night shift work, irregular sleep patterns or meal timing, and exposure to artificial light during the night, all of which can perturb the harmonious coordination among clocks, leading to aberrant epigenetic modifications and adverse health outcomes[8,9].

It is worth noting that circadian system dysregulation has been linked to a wide range of adverse health issues, including metabolic syndrome, cardiovascular diseases, susceptibility to infections, and even certain types of cancer, highlighting the pivotal role of biological clock homeostasis in human health[10]. Given this association, it may be that novel therapeutic approaches could be considered for neuropsychiatric diseases and cardiometabolic disorders. A growing body of research into circadian rhythms regarding cancer pathogenesis has shed light on the possible role of chronotherapeutic interventions[11].

The aim of this narrative review was to summarize our understanding of the critical interplay between circadian disruption and its clinical implications in a wide array of related diseases. Additionally, we discussed the latest evidence that connects molecular mechanisms of circadian disruption to tumorigenesis. We aimed in this way to highlight the importance of integrating biological timing into the clinical setting and the need to consider circadian-based approaches in personalized health care. Please note that in this review in murine (mouse and rat) gene nomenclature, gene symbols are typically italicized with only the initial letter capitalized, followed by lowercase letters (*e.g.*, *Gfap*). Corresponding protein symbols maintain the same designation as the gene symbol but are not italicized with only the initial letter capitalized, followed by lowercase letters (*e.g.*, Gfap). In human gene nomenclature, gene symbols are italicized and presented in all uppercase letters (*e.g.*, *TP53*). Protein symbols follow the same naming convention as the gene symbols, except they are not italicized and remain in all uppercase letters, reflecting their human origin (*e.g.*, TP53). mRNAs and cDNAs adopt the same formatting conventions as their respective gene symbols.

CIRCADIAN CLOCK GENES

The CGs constitute a group of genes identified in mammals that collectively bear the responsibility of maintaining independent circadian rhythms in every individual cell[12]. To achieve this, CGs form three major transcriptional-translational feedback loops. The first identified CG, Period (*Per*), was discovered in Drosophila. In humans, *PER* encodes the PER protein, and its mRNA has been demonstrated to oscillate periodically[13,14]. The circadian locomotor output cycles kaput (*Clock*) gene, discovered in mice, encodes a regulatory transcriptional protein with a DNA-binding domain, a PAS dimerization domain, and a Q-rich transactivation domain[15]. While *CLOCK* mRNA does not exhibit periodic oscillation, its cellular localization between the nucleus and cytoplasm varies during the 24-hour cycle[16]. Brain and Muscle ARNT-Like 1 (BMAL1) protein serves as the binding partner of the CLOCK protein[17] and is the primary functional component in the BMAL1-CLOCK complex. Cryptochrome (*CRY1* and *CRY2*) genes, found in the SCN, retina, and ganglion cells[18], exhibit regulatory properties akin to the period genes. CRY1 and CRY2 can form dimers with PER1, PER2, and PER3, and these complexes have the ability to inhibit the CLOCK-BMAL1 heterodimer[19]. The casein kinase 1 epsilon (*CK1e*) gene possesses the capacity to phosphorylate PER proteins, leading to their degradation and disrupting the inhibition of the CLOCK-BMAL1[20].

There are three transcriptional feedback loops governing CGs. The primary loop involves the transcription of *CLOCK* and *BMAL1* genes in the cytoplasm of mammalian cells. These proteins form a complex, CLOCK-BMAL1, which translocates to the nucleus and binds to enhancer box sequences (E-box), thereby regulating transcription[17]. The period (*PER1, PER2, PER3*) and cryptochrome (*CRY1, CRY2*) CGs, when activated by CLOCK-BMAL1, form a PER-CRY protein dimer that is translocated from the cytoplasm to the nucleus. This complex interacts with CLOCK-BMAL1, thereby halting its transcription in a negative feedback loop[21]. Once the protein levels of PER and CRY have decreased, the repression ceases, allowing CLOCK-BMAL1 to initiate gene transcription and commence a new oscillatory cycle[22].

The second loop involves the nuclear receptors *REV-ERBα, REV-ERBβ (REV-ERBs)*, and the retinoic acid orphan receptor *ROR (RORα, RORβ, RORγ)*, which bind to *BMAL1* binding sites[23]. Specifically, *REV-ERBs* nuclear receptors repress the transcription of *BMAL1*, in contrast to the *RORs*, which positively regulate its expression by binding to retinoic acid receptor-related orphan receptor element (*RORE*) on the *BMAL1* gene promoter[23].

The third loop involves CLOCK-BMAL1 and CRY1, which regulate D-box binding protein (DBP) and interleukin-3 regulated protein (NFIL3). These proteins bind to D-box elements, including *RORα* and *RORβ*[24]. NFIL3 can also bind to E-box and repress the transcription of *PER2*[24]. DBP can bind to the *CRY1* promoter, influencing the timing of transcription and playing a role in the PER-CRY negative feedback loop[25]. Figure 1 provides a schematic illustration of the intricate functions of the mammalian circadian clock.

Regulators of the core circadian CGs include certain genes forming minor transcriptional feedback loops in addition to the major transcriptional feedback loops. F-box protein 3 and 21 have been identified as degraders of CRY1[26,27]. Neuronal PAS family member 2 *(NPAS2)* shares homology with the *CLOCK* gene and is the largest member of the family [28]. Differentially expressed in chondrocyte (DEC1) and DEC2 inhibit CLOCK-BMAL1 transactivation by either binding with BMAL1 or E-boxes[29]. Other factors that may intervene in circadian clock rhythms include cAMP signaling, intracellular calcium flux, and membrane depolarization[30,31]. These factors are crucial for the SCN, potentially forming positive feedback loops on the central pacemaker of the circadian clock.

Post-translational regulation of the clock proteins includes phosphorylation, O-GlcNAcylation, and acetylation of the CLOCK-BMAL1 complex. These processes lead to either ubiquitination and degradation of core clock proteins or inhibition of their destruction, thereby promoting stabilization and a prolonged half-life. This delicate balance is crucial for maintaining the period of the molecular clock[32,33]. Molecules responsible for the amplitude of the clock period primarily include casein kinase II, PI3-kinase, and c-Jun N-terminal kinases[34].

CIRCADIAN CLOCK GENES AND METABOLIC DISORDERS

Disruption of circadian rhythms has been increasingly linked to metabolic disorders. Recent guidelines for the management of type 2 diabetes mellitus (T2DM) emphasize the importance of adequate sleep[35]. Circadian misalignments may lead to a notable reduction in muscle insulin sensitivity and an elevated fasting glucose level[36]. Meta-analyses support the idea that shift workers have a greater risk of T2DM[37] and that abdominal obesity is more prevalent among shift workers[38]. Moreover, shift work has been linked to a higher risk of metabolic syndrome[39], and permanent night shift workers tend to have higher levels of total cholesterol and triglycerides and lower levels of high-density lipoprotein cholesterol[40].

In line with epidemiological studies, there is ample evidence that circadian gene variations are associated with metabolic disorders. A *CLOCK* gene single nucleotide polymorphism has been associated with a lower risk of T2DM[41], while polymorphisms in *CLOCK* and *ARNTL* in patients with T2DM have been linked to myocardial infarction[42]. In recent years, research has focused on interventions that could improve metabolic profiles by influencing circadian rhythms. Time-restricted eating between 8 am and 2 pm appears to decrease morning fasting glucose and mean daily glucose levels and affect the expression of circadian CGs, such as *BMAL-1, CRY1, CRY2*[43]. Furthermore, according to a recent cross-sectional study, chronotype-aligned exercise has better outcomes in HbA1c, fasting glucose, and lipidemic profile of individuals with T2DM compared to exercise disregarding chronotype[44]. In addition, a three-meal diet with a rich carbohydrate breakfast appears to optimize HbA1c, reduce body weight and insulin requirements, and concomitantly upregulate the expression of CGs in patients with T2DM compared to a six-meal isocaloric diet[45]. Moreover, a 12-wk warm light exposure can alter the expression of *REV-ERBα* in shift workers[46], suggesting that light therapy could

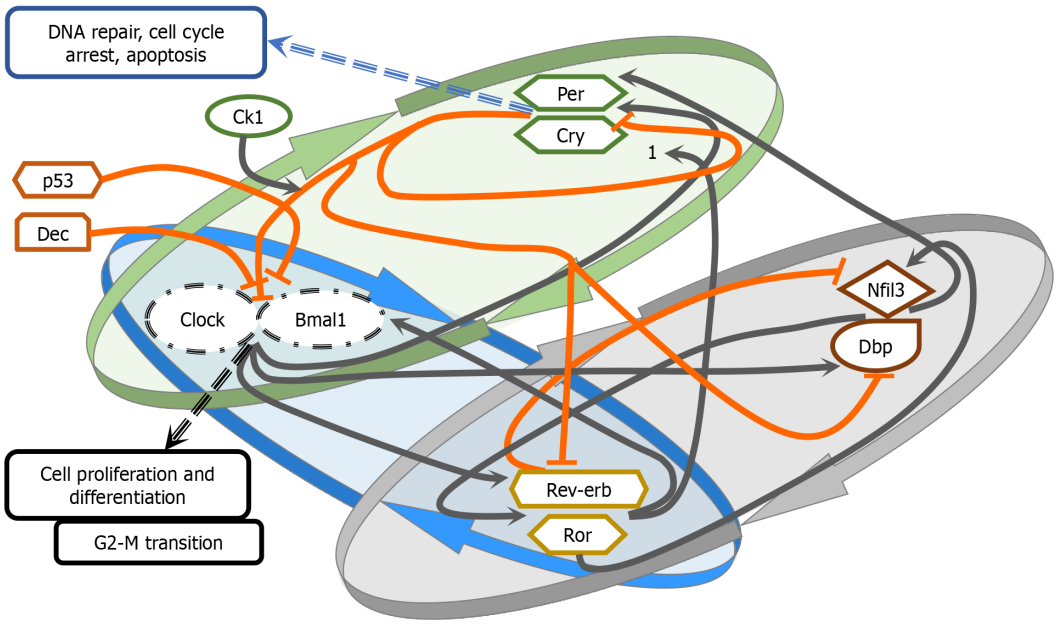

Figure 1 Schematic illustration of the intricate functions of the mammalian circadian clock. Transcriptional-translational feedback loops are highlighted along with the regulatory mechanisms of the clock, interactions of circadian clock genes with cellular processes and regulation of complex biological mechanisms. The circadian clock mechanism primarily relies on a core feedback loop (green area) involving the transcription factors BMAL1 and CLOCK. These factors heterodimerize and bind to the promoters of target genes, such as *PER* and *CRY*. The proteins encoded by these genes form complexes that inhibit their own transcription by interfering with the activity of *BMAL1* and *CLOCK*. A second feedback loop (blue area) features the transcriptional roles of *REV-ERB*. Ck1 and p53 are involved in phosphorylating PER for degradation. ROR/REV-ERB regulates *BMAL1* transcription. The *DEC* gene contributes to circadian gene regulation. A third feedback loop (grey area) features the interrelationship between *ROR/REV-ERB* and *DBP/NFIL3*. There are additional loops and components that contribute to the regulation of the circadian clock. PERs can form a complex (not shown) with the ATM kinase and the checkpoint kinase Chk2, thereby influencing DNA repair, cell cycle arrest, and/or apoptosis. The diagram shows how these circadian components influence critical cellular functions such as cell proliferation and differentiation and the G2-M transition in cell cycle progression (from the G2 phase to the mitotic phase). Each of these processes is essential for the normal functioning of cells and organisms. They work together to ensure that cells divide properly, maintain their genetic integrity, differentiate into various cell types as required, and eliminate cells that are no longer needed or are potentially harmful. Disruptions in any of these processes can lead to serious health issues, including developmental abnormalities, immune system dysfunction, and various forms of cancer. Dark grey lines: Positive regulation of transcription in a loop. Orange lines: Negative regulation of transcription. [1]*CRY1* gene.

be used to rectify circadian disturbances. Based on current data, future research could uncover therapeutic methods for metabolic disorders based on circadian rhythms.

ROLE OF CIRCADIAN CLOCK GENES IN CANCER

Several studies support the notion that disruption of the circadian clock can lead to oncogenesis through various pathways. Interestingly, CGs appear to regulate the expression of the majority (60%-80%) of the proteins of cells. Simultaneously, the tumor itself can influence normal circadian function. Mechanisms contributing to oncogenesis include the disruption of cellular homeostasis, interference with gene expression and DNA repair, as well as alterations in the tumor microenvironment (TME) and the immune response that favor tumor growth, survival, and metastasis[47-50].

The circadian system and the cell cycle are tightly interconnected. CGs control the transcription of key cell cycle regulators, gating the initiation of different phases (G1, S, G2, M)[51]. Transcriptional regulation can be facilitated either through E-boxes in gene promoters (*Cyclins A, B1, D1, p53, c-Myc, and Wee1*)[52,53] or through RORE regions on gene promoters that are targets of *REV-ERBα*[54]. For example, *C-MYC* expression (G0/G1 checkpoint and oncogene) is negatively regulated by BMAL1- CLOCK/NPAS through its E-box[52,55]. Bmal1-Clock controls both cyclin B1, an enhancer of G2/M transition, and Wee1, an inhibitor[56]. This relationship is bidirectional, as both *Per2* and *Rev-Erb* transcription is regulated by genes like *p53* and other tumor suppressor or cyclin kinase genes[57,58]. Therefore, CG disruption could contribute to tumorigenesis by interfering with different phases of the cell cycle[49,51].

A normal part of the cell cycle is the process of ensuring that any damage in the DNA are identified and repaired. Cryptochrome genes seem to be stimulated in states of genotoxic stress, and *Cry*2-deficient cells have been found to sustain damaged DNA[59]. CRYs and PER1 interact with the ATR/CHK1,2 signaling pathway involved in repairing DNA strands destroyed by ionizing radiation[60-62]. An attribute of cancer cells is their infinite replication potential. Telomerase activity, crucial for maintaining telomere length and preventing reproductive senescence[50], seems to be associated with *CLOCK-BMAL* expression[63]. Moreover, the circadian clock controls genes affecting cellular duplication (Ki-67)[64,65], the *MDM-2* oncogene[52,66], cell apoptosis through Bax and Bcl-2[67], invasion and metastasis (MMP9)[68,69], and angiogenesis (VEGF)[64,70,71].

Dysregulation of the circadian clock can cause disruption of cellular metabolism. Chronic jet lag may be associated with the appearance of hepatocellular carcinoma *via* nonalcoholic fatty liver disease[72]. Increased glycolytic metabolism (Warburg effect) is crucial for cancer cell nutrition. For example, PI3-kinase/PdK1/AKT and hypoxia-induced factor 1 (HIF-1) pathways, which increase cell glycolysis, are influenced by circadian clock components[73,74].

Furthermore, the circadian clock controls the immune system and maintains homeostasis during inflammation. Disruption of the circadian clock can lead to immune dysfunction and immunosuppression through interference with antigen presentation, cell trafficking, and the function of T and B lymphocytes, natural killer cells, and monocytes[75,76]. Disruption of the circadian clock is also associated with chronic inflammation *via* cytokines, which have both paracrine and endocrine activity and affect cells locally and in distant tissues[47,48,50,77]. The TME, consisting of many different cells[78], dysfunctional vessel networks, cytokines, and deleterious intercellular signaling, is affected by CGs. This can be through the regulation of lymphocyte TME infiltration, impaired vigilance toward cancer cells, as well as the interaction between CGs and HIFs[71,79]. These processes can contribute to angiogenesis, metastasis, and immune system evasion [80,81].

Animal studies have shown that mutated CGs may act as tumor suppressors or oncogenes in various tissues[82-85]. These mutations might cause different disorders in different tissues. Genetic and genomic studies have shown that variations in the transcription of CGs are more common than mutations. Interestingly, it could be cancer cells themselves that disrupt the circadian clock, enhancing tumorigenesis[50].

Can shift work be solely responsible for the detrimental effects of circadian disruption? Studies have shown that night shift workers have an increased incidence of breast, prostate, and colorectal cancer[86-88]. Environmental factors such as light exposure and food consumption are indeed known circadian modulators. However, the effect of nocturnal activity, be it work or social life, is multifactorial, often mixed with other habits that increase cancer risk, such as alcohol or tobacco use, junk food consumption, and reduced exercise[89-93]. Some are skeptical of the association between cancer and the circadian clock, given certain reports of clockless animals that appear to be resistant to certain cancers[94]. Nevertheless, generalizations should be avoided; research should hone on the specific effects of distinct CGs on distinct forms of cancer and vice versa[94]. More studies that illustrate in detail the connections between the circadian clock and cancer and enable the design of new treatments are necessary.

CIRCADIAN CLOCKS IN CANCER PATIENTS WITH METABOLIC DISORDERS

An interesting but complex issue to address is the effect of circadian disruption in patients with metabolic disorders on the development and progression of cancer. In patients with diabetes, circadian clocks and sirtuins (SIRTs) influence oxidative stress, inflammation, and aging, contributing to organ-specific damages such as those seen in diabetic lung disease[95]. An imbalance of the circadian clock systems can lead to immune dysregulation and chronic inflammation that is linked to diabetes and obesity but additionally promotes cancer cell proliferation and invasion as well as evasion of immune surveillance[96]. Alterations in microbiota that are known to have circadian rhythmicity have been linked to metabolic disorders and could promote carcinogenesis especially in the colon[97]. Further exploration of the interconnections between metabolically-induced circadian disruption and carcinogenesis is beyond the objective of this review albeit being an exciting field.

CIRCADIAN DISRUPTION AND CLOCK GENES IN ENDOCRINE TUMORS

Breast cancer

Breast cancer (BC) is the most common cancer in females. According to a systematic review[98], in which the authors examined the relationship between BC and night shifts among nurses, most studies suggested a relationship between increased BC risk and cumulative years working in night shifts, particularly with three or more nights per month for at least 15 years. Furthermore, long-duration shift work is associated with estrogen and progesterone receptor-positive tumors, especially among young women with intensive shifts (12-h shifts). Night work schedules may shorten telomere length, a potential contributing factor to BC risk, and are associated with irregular menstrual cycles, which are considered a risk factor for BC.

The early onset and high mortality of BC are linked to a heterogeneous TME, consisting of various cell types such as cancer-associated fibroblasts, immune cells, and endothelial cells. Cancer-associated fibroblasts, in particular, contribute to tumor progression, metastasis, and drug resistance. Circadian CGs can modulate the TME, and their disruption can impact the biology of breast tissue, causing metabolic disturbances and immune dysfunction and potentially promoting tumor growth[99]. Additionally, in BC, there is lower expression of *PER* genes compared to normal breast epithelial cells. Loss-of-function mutations in *PER2* have been linked to higher cancer incidence, especially radiation-induced cancer. Loss of *PER2* inhibits programmed cell death, affecting p53 and cell cycle regulation[100]. Single nucleotide polymorphism in circadian rhythm genes are associated with altered expression of cell cycle-regulating genes. For example, *NPAS2* polymorphisms are linked to a higher risk of BC, especially in females[101]. Sirtuin-1 (SIRT1), a histone deacetylase, is involved in many cancer cases, and polymorphisms in the *SIRT1* gene are considered a risk factor[102]. Circadian genes, through the regulation of estrogens, glucocorticoids, and melatonin, as well as estrogen receptor transcription, could be involved in BC development[103].

The role of protein arginine methyltransferase 6 (PRMT6) and poly ADP-ribose polymerase 1 (PARP1) in BC progression and their involvement in circadian rhythm disruption have been recently examined[104]. PRMT6 binds to PARP1, leading to the recruitment of the Cullin4B-Ring E3 Ligase (CRL4B) complex. Together, these components stimulate histone methylation and ubiquitination, which promotes BC progression through the disruption of circadian rhythm and by repressing key DNA repair genes like *PER1* and *PER3*. PRMT6 and PARP1 have individual roles in DNA repair by interacting with different proteins[105]. Furthermore, PRMT6 acts as a TP53 transcriptional repressor and a transcriptional coactivator in different contexts. It enhances BC cell proliferation, invasiveness, metastasis, and epithelial-mesenchymal transition[106]. PARP1 also interacts with PRMT6 and DDB1 in the CRL4B complex for transcriptional regulation. Inhibition of PARP1 enzymatic activity by olaparib disrupts the assembly of the PRMT6/PARP1/CRL4B complex, impacting circadian clock oscillation. As a result, PRMT6 and PARP1 inhibitors are suggested as potential treatments to restore natural circadian rhythms and obstruct tumor progression in BC cells with upregulated PRMT6 expression[104].

Ovarian cancer

Ovarian cancer is a common and deadly gynecologic malignancy, and research has shown that disturbances in circadian rhythms, such as shift work or irregular sleep patterns, might entail an increased risk[107]. Ovaries express circadian genes, controlling hormones during reproductive cycles, and lower expression of *PER1, PER2, CRY2*, and *CLOCK* in ovarian cancer compared to normal ovaries has been demonstrated[108]. Low expression of both *BMAL1* and *CRY1* was connected with a reduced overall survival rate. In contrast, *CRY1*, *PER3*, and *BMAL1* showed higher and antiphasic (opposing) expression in ovarian malignancy.

CLOCK gene expression was linked to cisplatin resistance in ovarian cancer cells, and particularly upregulation of *CLOCK* reduced sensitivity to cisplatin. *CLOCK* knockdown increased the inhibitory effects of cisplatin on cell proliferation and induction of apoptosis[109]. Furthermore, Piwil2 and Pasd1, which are cancer/testis antigens, can interact with CGs like *Bmal1* or *Clock* and interfere with circadian rhythms both in normal testis and cancer cells. Moreover, they negatively regulate the transcriptional activation of clock-controlled genes[110].

Prostate cancer

Prostate cancer (PCa) is a leading cause of cancer-related deaths in males. Studies that included immigrant populations suggested that environmental, lifestyle, and circadian rhythm disruptions may contribute to PCa formation. Both exogenous and endogenous factors might contribute to this process. Aging is closely connected to the circadian clock and changes in the SCN[111]. Sleep patterns, sleep quality, and duration are also factors that may affect PCa risk. Intermittent fasting and its effect on circadian rhythm regulation might offer protection against carcinogenesis, including PCa[112]. The circadian genes *NPAS2*, *PER1*, *PER2*, and *PER3* play roles in controlling DNA damage, cell growth, and cell cycle regulation. Alterations in these genes can influence PCa risk and growth[113-118].

Chronic inflammation is proposed to be implicated in prostate carcinogenesis, and circadian rhythm disruption may contribute to the proinflammatory environment in PCa. The downregulation of *PER2* is associated with the induction of epithelial–mesenchymal transition, which plays a role in cancer dissemination[119]. Increased melatonin is associated with protection against PCa progression[120], while inverse relationship of cortisol with the melatonin/cortisol ratio is linked to PCa emergence and stage[121]. The role of osteoblastic protein kinase D1 (PKD1) in promoting dormancy in PCa cells has been highlighted[122-124]. The results indicated that osteoblastic PKD1 induced dormancy in co-cultured PCa cells by activating cAMP responsive element binding protein 1 and increasing growth arrest specific 6 secretion. This osteoblastic PKD1-induced dormancy also enhanced the expression of core circadian clock molecules in PCa cells, which was linked to recurrence-free survival in metastatic PCa patients[122].

Thyroid and parathyroid glands

The rapid increase in the detection rate of thyroid cancer (TC) recently has been largely attributed to screening[125]. TC accounts for 3.4% of all cancers diagnosed annually worldwide[126], and recent data suggest that TC is increasing globally faster than other malignant lesions[127,128]. Several risk factors for TC have been identified by epidemiological research, namely female sex, advanced age[129], ionizing radiation[130,131], non-Hispanic white race[132], alterations in thyroid stimulating hormone (TSH) levels[133,134], obesity[135,136], and last but not least iodine deficiency[137]. However, even though the above-mentioned risk factors have been studied thoroughly, they cannot fully explain the variation in TC risk.

Growing evidence suggests that the disruption of circadian rhythm is a potential factor in thyroid tumorigenesis[138]. An epidemiological study in post-menopausal non-obese women proposed an association between insomnia and a higher incidence of TC[139], supporting the role of circadian dysregulation in TC development caused by sleep disorders. Furthermore, night shift work has been an established circadian disruptor and related to altered TSH plasma levels[140]. Artificial light at night suppresses melatonin, a fundamental regulator of circadian rhythms, causing circadian disruption [141]. A study in the United States[142] evaluated the hypothesis of a positive association between higher exposure to light at night and the risk of TC, especially papillary thyroid carcinoma. The same study suggested potential sex differences with a stronger association observed in females and a higher risk of anaplastic thyroid carcinoma for higher exposure to artificial light at night.

Based on current evidence, the SCN exerts control over the endocrine system. In humans, thyrotropin-releasing hormone and TSH show a nocturnal peak around 2 am to 4 am, while free thyroxine 4 has a less prominent circadian profile. The abovementioned hypothalamic nucleus directs neuronal outputs into the paraventricular hypothalamic nucleus and may be responsible for the circadian pattern of thyrotropin-releasing hormone[143].

At the genomic level, alterations in the characteristics of CGs were observed recently[144] in thyroid follicular malignancies. The cells were *in vitro* synchronized primary thyrocytes and cells recuperated by tissue biopsies. *BMAL1* gene expression was 13-fold upregulated, while *CRY2* expression was about 2-fold downregulated in papillary thyroid carcinoma nodules compared with benign thyroid nodules. In follicular thyroid carcinoma, *BMAL1* showed 2-fold upregulated levels, with *CRY2* downregulated equally by 2-fold. It is worth mentioning that upregulated levels of tissue inhibitor of metalloproteinase 1 were found, in contrast to downregulated levels of growth arrest and DNA damage inducible gene 153 transcripts in papillary thyroid carcinomas, a finding that was in agreement with previously published studies[145,146].

The transformation of normal thyroid tissue to nodular thyroid tissue with benign characteristics does not alter the circadian oscillator function[144]. However, malignant transformation of thyrocytes might implicate a change in circadian oscillator properties, namely the alteration of *PER2* profile, especially in papillary thyroid carcinoma. PER2 can act as a tumor suppressor and has been found to play a key role by regulating responsive DNA damage pathways[52]. A recent cohort study evaluated the circadian rhythm genes involved in anaplastic thyroid carcinoma, a rare and extremely malignant type of endocrine cancer[147]. This work demonstrated that the *NPAS2* gene promoted malignant phenotypes of anaplastic thyroid carcinoma by modulating the cell cycle as well as focal adhesion signals. This finding could be useful in the development of new therapeutic agents for this challenging type of endocrine cancer.

Dysregulation of various CGs including *CRYs*, *PER1-2-3*, *REV-ERBs*, and *ROR α-β-γ* have been associated with a higher risk of TC development[101,148]. In addition, increased levels of the circadian clock factor DEC1 have been found to promote the induction of several cell cycle-related genes, potentially leading to the development of TC[149].

As far as parathyroid tumors are concerned, available data is scarce. In parathyroid adenomas, mRNA of *NFIL3*, a gene responsible for repression of *PER1* and *PER2* expression, was downregulated. Moreover, *NFIL3* and *CRY2* mRNA levels were following the same pattern of downregulation. It is interesting though that no statistical difference was found between parathyroid adenomas and parathyroid hyperplasia concerning the core CGs[107]. Nevertheless, the mechanisms implicated in the interaction between circadian clock gene abnormalities and malignant transformation of thyroid tissue remain to be clarified and elucidated by more clinical studies, providing new insights that could contribute to malignant nodule preoperative diagnosis and new treatment prospects.

Adrenal gland

Adrenal masses are encountered in 2% of the general population, and less than one-third of them are hormone-producing adenomas[150,151]. Adrenal carcinomas are scarce, with an incidence of 0.5-2.0 cases per million population per year[152,153]. Adrenal tumorigenesis is currently perceived as a gradual process of transformation from normal tissue to adenomatous tissue and consequently to a cancerous lesion[154]. Possible interactions between CGs and adrenal function, as well as the effect of circadian disruption on the development and progression of adrenal masses, are being investigated.

Cortisol-secreting adenomas

Cortisol-secreting adenomas (CSAs) were found to have reduced expression of *PER1*, *CRY1*, and *REV-ERB* mRNAs compared with adjacent normal adrenal tissue in humans[155]. The rhythmicity of glucocorticoid secretion is multifactorial and complex and has been extensively reviewed previously[156,157]. The various ways by which centrally or adrenal-expressed CGs regulate glucocorticoid secretion in humans remain to be elucidated.

Studies in mice show that the loss of core CGs like *PER1* leads to deranged rhythmicity of glucocorticoid production [158]. Lack of *Per1* or *Per2* in mice causes higher circulating levels of glucocorticoids[158], whereas the lack of both *Per2/Cry1* leads to the complete loss of the circadian rhythm of both adrenocorticotropic hormone and corticosterone, as well as other CGs[159]. Conversely, adrenal-specific knockout (KO) of *Bmal1* did not have an effect on basal secretion of glucocorticoids in mice, but an increased glucocorticoid response to acute stress was observed[160]. Therefore, *BMAL1* expressed in the adrenal glands has a local regulatory role.

The effect of circadian disruption on cortisol secretion is another interesting domain. Indicatively, shift work causes a partial adaptation in cortisol secretion in humans, as demonstrated by Koshy *et al*[161], who studied police officers after seven night shifts[161]. This was accompanied by a loss of morning/evening difference in *CLOCK* gene expression in both the oral mucosa and peripheral blood cells. Undoubtedly, more evidence is required, taking into consideration that work-related stress might be an additional driver of glucocorticoid production, independent of circadian rhythm disruption itself.

Aldosterone-producing adenoma

In human tissues from aldosterone-producing adenomas (APAs), all CGs were found to be upregulated compared to normal tissue but not with statistical significance[155]. Interestingly, *PER1* and *BMAL1* were more downregulated in APAs compared with CSAs[155]. Aldosterone stimulates *Per* gene transcription in mice[162]. *CRY1* was found to be upregulated in human tissues of APAs, while *CRY2* was downregulated[163]. Moreover, treatment with angiotensin II caused a significant upregulation of *CRY1* and downregulation of *CRY2*. These studies imply that high levels of circulating aldosterone or angiotensin II are affecting the expression of CGs with consequent circadian disruption but cannot prove the opposite effect.

Further studies have revealed increased aldosterone levels in male mice, with global *Per1* KO and kidney-specific *Per1* KO on a normal salt diet[164-166]. This was accompanied by altered Na+ handling and non-dipping hypertension after high-salt and mineralocorticoid treatment. *Per1* KO also caused an increase in *Cry2* expression in the adrenals[165]. Adrenal-specific *Bmal1* ablation in mice also led to changes in diurnal aldosterone levels and Na+ handling by the kidney [167]. These results would imply that *Per1* and *Bmal1* regulate the expression of aldosterone, but it is unknown if these

sex-specific findings could translate similarly into human tissues.

Pheochromocytoma

In the murine adrenal medulla, *Bmal*, *Per1*, and *Per3* seem to have a distinct circadian rhythm, while other CGs show weak expression[159]. There is yet no evidence of dysregulated CGs in human pheochromocytoma (PCC) tissues. However, research on PCCs and genes implicated in their development has revealed an interesting association between the hypoxia signaling pathway and the circadian clock; *BMAL1*, *CLOCK*, and *PERIOD* are heterodimerizing transcription factors that belong to the same family (bHLH-PAS) as *HIF1α*, *1β*, *2α*[168]. It is well known that mutations in *CLUSTER 1* and *2* genes in PCC cells lead to stabilized and therefore increased hypoxia-inducible factors. As a result, there is increased hypoxia signaling in the environment of PCC cells and consequent overexpression of genes that control apoptosis, cell growth and proliferation, as well as VEGF, which leads to angiogenesis[169-171].

As members of the same family, BMAL1 might form a heterodimer with CLOCK or HIF-1β and HIF-1β a heterodimer with HIF-α or CLOCK, and they can bind to DNA regions that modulate gene expression of either the circadian or the hypoxia pathway. This leads to a bidirectional interaction. Animal studies have demonstrated how VEGF expression can be controlled by *Bmal1* and *Per2*, causing angiogenesis driven by the circadian pathway[71,79]. Rutter *et al*[172] described an association between the redox state within the cell and the binding of CLOCK2-BMAL1 on E-box sites, indicating that circadian clock disruption can occur in states of oxidative stress[172].

One known clock-controlled gene in PCC cells is *Atf5*, which was found to be negatively regulated by Clock-Bmal1 in PC12 cells[173]. In the absence of Bmal, this gene is overexpressed[174], having a negative effect on neuronal differentiation in PC cells. On this occasion, cell differentiation is disrupted by a clock gene.

Adrenocortical carcinoma

Recent studies on human adrenal tissue proclaim that there are different patterns of clock gene disruption in benign compared to malignant adrenal tumors. *CLOCK*, *CRY1*, and *PER1* gene expression were amplified in adrenocortical carcinomas (ACCs) compared to CSAs. On the contrary, *BMAL1*, *RORa*, and *REV-ERB* expression were decreased[155]. Differences have been observed between ACC cells and normal tissue: Upregulation of *CRY1* and *PER1* and downregulation of *BMAL1*, *RORa*, and *REV-ERB* genes in ACC cells were noted[155]. The exact effects of clock gene disruption on tumorigenesis are not yet known.

Pituitary gland tumors

Pituitary adenomas consist of typically monoclonal cell populations that can be either sporadic or familial. Four to five percent of pituitary adenomas are associated with clinical syndromes like multiple endocrine neoplasia 1 (Carney complex) and familial isolated pituitary adenoma, whose diverse genetic profiles are still under investigation[175]. A recent work has revealed the role of *PER2*, a key clock gene, in the pathogenesis of pituitary adenomas[176]. In human tissues obtained from prolactinomas and growth hormone-producing adenomas, the expression of several CGs was dysregulated compared to controls, with *PER2* being consistently overexpressed. This overexpression of *PER2* was confirmed in TSH-producing and adrenocorticotropic hormone-producing adenomas as well as non-functioning pituitary tumors.

Jet-lagged mice that had been inoculated with GH3 cells exhibited a faster rate of tumor growth that had a time-specific pattern[176]. The timing of higher cell proliferation was different compared to mice with intact circadian rhythm and correlated with elevated *Per2* expression. In other groups of mice, one with estrogen-induced prolactinomas and one with xenograft GH3 tumors, KO of *Per2* led to slower progression of the tumors as indicated by decreased Ki67 or smaller tumor mass and volume[176]. Apparently, *Per2* plays an important role in cell cycle regulation, as its loss halts cells in the G2/M phase and negatively affects the number of pituitary cells in mitosis and positively those in apoptosis. More specifically, *Per2* seems to act by upregulating key cell cycle genes (*Ccnb2*, *Cdc20*, *Espl1*) through HIF-1α[176].

Furthermore, a REV-ERBα antagonist administered to mice with GH3 tumors was found to counteract tumor growth by inhibiting *Per2* expression. Interestingly, this agent was injected at a specific time of day that correlated with peak Per2 levels[176]. Patterns of *PER2* expression in pituitary adenoma cells that might reflect times of higher cell proliferation could be useful guides for the timing of pharmacotherapeutic interventions in the future.

Neuroendocrine tumors

The expression of CGs has also been studied recently in gastric neuroendocrine tumors. In human gastric neuroendocrine tumor cells, *CLOCK* and *BMAL1* were significantly upregulated, and *REV-ERB* was downregulated compared to normal tissue. On the contrary, the expression of *PER2* and *CRY1* was not altered significantly[177].

CLOCK GENES AND CANCER THERAPY

During the last decades, an increasing number of studies have investigated the interaction between circadian clocks and cancer therapy as well as the clinical utility of chronotherapy, which consists of three approaches[178,179].

The first approach is to promote and preserve an ideal circadian rhythm by entraining the circadian clock using daytime exposure to LED light[180], administering melatonin (apart from its antiproliferative, antioxidant, and immunological effects)[181], following intermittent fasting[182], doing exercise at different times of the day[183], or administering glucocorticoids[184] (the latter can alter the expression of CGs and display time-dependent pharmacokinetics)[185].

The second approach is to optimize chemotherapy and/or radiotherapy administration to maximize therapeutic results and reduce adverse effects by selecting a specific dosing time during the day[11,186,187]. This is based on the time-dependent expression of CGs, which affects the sensitivity of tumors to anticancer drugs[188] as well as the improvement of radiotherapy outcomes based on chronomodulation[189].

The third approach is to use small molecules that alter a circadian clock gene and can improve efficacy in combination with other anticancer treatments[178,179]. Almost all tumors are characterized by a disruption in the expression of CGs [190], and a number of small molecule modulators have been studied in several types of cancer. Additionally, chemotherapeutic agents have been shown to exhibit rhythmic cytotoxic activity. However, there is a lack of data concerning the use of these molecules and the specific time-of-day administration of chemotherapy in endocrine cancer, and assumptions can be made about their utility in that field.

Some small molecules have been shown to be effective against certain types of cancer. SR9009 and SR9011 are agonists of nuclear receptors Rev-Erbα/β, which reduce *Bmal1* transcription[179], and appear to be specifically lethal to glioma cells without affecting normal cells. KL001, a stabilizer of Cry1/2, reduces glioma stem cell proliferation[191]. These molecules could potentially be useful in endocrine cancers, considering the significant upregulation of *BMAL1* and downregulation of *CRY2* in follicular and papillary TC[144], the synergistic interaction between *Bmal1* and *Hif-1a* at the genomic level in PCC[73], as well as the significant increase of *Bmal1* and reduced expression of *REV-Erbs* in gastric neuroendocrine cells compared to adjoining enterochromaffin-like tissue[177].

Another small molecule, LYC-55716, a RORγ agonist involved in the regulation of circadian rhythms and the immune system, has been successfully tested in a phase 1 open-label multicenter study in advanced tumors[192]. In addition, SR8278, a REV-ERB antagonist leading to the downregulation of pituitary expression of *Per-2*, reduces pituitary tumorigenesis[176]. Nevertheless, CGs display differential expression in different types of cancer[190]. Therefore, further clinical studies are required to elucidate the possible effects of chronomodulating small molecules in accordance with the diverse expression of CGs in cancerous tissues, including endocrine cancer. On the other hand, core clock proteins could be used as tumor biomarkers[193] or diagnostic preoperative markers[144].

PROGNOSTIC VALUE FOR CIRCADIAN CLOCK GENES IN CANCER DIAGNOSIS

Circadian CGs, particularly the PER gene family, play a crucial role in cancer progression and patient prognosis[194]. Mutations in these genes can affect cell function, metabolism, immunity, and response to treatment, contributing to varying cancer outcomes[194,195]. Studies have shown that the expression levels of circadian genes are significantly altered in cancers such as colorectal carcinoma, HER2-positive advanced gastric cancer, BC, pancreatic cancer, and obesity-related cancers[196-200]. These alterations could serve as biomarkers for cancer prognosis.

In colorectal cancer, the variable expression of circadian genes correlates with tumor progression and patient survival [197,201,202]. In pancreatic cancer, targeting circadian genes may optimize treatment and improve prognosis[199]. In BC, disruptions in circadian rhythms and alterations in circadian gene expression have been linked to different BC subtypes, tumor progression, and response to chemotherapy and radiotherapy[196,203-205]. Notably, lower expression of *PER* genes has been correlated with more aggressive tumor phenotypes and poorer survival rates in some cases[194,202], whereas in adrenocortical carcinoma *PER1* expression is enhanced[155] and in pituitary adenomas there is marked overexpression of *Per2*[176]. It is evident that different types of tumors display distinct alterations in CGs that could be associated with prognosis and survival rates. Therefore, there is no single pattern that fits all. Further studies assessing the expression of circadian genes, including the PER family, can provide valuable prognostic information and guide personalized treatment strategies.

CONCLUSION

Disruptions in circadian rhythms, often a result of modern lifestyle factors such as shift work, irregular sleep patterns, and exposure to artificial light, lead to aberrant epigenetic modifications and adverse health outcomes. These disruptions have been linked to a range of diseases, including metabolic syndrome, cardiovascular diseases, and various types of cancer, emphasizing the critical role of biological clock homeostasis in human health. Circadian misalignments may lead to reductions in muscle insulin sensitivity, elevated fasting glucose levels, and an increased risk of T2DM among shift workers. Moreover, circadian gene variations have been associated with different metabolic disorders, highlighting the potential for interventions that could influence circadian rhythms to improve metabolic profiles.

The connection between circadian disruption and cancer involves multiple pathways, including interference with gene expression, DNA repair, and immune response. CGs control key cell cycle regulators and discuss the bidirectional relationship between the circadian system and the TME, which affects tumor growth, survival, and metastasis. An association between night shift work and increased BC risk, particularly with long-duration shift work, has been observed. Table 1 provides a comprehensive overview of how circadian disruption and CGs influence various endocrine tumors along with the related outcomes and interventions, highlighting the complex interplay between circadian rhythms and the pathology of endocrine tumors.

The evidence presented supports the potential for circadian rhythm-focused therapies, including chronotherapy, to treat endocrine tumors. Understanding the rhythmic patterns of drug efficacy and toxicity could optimize treatment schedules and minimize side effects. We call for further research to elucidate the precise mechanisms through which circadian genes influence tumor biology. Investigating specific pathways and molecular mechanisms involved can help

Table 1 The role of circadian disruption and clock genes in different types of endocrine tumors

Endocrine tumor	Circadian gene influence	Associated findings/interventions
Breast cancer	*PER* genes, *PRMT6*, *PARP1*	Night shifts linked to increased risk, *PER* genes involved in tumor progression, *PRMT6* and *PARP1* implicated in cancer progression
Ovarian cancer	*PER1, PER2, CRY2, CLOCK*	Shift work/irregular patterns linked to risk, gene expression alterations, *CLOCK* gene linked to cisplatin resistance
Prostate cancer	*NPAS2, PER1-3*	Environmental/lifestyle factors contribute, aging and sleep patterns, *PER2* linked to cancer dissemination, intermittent fasting as a protective factor
Thyroid cancer	Various clock genes	Disruption as a potential contributing factor, alterations in gene expressions in follicular malignancies, *NPAS2* gene promotes malignant phenotypes
Parathyroid tumors	*NFIL3, CRY2*	Downregulation observed in adenomas, further research needed
Adrenal tumors	*PER1, BMAL1, CRY1*	Altered expression in cortisol-secreting and aldosterone-producing adenomas, adrenal-specific gene influences, implications in glucocorticoid secretion and regulation
Pituitary tumors	*PER2*	Overexpression linked to tumor growth, potential timing for pharmacotherapeutic interventions

Clock genes abbreviations: BMAL1: Basic Helix-Loop-Helix ARNT Like 1; CLOCK: Circadian locomotor output cycles kaput; CRY2: Cryptochrome Circadian Regulator 2; NFIL3: Nuclear Factor, Interleukin 3 Regulated; NPAS2: Neuronal PAS Domain Protein 2; PARP1: Poly(ADP-Ribose) Polymerase 1; Per: Period; PER1: Period Circadian Regulator 1; PER2: Period Circadian Regulator 2; PER3: Period Circadian Regulator 3; PRMT6: Protein arginine N-methyltransferase 6.

identify new therapeutic targets and improve prognostic tools for various cancers. Given the associations between lifestyle factors like shift work and increased cancer risk, there is a significant opportunity for public health interventions. The importance of circadian rhythms in human health and disease is critical, and the need to consider the circadian dimension in understanding disease mechanisms and developing more effective, time-based therapeutic interventions should be emphasized.

FOOTNOTES

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