

The role of circadian clock genes in tumors

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Circadian rhythms are generated via variations in the expression of clock genes that are organized into a complex transcriptional–translational autoregulatory network and regulate the diverse physiological and behavioral activities that are required to adapt to periodic environmental changes. Aberrant clock gene expression is associated with a heightened risk of diseases that affect all aspects of human health, including cancers. Within the past several years, a number of studies have indicated that clock genes contribute to carcinogenesis by altering the expression of clock-controlled and tumor-related genes downstream of many cellular pathways. This review comprehensively summarizes how clock genes affect the development of tumors and their prognosis. In addition, the review provides a full description of the current state of oral cancer research that aims to optimize cancer diagnosis and treatment modalities.

Keywords: circadian rhythms, clock genes, oral squamous cell carcinoma, carcinogenesis, oral cancer

Introduction

The rotation of the earth produces a day–night cycle. Organisms align their biochemical and behavioral processes to adapt to the resulting periodic environmental changes. Most activities, such as those related to sleep–wake cycles, blood pressure, body temperature, and hormone secretion, fluctuate over an approximately 24-h period. These fluctuations, known as circadian rhythms, allow diverse physiological and behavioral activities to be coordinated and organized to benefit the survival and reproduction of organisms.^{1,2} Another advantage in restricting the DNA synthesis stage to the night is the reduction in DNA damage caused by strong ultraviolet radiation during the day.³ This is also a beneficial adaptation for nature in terms of the course of evolution. Circadian rhythms are affected not only by environmental cues such as light and food but also by hidden factors that comprise the “circadian clock” that controls and maintains these rhythms.^{1,4,5} Nearly every cell, from single-celled bacteria to those that compose fungi and mammals, including humans, possesses a self-sustained circadian clock; however, the clock differs in various species, even though it is highly conserved.^{5,6}

The circadian clock is an intrinsic time-tracking system that is composed of central and peripheral clocks.^{4,7,8} The central clock is the master pacemaker of circadian rhythms and is located in the hypothalamic suprachiasmatic nucleus (SCN), which contains 10,000–15,000 neurons. Light is the only factor that influences the central clock; it is perceived by the retina and then transmitted via electrical signals to SCN neurons. These signals transmit instructions to an organism and thereby affect the peripheral clock via neurotransmitters, endocrine factors, and bodily fluids.^{7–9} The peripheral clock can be found in peripheral tissues such as the liver, brain, lung, heart,

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and kidney.^{8,10} Unlike the SCN, peripheral tissues seem to require a physiological stimulus to maintain circadian rhythms in mammals, and the source of this stimulus may be the SCN or SCN-mediated messages.¹¹ Evidence suggests that restricted access to food can affect peripheral rhythms without affecting the central pacemaker function of the SCN. Thus, it is likely that the peripheral clock is hierarchically coordinated by the central clock and can also generate circadian rhythms independently.^{5,12} In addition, the peripheral clock could be reset in response to nonlight factors such as hormones and food.^{6,13} At the molecular level, the mechanisms underlying circadian rhythms generated by central and peripheral clocks are similar. There are periodic oscillations in the products of a series of clock genes that are organized into a complex transcriptional–translational autoregulatory network.^{7,9}

To date, the main clock genes that have been reported include Period1 (Per1), Period2 (Per2), Period3 (Per3), Cryptochrome1/2 (Cry1/2), Circadian locomotor output cycles kaput k (Clock), Brain and muscle Aarnt-like protein 1 (Bmal1; also known as ARNTL or MOP3), Casein kinase 1 δ/ϵ (CK1 δ/ϵ), Neuronal PAS domain protein 2

(NPAS2), nuclear receptor subfamilies (Rev-erbs, also known as NR1D), Differentiated embryo-chondrocyte expressed gene 1/2 (Dec1/2), and retinoid-related orphan receptors (Rors).^{5,8,14} At the molecular level, the circadian clock system is mainly composed of multiple positive and negative transcription–translation autoregulatory feedback loops that cause clock genes to oscillate for approximately 24 h and thereby produce circadian rhythms via the output system (Figure 1) (1). BMAL1 protein interacts with CLOCK or NPAS2 to produce BMAL1:CLOCK or BMAL1:NPAS2 dimers in the cytoplasm, which are then transferred to the nucleus where they recognize E-box (CACGTG) elements present in the promoters of the downstream clock genes Per, Cry, and Dec and result in transcriptional activation by binding to these sites. When PER and CRY proteins reach a certain concentration in the cytoplasm, they will be transferred to the nucleus and act on BMAL1:CLOCK or BMAL1:NPAS2 dimers, suppressing the expression of the Per and Cry genes. Meanwhile, DEC proteins can also form dimers to inhibit the transcription of the Per and Dec genes by competitively binding E-box elements via BMAL1:CLOCK or BMAL1:NPAS2,

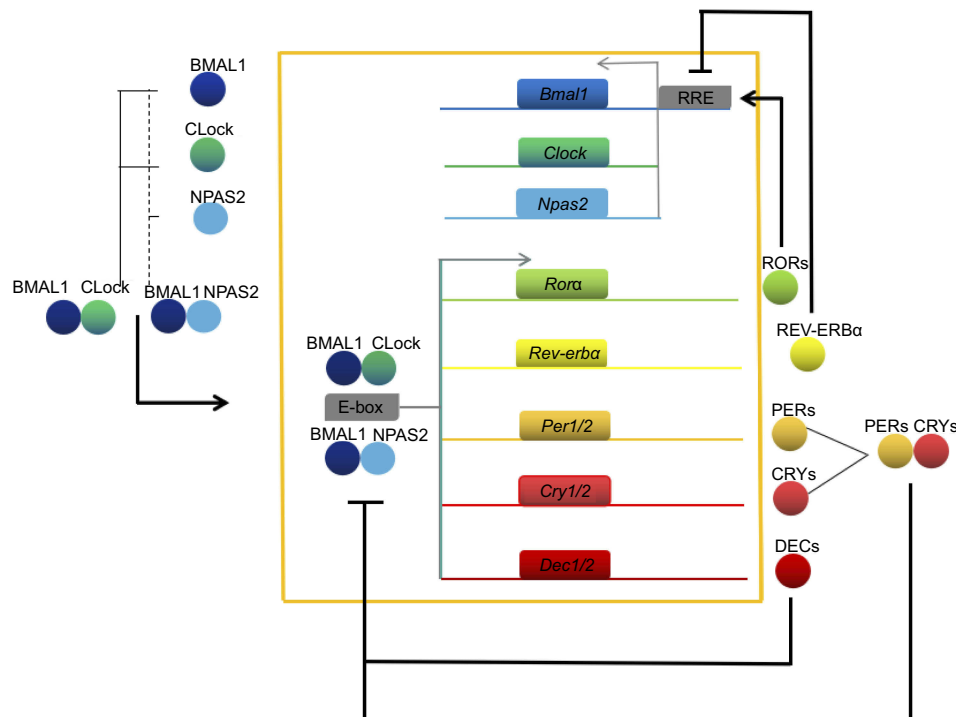


Figure 1 Mammalian circadian clock network. BMAL1 proteins combine with CLOCK or NPAS2 to generate BMAL1:CLOCK or BMAL1:NPAS2 heterodimers, which cause transcriptional activation of core clock genes (for example, Per, Cry, and Dec) via a combination of E-box elements; this in turn inhibits BMAL1:CLOCK/NPAS2 dimer activity. Meanwhile, the BMAL1:CLOCK/NPAS2 dimers activate the transcription of the Rev-erba and Rora genes, and the resulting translated proteins promote and inhibit the transcription of Bmal1, respectively.

Abbreviations: Bmal1/BMAL1, Brain and muscle Aarnt-like protein 1; Clock/CLoCk, Circadian locomotor output cycles kaput k; Cry/CRY, Cryptochrome; Dec/DEC, Differentiated embryo-chondrocyte expressed; Npas2/NPAS2, Neuronal PAS domain protein 2; Per/PER, Period; Rev-erb, nuclear receptor subfamily; ROR, retinoid-related orphan receptor; RRE, ROR elements.

and thus achieve negative feedback regulation of circadian rhythms (2). The BMAL1:CLOCK or BMAL1:NPAS2 dimers in the cytoplasm can bind to the E-boxes in the promoters of the *Rev-erba* and *Rora* genes to activate transcription, and the resulting proteins can serve as transcription factors to promote and inhibit the transcription of *Bmal1*, respectively.^{8,15} Apart from the two feedback loops described briefly above, there are multiple loops that simultaneously regulate circadian rhythms.^{16,17} A recent study by Aryal et al¹⁸ found that PERs, CRYs, and CK1 δ could be assembled into an ~1.9-MDa repressor complex in mouse liver cell nuclei that quantitatively incorporates its CLOCK-BMAL1 transcription factor target. Indeed, many new studies have been proposed each year; however, the exact molecular mechanisms for complexing of the clock machinery remain, to a large extent, unclear.

Circadian rhythms and tumors

Studies have shown that many factors, such as drugs and radiation, can disrupt the circadian clock.⁶ Circadian desynchrony is correlated with a heightened risk of diseases, including obesity, depression, metabolic diseases, and cancer, that affect all aspects of human health.^{19–21} As the world industrializes and the pressures of living increase, the accelerated pace of the modern lifestyle causes endogenous homeostasis to be constantly disrupted by external cues in modern societies. These disruptions have been linked to a high incidence of cancers, such as lung, breast, ovarian, prostate, pancreatic, colorectal, and endometrial cancers, hepatocellular carcinoma, osteosarcoma, acute myeloid leukemia, non-Hodgkin's lymphoma, and head and neck squamous cell carcinoma (HNSCC).^{5,21–23}

Epidemiological investigations have also found that women workers who frequently have rotating work schedules or work at night are more prone to endometrial and breast cancers; in particular, women who work the night shift for more than 20 years may have an ~10–60% increased risk of breast cancer.^{24–26} This was initially discovered to be due to a decreased plasma melatonin level that resulted from light exposure at night via specialized retinal photoreceptors,^{27,28} since blind individuals were shown to have a lower incidence of breast cancer than the general population.^{29,30} However, evidence from observational studies has revealed obvious changes in circadian rhythms of cancer patients that are due not only to changes in the melatonin level but also to factors that are independent of the melatonin level.^{30,31} An

increasing number of studies of carcinogenic risk factors have suggested that disruptions in circadian rhythms play a more central role in tumor evolution and progression than genetics.^{32,33} Therefore, it has been hypothesized that tumorigenesis may be related to alterations in the clock genes involved in maintaining circadian rhythms. Recent studies have revealed the phosphorylation, methylation, and the modification of histones in the promoters of clock genes in cancerous tissues that result in the deregulation of clock gene expression.^{14,34,35} Based on these data and the prevalence of night-shift work schedules, shift work associated with disrupted circadian rhythms was classified as a probable carcinogen by the World Health Organization in 2007.³⁶

Disrupted circadian rhythms are not only associated with the occurrence of malignant tumors but also affect the development of cancer and the prognosis and treatment outcomes of cancer patients. In mouse models, chronic circadian misalignment has been shown to induce susceptibility to spontaneous hepatocarcinogenesis.³⁷ Altered light–dark cycles speed the development of breast tumors and are more likely to lead to resistance during tamoxifen therapy.³⁸ In humans, unhealthy states are usually characterized by poor circadian coordination, and the loss of circadian homeostasis could be utilized as an independent prognosis factor for survival and the therapeutic responses of patients with lung, head and neck, metastatic breast, and colorectal cancers.^{38–40} Therefore, the question remains: how do aberrant circadian rhythms exert an effect on the development and prognosis of tumors? This review will provide an up-to-date and comprehensive report of circadian mechanisms with a full description of the current state of oral cancer research to further optimize cancer diagnosis and treatment modalities.

Circadian clock genes and tumors

Circadian rhythms are generated via circadian variations in the expression of clock genes over an approximately 24-h period. Comparisons of transcripts in both normal and tumor cells from various organs and tissues at different time points and assayed using DNA microarray technology have revealed that almost every type of cell activity, including those involved in energy metabolism, cell division, proliferation and apoptosis, ion channels, and signal transduction, has a significant circadian rhythm.^{41,42} Circadian rhythms not only make complicated physiological processes synchronized and coordinated, but also allow a system to reset in response to external cues to produce improved adaptation to the environment.^{6,12} Notably,

clock genes regulate between approximately 50% and more than 80% of the genes in the mammalian genome; these genes are known as clock-controlled genes (CCGs) and include the oncogene c-Myc and the tumor suppressor gene p53. CCGs, containing E-box regulatory elements, integrate cellular rhythmic information and encode various protein products.^{43,44} Circadian clock genes can participate in tumor development directly or indirectly by altering the expression of downstream CCGs involved in cell cycle regulation, DNA damage repair, cell proliferation and apoptosis, and tumor immunity.^{45,46}

Clock genes and the cell cycle

One characteristic of malignant tumors is uncontrolled and disordered cell proliferation. This loss of control is inevitably reflected in abnormalities in cell cycle events, and the disordered nature of these cells is necessarily reflected in the disruption of their time rhythm, which exhibits a difference of 8–12 h from normal cells.^{47,48} It is remarkable that circadian rhythms share some common features with the cell cycle; in addition, both are the result of the periodic and sequential activation and repression of the products of clock genes at the transcriptional, posttranscriptional, and translational levels.^{46,49} Alterations in circadian rhythms and the cell cycle contribute greatly to carcinogenesis.^{34,49}

As early as the discovery of clock genes, circadian rhythms have been found in cell cycle mitosis, nucleic acid (DNA and RNA) synthesis, liver weight, glycogen content, and cell cycle protein expression in the mouse liver.^{50,51} As research has progressed, it has become evident that a number of cell cycle genes contain E-boxes in their promoters, and the expression of those genes, such as Cyclin A, CyclinB1, Cyclin D1, p53, and Wee1, exhibits a rhythmic pattern.^{52,53} The normal cell cycle is regulated by the cyclin/cyclin-dependent kinase (CDK)/cyclin-dependent kinase inhibitor (CKI) regulatory network in a precise and strict chronological order as it progresses through the G1–S–G2–M phases.⁵⁴ Various cell cycle genes in mammals possess E-box regulatory elements. BMAL1:CLOCK/NPAS2 dimers recognize the E-box and produce transcriptional activation. Clock genes can influence cell cycle progression by regulating the expression of cell cycle-related genes and thus participate in the development of tumors.⁴⁹

The initiation of the cell cycle is strictly controlled via an extracellular proliferation stimulus, which immediately activates the early responsive gene c-Myc that then plays

an important role in the initiation of the G1 phase as well as cell growth and death.⁵⁵ BMAL1:CLOCK/NPAS2 dimers can downregulate c-Myc transcription, directly or indirectly, by blocking cell cycle progression.^{52,55} Cell cycle checkpoints guarantee the completion of the biochemical reactions that constitute regulatory pathways.^{54,56} The G1 phase is the longest phase of the cell cycle, during which most biosynthesis that supports cell cycle progression occurs. Activating the G1 checkpoint causes cells to pause for a check prior to entering the S phase or exit the cell cycle to enter the G0 phase.⁵⁴ The G1/S transition is negatively regulated by p21, which is one of the critical products of p53 that arrests the cell cycle; the clock genes Rev-erba and Rora inhibit or activate p21 expression, respectively.⁵⁷ During the G2 phase, activation of the G2/M checkpoint is controlled by Wee1, which serves as an important link between the circadian clock and the cell cycle. Wee1 inhibits the activity of CDK1 to prevent inappropriate M phase entry and can be activated by BMAL1:CLOCK/NPAS2 dimers or, conversely, inactivated by PER and CRY proteins.^{49,51}

Clock genes affect many biological pathways, including those involved in cell proliferation and apoptosis, by controlling the expression of cell cycle genes. Per1 overexpression induces c-Myc and suppresses p21 in response to ionizing radiation. Meanwhile, Per1 also inhibits the expression of Wee1, CyclinB1, CyclinD1, and CDK1, which leads to a decrease in cancer cell proliferation.^{58,59} Per2-deficient mice are more prone to develop cancer induced by γ irradiation and exhibit reduced p53 expression and an elevated level of c-Myc.⁵² Furthermore, mutations in Per1 and Per2 cause a shortening of the cell cycle and an elevation in the proliferation rate.^{22,52,60} It is also worth noting that the role of Per1 in some studies is in conflict with that shown in previous reports, as mentioned above, and this discrepancy may be due to differences in the methods (knockdown vs overexpression) that were used in experiments or characteristics of the cell lines that were used.^{61,62} Bmal1 knockout leads to cell cycle disruption and the deregulation of Wee1, CyclinB, and p21 and upregulation of CyclinE, as well as a substantial increase in the apoptotic cell population in malignant pleural mesothelioma.⁶³ In Clock mutant mice, inhibitory cell cycle genes, including p21 and Wee1, are generally upregulated or become nonrhythmic, whereas proliferative genes, such as CDK2, CyclinD3, and CyclinE1, are downregulated.⁴⁵ In Cry double-knockout mice, the expression levels of Wee1, CyclinB1, and Cdc2 are

markedly deregulated, contributing to slower than normal liver regeneration.⁵¹ Despite the identification of Tim as an additional clock gene that primarily functions outside the main transcriptional–translational loops, its protein, TIM, has proven to have a checkpoint function that closely connects the circadian clock with the cell cycle.¹⁶

These data indicate that many genes crucial to the cell cycle and the phases of cell division are under the control of clock genes that are aberrantly expressed in many tumor tissues. As a consequence, personalized chronotherapy for cancer has emerged, with the aim of coordinating the time of delivery of chemotherapeutic drugs with the clock and cell cycle to optimize therapeutic efficacy while simultaneously minimizing side effects.^{64,65} It is well recognized that a reasonable time regimen for chemotherapeutic drugs is as important as the drug dosages that are used.⁶⁶

Clock genes and DNA damage repair

In response to DNA damage, mammalian cells activate the G1/S and G2/M checkpoints of the cell cycle, during which ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) kinases, which are DNA-damage response amplification factors, phosphorylate mammalian checkpoint kinase 2 (CHK2) and CHK1, respectively, via binding to DNA-damage sites, and thus suppress CDK activity and activate CKIs to arrest the cell cycle and provide time for DNA-damage repair.^{67,68} Many critical players confirm circadian rhythmicity during the process of repairing damaged DNA, and P53 is the most important transcription factor among them.⁶⁹ Both the ATM and CHK2 kinases phosphorylate P53, leading to P53 protein stabilization and activation. Subsequently, the activated P53 protein blocks the cell cycle progression by inducing the expression of cell cycle inhibitors such as P21, allowing the cell to enable repair or to induce apoptosis events if the DNA damage is beyond repair.⁶⁹

It is noteworthy that the core clock proteins can interact with checkpoint proteins and thereby induce proliferation, apoptosis, and/or tumorigenesis. Recent studies in oral cancer cells have found that Per1 knockdown significantly increases the transcript expression levels of CyclinD1, CyclinE, CyclinB1, CDK1, and Wee1, whereas it decreases those of c-Myc, p53, and p21; PER1 protein levels modulate p53-dependent signals via the ATM and CHK2 kinases, which leads to G1/S and G2/M arrest and apoptosis.^{70,71} Additionally, deregulated Per2 is associated with decreased levels of WEE1, CYCLINB1, and P53, and also delays DNA damage-induced CHK2 activation,

overrides DNA damage-induced apoptosis, and abolishes the gating of cell cycle entrance and G2/M arrest.^{72–74} When DNA replication is blocked by ultraviolet irradiation, TIM, which serves as a checkpoint protein, switches the replication checkpoint signal from ATR to Chk1, which is important for S-phase checkpoint regulation.^{16,75} In addition, TIM is necessary for the ATM-dependent activation of Chk2 and G2/M checkpoint arrest, and is also required for ATM activation.⁷⁶ There is additional research indicating that TIM interacts with both CHK1 and CRY1 to coordinate the internal clock with the cell cycle.⁷⁷ CRY1 and CRY2 have distinct responses to DNA damage in terms of protecting genomic completeness via posttranslational modification and coordinated regulation of downstream transcription.⁷⁸ Additionally, the regulated degradation of DEC1 has been found to be important for G2/M checkpoint recovery via inhibition of the downregulation of p53 during the DNA-damage response.⁷⁹ The Clock gene knockdown upregulates the transcript levels of p53, p21, Chk1, and Chk2 and changes the rhythmic profile of Wee1.^{80,81} Moreover, the Clock gene has been shown to play a direct role in the DNA-damage response as a result of its localization to the sites of DNA double-strand breaks induced by γ radiation.⁸¹ Bmal1 has been reported to exert an effect on γ -radiation-induced p53 and p53-dependent p21 activation to arrest the cell cycle upon DNA damage.⁸² Genetic ablations of Bmal1 and Clock lead to delayed cell cycle exit through additional rounds of cell division and high levels of cell proliferation.⁸² These findings suggest that many clock proteins that are closely linked to DNA damage repair during cell cycle progression are subject to the control of the circadian rhythm; however, the timing of the resulting modifications has not been defined.

Clock genes and the tumor suppressor gene p53

It is well recognized that p53 is an important anti-oncogene that safeguards genomic integrity. When DNA damage or proto-oncogenic mutation occurs, p53 receives upstream signals and triggers the stress response, which promotes the repair or apoptosis of damaged cells.^{69,83} The function of the anti-oncogene p53 is tightly connected with the modulation of protein stability, and the P53 protein serves as the most important transcription factor involved in diverse biological processes, including the cell cycle, apoptosis, and DNA-damage response, that are important

in maintaining cell homeostasis, preventing gene mutation, and inhibiting tumor formation and development.^{69,84} The deletion or mutation of the 53 gene is a frequent occurrence in approximately half of all human cancers, including oral cancer.^{85,86}

G1 phase arrest is p53 dependent and is negatively regulated by P21, which is one of the critical products of p53.^{87,88} PER1 can directly modulate p53-dependent signals via the ATM and CHK2 kinases to control the G1 checkpoint during responses to DNA damage. G2 phase arrest after DNA damage also requires p53 and p21, and the ATM/CHK2/p53 pathway is activated to repair the damaged DNA or initiate the apoptosis programme. The ATM/CHK2/p53 signaling pathway has been recognized as a common pathway that allows cells to cope with environmental hazards that threaten genomic stability.⁵⁹

Previous research has shown that decreases in the expression of Per2 can directly inhibit the activation of the P53 protein and lead to accelerated tumor development.⁵² In addition, Per2 overexpression increases the mRNA and protein levels of p53, alters those of apoptosis-related genes, including c-Myc, and promotes p53-dependent G2/M arrest, all of which induce apoptotic cell death to play a role in tumor suppression.^{89,90} The p53 response element overlaps with the E-box and competes with BMAL1:CLOCK/NPAS2 dimers to bind to the Per2 gene promoter, and thereby indirectly participates in the regulation of the circadian clock.^{84,91} As we know, one p53 transcriptional targets is Murine double minute 2 (Mdm2), which encodes the E3 ubiquitin ligase MDM2 that inactivates or degrades the P53 protein. Meanwhile, MDM2 functions as an enzyme within a feedback loop that exhibits circadian variations in its expression in mouse liver.^{52,69} P53 and MDM2 are regulated indirectly by the Per genes via the tumor suppressor ATM at the posttranscriptional level.⁹² In unstressed cells, Per2 directly associates with the C-terminus region of p53 to prevent Mdm2-mediated ubiquitination of p53.⁹¹ Therefore, low levels of p53 exist at all times in the presence of Per2, and the response of p53 to genotoxic stress depends not only on its availability but also on its dissociation from Per2 in the nucleus.⁷⁴ In addition, a recent study has shown that MDM2 may target PER2 for degradation, and this is important for defining the circadian period length in mammalian cells.⁹³ The above results indicate that there is a dual-direction regulation between p53 and Per2.

It has been suggested that Bmal1 affects the capacity of p53 toward its target P21 to arrest the cell cycle upon

cellular stress signals such as DNA damage, not directly modulating the activities of P21, although the exact molecular mechanism underlying its action is still unclear.^{58,63,82} Additionally, ROR α agonists can heighten P53 protein stability and lead to increased p53 activity and subsequent apoptosis.⁹⁴ Silencing the Clock gene upregulates the P53 protein level and increases apoptosis, coupled with cell cycle arrest.⁸⁰ Overall, these studies support the important and multiple roles of the circadian clock in the administration of p53 pathways and have shown that the loss of p53 function in oral cancer will certainly accelerate the occurrence and development of tumors.

Clock genes and the oncogene c-Myc

The c-Myc proto-oncogene possesses E-box regulatory elements, which can be recognized by BMAL1:CLOCK/NPAS2 dimers to exert transcriptional suppression.⁵⁵ c-Myc takes charge of an early responsive regulator that responds to diverse extracellular proliferation stimuli and plays an essential role in cell division, apoptosis, and metabolic pathways.^{55,95}

When c-MYC is expressed at a high level, it tends to form a repressive complex with MIZ1 (ZBTB17) that downregulates a range of target genes.⁹⁶ Ectopic c-Myc levels also allow cells with damaged DNA to progress through cell cycle checkpoints, which contributes to the genesis of many cancers in humans.^{55,97} Intriguingly, c-Myc can simultaneously promote the proliferation and apoptosis of tumor cells by acting via the P53-dependent proapoptotic pathway ARF/MDM2/P53 or via direct interaction with ARF.⁹⁸ Although c-Myc promotes the apoptotic progression of tumor cells, it does not contradict itself as a proto-oncogene.⁹⁹ Researchers speculate that c-Myc may be initially elevated and promote tumorigenesis, and then subsequently become decreased or silenced to suppress the formation of tumors, which balances cell regeneration and death during malignant cell transformation to facilitate tumor cell progression.^{100,101} These results also indicate the unique complexity of the function of the c-Myc gene.

MYC, as a transcription factor, can bind to almost all promoter regions within the genome and trigger widespread gene expression.^{102,103} Therefore, two conflicting viewpoints have been proposed to explain how MYC regulates gene expression: one posits that MYC regulates the expression of all genes,¹⁰⁴ while the other suggests that MYC enhances the expression of specific sets of genes

that, in turn, affect the expression of other genes.¹⁰⁵ Although it is not clear which viewpoint is correct, the hypothesis that states that promoters differ in their affinity for MYC may provide an explanation regarding the differences in gene expression programmes.¹⁰⁶

Altered expression of clock genes is likely to result in aberrant c-Myc levels, which increases the risk of cancer susceptibility. Clock gene knockout results in the downregulation of c-MYC and CYCLINB1 and the upregulation of P53, which is concomitant with the reduced proliferation and accelerated apoptosis of glioma cells.⁸⁰ Loss of Cry2 facilitates the stabilization of c-MYC, and CRY2-FBXL3 cooperatively drive c-MYC ubiquitination and degradation, which limits malignant cellular transformation.¹⁰⁷ Per1 overexpression results in an elevated level of c-MYC in colon cancer cell lines after irradiation.⁵⁹ Deregulation of Per2 abolishes the oscillatory expression of c-Myc and then causes alterations in p53 function.⁵² BMAL1:CLOCK/NPAS2 dimers induce the transcription of the Per genes and inhibit c-Myc; therefore, PERs can indirectly suppress c-Myc transcription by regulating BMAL1:CLOCK/NPAS2 dimers.^{52,55} Additionally, the Per1 and c-Myc transcript levels consistently follow the same rhythmic pattern, although BMAL1:CLOCK/NPAS2 dimers regulate Per1 and c-Myc expression in an opposing fashion.¹⁰⁸ Recent reports have highlighted the importance of the interactions between MYC and the circadian clock. MYC may repress the clock and promote proliferation via its interaction with MIZ1, thereby inducing REV-ERB α to restrain the rhythmic expression of BMAL1.^{95,109} In addition, the overexpression of c-MYC represses Per1 transactivation by targeting selective E-box sequences, which affects the expression of clock genes at the posttranscriptional level.¹¹⁰

Clock genes and tumor proliferation and apoptosis

Tumorigenesis is a very complex and diversified process. In addition to producing abnormal changes in the cell cycle, it also needs to inhibit the apoptotic signals generated via cell contact, develop new blood vessels to provide nutrition and oxygen to support tumor growth, and induce the capacity to migrate and invade.^{71,111–113} To date, many crucial genes involved in the cancer-related regulation of cell proliferation, apoptosis, invasion, metastasis, and angiogenesis have been documented to have periodic patterns of expression over a 24-h cycle, such as the proliferation gene Ki-67,^{114,115} the proto-oncogene Mdm2,^{52,89} the proapoptotic gene Bax, the

antiapoptotic gene Bcl-2,¹¹¹ the invasion and metastasis gene MMP9,^{116,117} and the angiogenic gene Vegf.^{112,114,118} These genes appear to function as CCGs that are controlled by clock genes.

The circadian clock participates in tumorigenesis by regulating downstream tumor-related genes. Per1 and Per2 have been reported to be associated with the upregulation of Ki-67, Mdm2, Bcl-2, Mmp9, and Bax and the downregulation of Bcl-2, c-Myc, and p53 in lung, mammary, pancreatic, hepatocellular, and oral carcinoma cell lines. Similar alterations related to Per2 have also been observed at the protein level.^{71,89,119} The altered expression of these genes impacts tumor cell proliferation, apoptosis, migration, and invasion. At the same time, mutations in Per1 and Per2 cause a shortening of the cell cycle, an elevation of the proliferation rate in mice, attenuated proapoptotic processes, and decreased sensitivity to x-irradiation.^{22,52,60,120} Silencing Clock diminishes the protein levels of c-MYC and CYCLINB1 and enhances the P53 protein level, which results in increased apoptosis.⁸⁰ In addition, interrogation of the mouse protein-encoding transcriptome using a DNA array assay has suggested that a number of genes that are involved in the cell cycle and cell proliferation are regulated by the Clock gene and that cell cycle inhibitory genes are generally upregulated in Clock mutant mice while pro-proliferative genes are downregulated.⁴⁵ Knockdown of Dec2 has been shown to stimulate mRNA or protein expression of factors, such as c-Myc, Caspase-8, and Bax, that are correlated with apoptosis events, and overexpression of Dec2 has been shown to inhibit the proapoptotic factor BIM and reduce the amount of Caspase-8 in human breast cancer cells; however, Dec1 has been shown to exhibit opposing function.^{121,122} Of note, there are many signaling pathways that cooperate with clock genes to participate in tumorigenesis. For instance, BMAL1 depletion leads to cell cycle disruption, which results in a substantial increase in the apoptotic cell population and the acceleration of cell invasion by activating the PI3K/Akt/MMP2 pathway.^{63,123} In addition, there is a strong connection between BMAL1 regulation and the PI3K/mTOR signaling pathway, which is one of the most active pathways in human cancers.^{124,125} Mutations in Cry have been shown to sensitize a p53 mutant and enhance apoptosis by interfacing with the nuclear factor- κ B signaling pathway.¹²⁶

The occurrence and metastasis of tumors are inseparable from developmental angiogenesis. Studies suggest

that the hypoxia-induced expression of Vegf plays a key role in tumor-induced revascularization, and the transcript level of Vegf was shown to exhibit circadian rhythmicity in sarcomas that were transplanted subcutaneously in mice and in cancer cells in response to hypoxia.^{112,114} This is because Bmal1 binds to the Vegf promoter and activates it, thereby controlling its rhythmic expression; indeed, Vegf is a direct transcriptional target of Bmal1.^{118,127} In contrast, Per2, Cry2, and Dec2 exert opposing angiogenic effects via the regulation of Vegf expression. The peak mRNA expression of Per2, Cry2, and Dec2 occurs at night, while that of Vegf occurs during the day.^{112,128} This also suggests that the selective timing of the clinical administration of antiangiogenic factors increases their efficacy.

The abnormal expression of clock genes, including Per1 and Per2, has been observed in oral cancer.^{86,129} As noted above, aberrant clock gene levels can alter a range of downstream CCGs and tumor-related genes, cooperating with many signaling pathways involved in cancer development.

Clock genes and tumor immunity

Studies have shown that the mammalian immune system possesses a molecular circadian clockwork that involves various populations of immune cells, such as monocytes, natural killer (NK) cells, and T and B lymphocytes, as well as the responses to signals and their defensive functions, including the levels of cytokines and other effectors, that are regulated according to a cycle of approximately 24 h.^{130,131} The underlying mechanism depends upon the humoral and neural regulations of the immune system by clock genes to allow immune activity to be highly ordered in space and time.^{131,132} When circadian homeostasis is disrupted, deregulation of the immune system alters the function of immune cells, such as NK cells, which leads to immune suppression and the accelerated development of tumors.¹³³ In recent years, the absolute reduction of NK cells and high levels of interleukin 6 (IL-6) have been linked to faster tumor progression, higher cancer stage, and poorer prognosis for cancers in general, including HNSCC.^{40,134,135}

BMAL1 is the central mediator of the circadian control of the immune system and promotes an anti-inflammatory state.¹³⁶ Downregulation of BMAL1 has been found in hematologic malignancies such as diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and acute myeloid leukemia.¹³⁷ Knockout of Bmal1 affects B-cell development, which indicates a close relationship between

circadian genes and immune regulation.¹³⁸ In addition, the ablation or deregulation of the clock genes Per1/2, Cry1/2, Bmal1, Rev-erba, or Clock induces an array of abnormalities in the immune system, including a reduction in proinflammatory cytokines, cytotoxic receptors, and NK and mast cell activity, as well as the inhibition of B-lymphocyte differentiation.^{130,132,136,139,140} Moreover, Bmal1, Clock, Rev-erba, and Rora have also been reported to regulate immune functions (including migration, chemotaxis, phagocytosis, and cytotoxicity) and inflammation by modulating CCGs that encode a variety of proteins, including cytokines, chemokines, and receptors.^{136,141}

The central pacemaker controls the functioning of the immune system but is also modulated by immune factors such as proinflammatory cytokines, IL-1/6, and anti-inflammatory drugs, at the molecular, cellular, and behavioral levels, which results in subsequent alteration of the intracellular expression of Bmal1, Npas2, Cry1, and Per2.^{142–144}

In summary, the circadian clock and the immune system exert bidirectional control.¹³¹ Disturbances in the circadian clock and the rhythmic patterns that influence neuroendocrine and immune system factors impact tumor onset and progression. Therefore, it is necessary and important to take biological time into account when using cancer chronotherapy to improve cancer therapy.

Clock genes in oral cancer

Oral cancer is a multifactorial disease; chronic tobacco use and alcohol intake are two major risk factors, while betel quid chewing, chronic inflammation, human papilloma virus infection, and genetic polymorphisms also contribute to its pathogenesis.^{145,146} Oral squamous cell carcinoma (OSCC) accounts for approximately 90% of malignant oral cancers and ranks as the eighth most common cancer worldwide.^{145,147} The majority of oral cancer patients undergoing surgery are already at an advanced stage, and despite some advances in surgical techniques and chemotherapy, the 5-year overall survival of patients is estimated to be only 50–60%.^{148,149} Therefore, it is indispensable to understand the basic molecular mechanisms that contribute to oral tumorigenesis to enhance preventative and therapeutic options that can be used to decrease OSCC morbidity and mortality.

As mentioned above, circadian clock genes affect tumor development and prognosis by regulating downstream CCGs that are involved in cancer-related pathways. A number of studies have reported the role of clock genes in oral carcinogenesis (Table 1). In a model of nude mice inoculated with human OSCC cells, the tumor volume and

Table 1 Clock genes in oral cancer

Ref.	Cell type/origin	Methods	Results
Sato et al ⁶¹	CA9-22 cell line; human gingival cancer tissue and noncancerous tissue from 13 patients	Knockdown and over-expression of PER1 and PER3; RT-qPCR; western blotting	PER1 knockdown enhanced apoptosis, while PER3 knockdown inhibited apoptosis in CA9-22 cells induced by CDDP treatment; PER1 overrepresented in cancerous tissue; PER3 overrepresented in noncancerous tissue
Hsu et al ¹²⁹	Human cancerous and noncancerous tissue from 40 HNSCC patients	RT-qPCR	PER1, PER2, PER3, CRY1, CRY2, BMAL1, and CK1 α were significantly downregulated; downregulated PER3, CRY2, and BMAL1 expression was correlated with more advanced cancer stages, while downregulated PER3 correlated with larger tumor size, deeper tumor invasion, and poor survival
Chen et al ¹⁵²	Human cancerous and healthy adjacent tissue from 41 OSCC patients	Immunocytochemistry; RT-qPCR	Decreased expression of PER1 mRNA and protein in cancerous tissues; gradually decreased expression during cancer development
Zhao et al ¹⁵⁰	32 mice injected with human OSCC cell line BcaCD885	Nude mouse model of OSCC	Circadian rhythm in tumor volume and proliferative index, not in apoptotic index
Hsu et al ¹⁵¹	PB leukocytes from 94 patients with HNSCC and 56 healthy individuals	RT-qPCR; immunocytochemistry	9 CCGs were significantly downregulated in PB leukocytes of patients with HNSCC; PER1 and CLOCK expression in PB leukocytes can be a marker for prognosis evaluation during postoperative follow-up in patients with HNSCC
Ye et al ¹¹⁴	Dimethylbenzanthracene-induced cancer, precancerous lesions, and normal tissues from 90 Syrian golden hamsters	RT-qPCR	Variations in the daily rhythm characteristics of the clock genes PER1, C-MYC, and P53 correlate with the development of cancer
Tan et al ¹⁵³	Dimethylbenzanthracene-induced cancer, precancerous lesions, and normal tissues from 90 Syrian golden hamsters	RT-qPCR	Variations in the daily rhythm characteristics of the clock genes PER2, P53, Cyclin D1, CDK1, and Cyclin B1 correlate with the development of cancer
Fu et al ¹⁷⁰	SCC15 cell line nude mice	PER1 knockdown; RT-qPCR; flow cytometry assay; in vivo tumorigenesis assay	Increased expression of Cyclin D1, Cyclin E, Cyclin B1, CDK1, and WEE1; decreased expression of P53, Cyclin A2, P16, P21, and CDC25; fewer cells in S phase and more cells in G2/M phase; enhanced proliferation and reduced apoptosis; enhanced tumorigenicity in vivo
Li et al ⁷¹	SCC15 cell line nude mice	PER1 knockdown; RT-qPCR; western blotting; colony formation; flow cytometry assay; cell migration/invasion assay; in vivo tumorigenesis assay	Increased mRNA levels of Ki-67, Mdm2, Bcl-2, Mmp2, and Mmp9; decreased c-Myc, p53, Bax, and Timp-2; proliferation, migration, and invasion increased whereas apoptosis decreased; enhanced in vivo tumorigenesis

(Continued)

Table 1 (Continued).

Ref.	Cell type/origin	Methods	Results
Wang et al ⁸⁰	Tca8113 cell line	Per2 downregulation; RT-qPCR	Increased Cyclin A2, B1, and D1, CDK4, CDK6, and E2F1; decreased p53, p16, and p21; increased proliferation; decreased apoptosis
Su et al ¹⁵³	SCC15 cell line nude mice	PER2 knockdown; RT-qPCR; in vivo tumorigenesis assay	Cell proliferation, migration, and invasion markedly increased, while cancer cell apoptosis and number of cells in the G1/G0 phase reduced; enhanced in vivo tumorigenesis
Tang et al ¹⁵⁴	53 cases of TSCC tissue and adjacent noncancerous tissue specimens; 50 cases of normal tongue tissue specimens; human TSCC cell lines (SCC9, SCC25, CAL27)	Knockdown and over-expression of Bmal1; chromatin immunoprecipitation assay; xenografted tumor model; western blotting	Bmal1 expression was down-regulated and its rhythmic pattern of expression was affected in TSCC samples and cell lines; Bmal1 inhibited cell proliferation, migration, and invasion in vitro and tumor growth in vivo; Bmal1 inhibited tumorigenesis and increased paclitaxel sensitivity, and its chronotherapy efficacy was correlated with fluctuations of Bmal1 mRNA level
Xiong et al ⁸⁶	OSCC tissues and cancer-adjacent tissues from 8 patients; paraffin-embedded tissue sections of 40 OSCC patients	RT-qPCR; western blotting; immunohistochemistry	PER2, PTEN, P53, PI4ARF, and Caspase-8 mRNA and protein expression levels in OSCC were significantly downregulated; reduced PER2 promoted the occurrence and metastasis of OSCC, and shortened the survival time; PER2 expression was negatively correlated with PIK3CA and P53 levels, and positively correlated with PTEN, PI4ARF, and Caspase-8 levels

Abbreviations: BMAL1, Brain and muscle Aarrnt-like protein 1; CCG, clock-controlled gene; CDK, cyclin-dependent kinase; CK1 α , Casein kinase 1 α ; CLOCK, Circadian locomotor output cycles kaput k; CRY, Cryptochrome; HNSCC, head and neck squamous cell carcinoma; Mdm2, Murine double minute 2; OSCC, oral squamous cell carcinoma; PB, peripheral blood; PER, Period; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

proliferative index, but not the apoptotic index, were shown to obey circadian rhythms.¹⁵⁰ Other studies have shown that variations in the circadian patterns of the clock genes *Per1* and *Per2*, as well as the tumor-related genes *p53*, *c-Myc*, *Vegf*, *CyclinD1*, *CDK1*, and *CyclinB1*, have been observed with the development of cancer,^{53,114} which indicates that carcinogenesis itself could alter circadian patterns at the cellular and molecular levels.

A retrospective study that investigated clock gene expression in cancerous and noncancerous HNSCC tissues obtained from 40 patients has shown that the transcript levels of *Per*, *Cry*, *Bmal1*, and *CKIε* were significantly downregulated in cancerous tissues. Meanwhile, downregulation of *Per3*, *Cry2*, and *Bmal1* were observed to be associated with more advanced cancer stages, while the decreased expression of *Per3* was associated with larger tumor size, increased tumor invasion, and poorer survival.¹²⁹ In the peripheral blood of patients with HNSCC, clock gene expression is similarly downregulated; *PER1* and *CLOCK* are believed to be potential circulating prognostic markers for HNSCC.¹⁵¹ Decreased levels of *Per1* mRNA and protein have been observed in cancerous tissues from OSCC patients, and *PER1* protein expression has been shown to gradually decrease as tumor development progresses in terms of clinical staging and lymph node metastasis, proving, once again, the important role of *Per1* in carcinogenesis.¹⁵²

To clarify how altered *Per1* expression affects tumor development, short hairpin RNAs were used in human OSCC cells. *Per1* knockdown was shown to promote cancer cell growth, proliferation, apoptosis resistance, migration, and invasion; changes in cell cycle phase distribution *in vitro*; and accelerated tumorigenesis *in vivo*. Additionally, *Per1* downregulation results in significantly increased levels of *Ki-67*, *Mdm2*, *Bcl-2*, *Mmp2/9*, *CyclinD1*, *CyclinE*, *CyclinB1*, *CDK1*, and *Wee1* transcripts and decreased levels of *c-Myc*, *p53*, *p16*, *p21*, *Bax*, *Timp-2*, and *CyclinA2* transcripts.^{70,71} These results suggest that *Per1* acts as an important tumor suppressor gene by regulating tumor-related genes that function downstream of the cell cycle, proliferation, and apoptosis pathways. Nevertheless, there have been results from oral cancer studies that conflict with those from previous reports, as was previously mentioned. *Per1* has been proven to have antiapoptotic effects, and *Per3* has been shown to have proapoptotic effects during cisplatin treatment in human gingival cancer;⁶¹ the discrepancies may be due to the characteristics of the cell lines that were used or the different procedures that were used in the experiments.

In addition to the *Per1* gene, the core clock gene *Per2* has also attracted much attention. In a recent study of OSCC tissues from 8 patients and paraffin-embedded tissue sections from 40 OSCC patients, the mRNA and protein expression levels of *PER2*, *P53*, *PTEN*, and *Caspase-8* were significantly reduced, and the downregulation of *PER2* accelerated the occurrence and metastasis of OSCC and shortened the survival time of patients. Additionally, *PER2* expression was negatively correlated with *PIK3CA* and *P53* levels and positively correlated with *PTEN* and *Caspase-8* levels, revealing associations between the *PER2* and *P53* *PI3K/AKT* pathways.⁸⁶ *PTEN*, a tumor suppressor gene, is also a key molecular controller of the *PI3K* signaling pathway, and the loss of *PTEN* results in the activation of the *BMAL1* protein, which ultimately connects the *PI3K* signaling pathway to the regulation of circadian rhythms.⁸⁶ In addition, deregulated *Per2* expression in OSCC cells leads to alterations in the cell cycle and a reduction in apoptosis, which is coupled with altered levels of downstream tumor-related genes.¹⁵³ Overall, the core gene *Per2* plays an extensive and complex antitumor role during tumor development and prognosis.

Circadian clock genes influence not only cancer development but also sensitivity to chemotherapy drugs. In OSCC specimens and cell lines, *Bmal1* expression is decreased, and its rhythmic pattern is changed. Furthermore, *Bmal1* overexpression results in an increase in the apoptotic cell population after exposure of cells to paclitaxel and enhances paclitaxel sensitivity *in vivo*. Other research shows that paclitaxel efficacy is influenced by the *Bmal1* expression level in OSCC. Consequently, *Bmal1* acts as a tumor suppressor gene that elevates the sensitivity of cancer cells to paclitaxel.¹⁵⁴

As previously stated, the circadian clock affects a variety of cellular processes, especially cell proliferation, DNA repair, and apoptosis, and it is no surprise that monitoring circadian rhythms will be beneficial during cancer treatment. In view of the differences in circadian rhythmicity between tumor and normal tissues, the delivery of drugs during phases in which the repair rate is increased in normal tissue would be expected to improve their therapeutic effects.

Acknowledgments

The author would like to thank Peng Zhao for his editing suggestions. Meanwhile, the author is grateful to Ting Tan for her companionship and support.

Disclosure

The author declares no conflict of interest in the work presented.

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