Journal of Zhejiang University-SCIENCE B 2025 26(10):935-948
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2500455

Check for updates

Circadian genes *CLOCK* and *BMAL1* in cancer: mechanistic insights and therapeutic strategies

Yuli SHEN[1,2*], Yuqian ZHAO[3*], Xue SUN[3], Guimei JI[1,2], Daqian XU[1,2,4✉], Zheng WANG[1,2✉]

[1]*Zhejiang Provincial Key Laboratory of Pancreatic Disease, The First Affiliated Hospital and Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou 310029, China*
[2]*Cancer Center, Zhejiang University, Hangzhou 310029, China*
[3]*Department of Surgical Oncology, Harbin Medical University Cancer Hospital, Harbin 150081, China*
[4]*Institute of Fundamental and Transdisciplinary Research, Zhejiang University, Hangzhou 310029, China*

Abstract: The circadian clock is a highly conserved timekeeping system in organisms, which maintains physiological homeostasis by precisely regulating periodic fluctuations in gene expression. Substantial clinical and experimental evidence has established a close association between circadian rhythm disruption and the development of various malignancies. Research has revealed characteristic alterations in the circadian gene expression profiles in tumor tissues, primarily manifested as a dysfunction of core clock components (particularly circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1)) and the widespread dysregulation of their downstream target genes. Notably, *CLOCK* demonstrates non-canonical oncogenic functions, including epigenetic regulation via histone acetyltransferase activity and the circadian-independent modulation of cancer pathways. This review systematically elaborates on the oncogenic mechanisms mediated by CLOCK/BMAL1, encompassing multidimensional effects such as cell cycle control, DNA damage response, metabolic reprogramming, and tumor microenvironment (TME) remodeling. Regarding the therapeutic strategies, we focus on cutting-edge approaches such as chrononutritional interventions, chronopharmacological modulation, and treatment regimen optimization, along with a discussion of future perspectives. The research breakthroughs highlighted in this work not only deepen our understanding of the crucial role of circadian regulation in cancer biology but also provide novel insights for the development of chronotherapeutic oncology, particularly through targeting the non-canonical functions of circadian proteins to develop innovative anti-cancer strategies.

Key words: Circadian rhythm; Circadian locomotor output cycles kaput (*CLOCK*); Brain and muscle ARNT-like 1 (*BMAL1*); Cancer; Therapy

1 Introduction

As an evolutionarily conserved timekeeping system, the circadian clock precisely regulates the temporal organization of physiological processes at multiple biological scales, exhibiting robust 24-h oscillations. At the molecular level, the core circadian oscillator is governed through the intricate transcription–translation feedback loop (TTFL) involving several key clock genes. The positive limb of this loop consists of transcriptional activators circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1, also known as ARNTL), which form heterodimers that bind to E-box enhancer elements, driving the periodic expression of clock-controlled genes (CCGs), including period (*PER*) and cryptochrome (*CRY*) (Ripperger and Schibler, 2006). Upon accumulation in the cytoplasm, the PER and CRY proteins form heterodimeric complexes that translocate into the nucleus, where they suppress CLOCK:BMAL1-mediated transcriptional activity, thus completing the negative feedback loop (Duong et al., 2011; Patke et al., 2020). As PER and CRY undergo temporally controlled proteasomal degradation, their suppressive action on the CLOCK:BMAL1 heterodimer diminishes, permitting the reactivation of the positive

✉ Zheng WANG, wangzheng22@zju.edu.cn
Daqian XU, xudaqian@zju.edu.cn
* The two authors contributed equally to this work
Zheng WANG, https://orcid.org/0000-0001-6277-3269
Daqian XU, https://orcid.org/0000-0003-0478-2997

Received July 30, 2025; Revision accepted Sept. 14, 2025; Crosschecked Sept. 28, 2025

© Zhejiang University Press 2025

limb of the circadian oscillator and the commencement of subsequent 24-h rhythmicity (Yoo et al., 2013). An auxiliary feedback loop involves the nuclear hormone receptor subfamily 1 group D member 1/2 (REV-ERBα/β) and retinoic acid orphan receptors (RORs), which competitively bind to ROR/REV-ERB response elements (RRE) in the BMAL1 promoter. During the day, RORs activate BMAL1 transcription, while at night, REV-ERBs repress it (Cho et al., 2012; Schrader et al., 2024), creating an additional oscillation that stabilizes and reinforces the core clock mechanism (Fig. 1).

Circadian rhythm disruption has been increasingly recognized as a critical factor in disease pathogenesis, particularly cancer development, with multiple causative factors including genetic mutations in core clock genes, shift work, chronic jet lag, sleep deprivation, and irregular eating patterns (Boivin and Boudreau, 2014; Papagiannakopoulos et al., 2016; Fagiani et al., 2022; Zhou et al., 2022; Shi et al., 2023; Peng et al., 2024). Intriguingly, emerging research reveals that core circadian regulators display tissue-specific dual roles, functioning as either tumor suppressors or oncoproteins depending on their cellular context (Zhang et al., 2014; Mure et al., 2018). This functional duality may be related to the extensive circadian regulation observed in mammalian genomes, where nearly half of all genes exhibit 24-h cyclic expression patterns. Importantly, circadian disruption promotes tumorigenesis via diverse molecular mechanisms, including genomic instability (Negrini et al., 2010; Sancar et al., 2010; Ortega-Campos et al., 2023), metabolic dysregulation (Wang Z et al., 2024), and impaired immune surveillance (Curtis et al.,

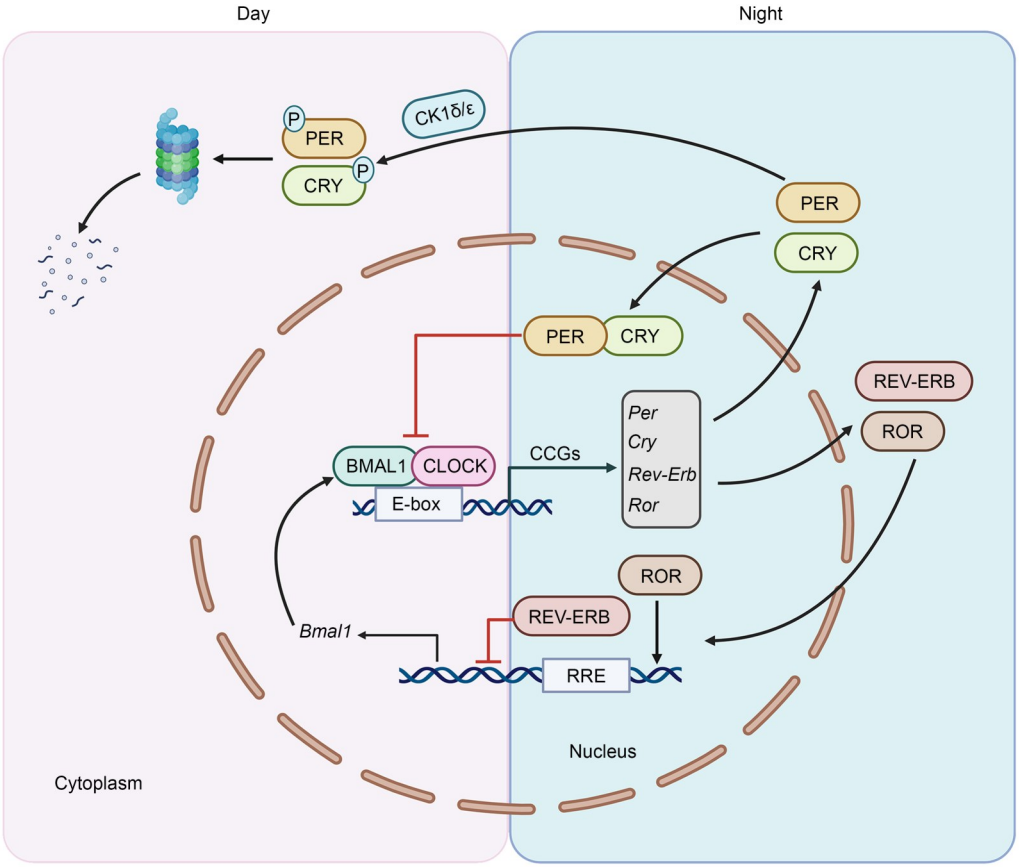

Fig. 1 Circadian gene transcription–translation feedback loop (TTFL) model diagram. The circadian locomotor output cycles kaput (CLOCK)-brain and muscle ARNT-like 1 (BMAL1) heterodimers bind to E-box elements in clock-controlled genes (CCGs) to activate their transcription. Subsequently, period (PER) and cryptochrome (CRY) proteins form heterodimers that suppress CLOCK-BMAL1-mediated transcription, establishing a negative feedback loop. Moreover, the stability of PER and CRY proteins is coordinately regulated by parallel E3 ubiquitin ligase pathways. Meanwhile, retinoic acid orphan receptor (ROR) and nuclear receptor subfamily 1 group D (REV-ERB) regulate BMAL1 expression by competitively binding to REV-ERB response element (RRE) in its promoter, with RORs enhancing and REV-ERBs repressing transcription, thereby forming an auxiliary feedback loop. CK1: casein kinase 1. Created with BioRender.com.

2014; Zhang et al., 2021). However, during malignant transformation, the normal oscillatory patterns of these circadian-regulated genes are frequently disrupted or completely lost in a tumor type-specific fashion (Grabe et al., 2024; Huang et al., 2024).

The core circadian regulators CLOCK and BMAL1 have been established as pivotal players in cancer pathogenesis. This review systematically synthesizes the current understanding of the mechanistic roles of these regulators in tumorigenesis and explores emerging associated therapeutic strategies. Through a comprehensive elucidation of circadian–oncogenic pathway interactions, the investigations discussed herein have yielded transformative insights into cancer biology while simultaneously unveiling novel chronotherapeutic opportunities. Building upon these advances, researchers can now rationally design temporally optimized treatment regimens that leverage precise dosing timing to maximize antitumor efficacy while minimizing off-target toxicity.

2 Cell cycle and apoptosis

The circadian clock and the cell cycle represent interconnected biological oscillators that exhibit extensive molecular crosstalk, with their dysregulation being frequently implicated in cancer pathogenesis (Gaucher et al., 2018). Emerging evidence demonstrates that the core clock components CLOCK and BMAL1 exert dual regulatory roles in tumor progression through cell cycle regulation and apoptosis modulation. Mechanistically, *CLOCK* or *BMAL1* knockdown was found to inhibit Cyclin B1 expression, leading to G2/M phase arrest and potentially delaying tumor progression (Farshadi et al., 2019). Inhibiting CLOCK or BMAL1 downregulates WEE1 G2 checkpoint kinase (WEE1) to promote apoptosis, while it concurrently upregulates p21 to induce cell cycle arrest, collectively suppressing hepatocellular carcinoma (HCC) progression (Qu et al., 2023). The upregulation of CLOCK promotes cellular proliferation and inhibits apoptosis in colorectal cancer (CRC) via enhancing the activity of the phosphorylated protein kinase B (p-AKT) and suppressing the expression of pro-apoptotic genes B-cell lymphoma-2 (Bcl-2)-associated X (*Bax*) and BH3-interacting domain death agonist (*Bid*) (Wang et al., 2015). Conversely, the upregulation of BMAL1 activates the ataxia-telangiectasia-mutated (ATM) signaling pathway to induce G2/M cell cycle arrest, thereby suppressing CRC progression (Zeng et al., 2014). BMAL1 overexpression in pancreatic cancer activates p53 to simultaneously induce apoptosis (via Bax/Puma upregulation and Bcl-extra large (Bcl-xL)/Bcl-2 downregulation) and G2/M arrest (through p21 activation and Cyclin B1 suppression) (Jiang et al., 2016). The activation of CLOCK-BMAL1 heterodimer inhibits melanoma and CRC cell proliferation by suppressing cellular-myelocytomatosis viral oncogene (c-Myc)-mediated Cyclin E activation, thereby arresting the cell cycle at the G1/S phase (Kiessling et al., 2017). Collectively, these findings demonstrate that circadian-clock-mediated cell cycle regulation represents a fundamental mechanism of tumor control, with CLOCK and BMAL1 exhibiting tissue-specific, sometimes paradoxical effects on cancer progression (Fig. 2).

3 DNA damage response

As one of the established hallmarks of cancer, DNA damage response deficiency-induced genomic instability actively contributes to carcinogenesis and promotes malignant progression through continuous mutational accumulation (Negrini et al., 2010). The core circadian clock components functionally govern the strength and coordination of cellular DNA damage response mechanisms (Sancar et al., 2010). Notably, CLOCK binds to various enhancer and transcriptional regulatory sites that control DNA damage-related genes, including the DNA double-strand break (DSB) repair genes breast cancer type 1 susceptibility gene (*BRCA1*) and radiation sensitive 50 (*RAD50*), suggesting its potential role as a genomic "caretaker" in CRC (Alhopuro et al., 2010). CLOCK accumulation occurred at laser-induced DSBs, indicating its direct involvement in DSB repair processes (Cotta-Ramusino et al., 2011). Moreover, BMAL1 was observed to facilitate the recruitment of CLOCK to DSB sites following ATM-mediated phosphorylation. A deficiency in BMAL1 resulted in reduced homologous recombination capacity and significantly increased the sensitivity of adrenocortical carcinoma to DNA damage-based therapies (Zhang et al., 2023). Additional molecular connectivity between the circadian clock and DNA damage response was established via the regulatory feedback

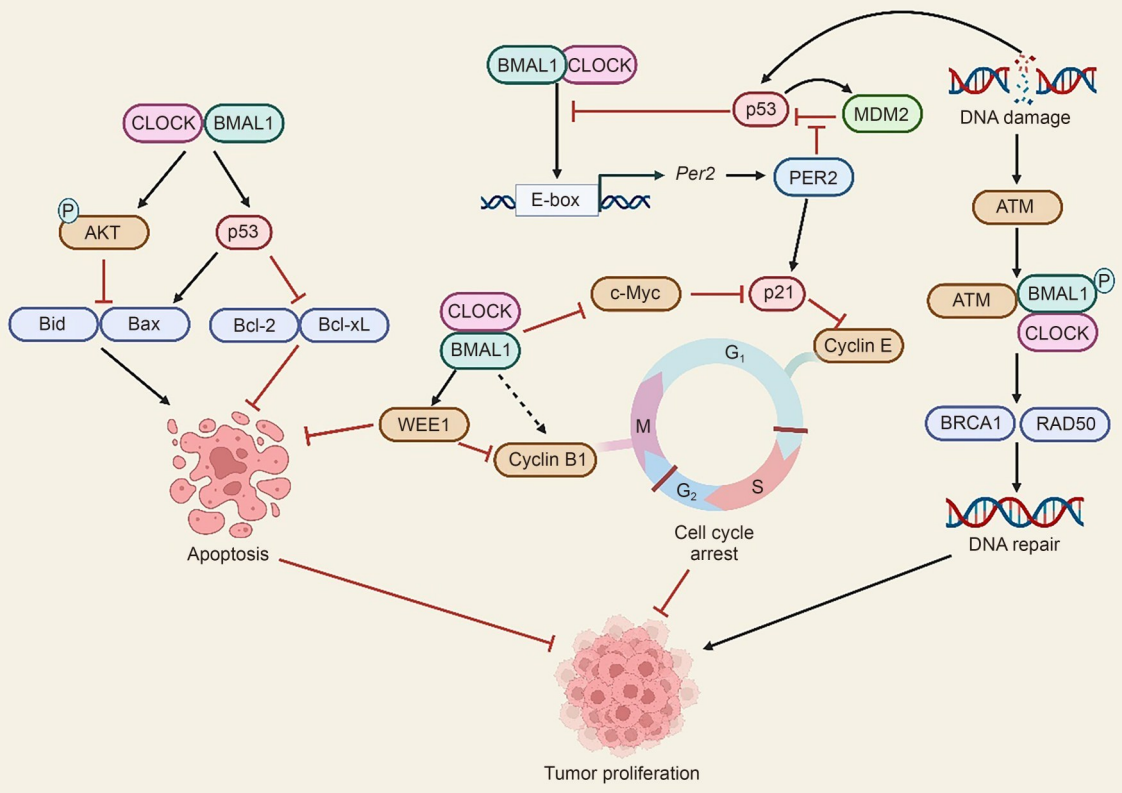

Fig. 2 Molecular mechanisms of circadian locomotor output cycles kaput (CLOCK)/brain and muscle ARNT-like 1 (BMAL1) in regulating the cell cycle, apoptosis, and DNA damage. CLOCK/BMAL1 exerts dual effects on tumorigenesis through its multifaceted regulation of cell cycle progression, apoptotic pathways, and DNA damage repair. AKT: protein kinase B; Bid: BH3-interacting domain death agonist; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X; Bcl-xL: Bcl-extra large; MDM2: murine double minute 2 homolog; PER2: period 2; c-Myc: cellular-myelocytomatosis viral oncogene; ATM: ataxia-telangiectasia-mutated; WEE1: WEE1 G2 checkpoint kinase; BRCA1: breast cancer type 1 susceptibility protein; RAD50: radiation sensitive 50. Created with BioRender.com.

loop involving the tumor suppressor and checkpoint proteins p53 and PER2. Mechanistically, wild-type p53 has been shown to suppress PER2 expression though competing with the CLOCK-BMAL heterodimer for binding to the PER2 promoter, thereby disrupting its circadian activation (Miki et al., 2013). The p53–PER2 protein interaction serves as a critical regulatory nexus that synchronizes p21 transcriptional activation with G1/S phase cell cycle progression. PER2 functions as a novel downstream effector in the DNA damage response pathway by binding both p53 and its inhibitor murine double minute 2 (MDM2), thereby preventing the MDM2-mediated targeting of p53 for proteasomal degradation (Gotoh et al., 2014). Collectively, the above studies demonstrate that the circadian clock influences the DNA damage response, highlighting the importance of robust circadian rhythms in maintaining genome integrity. Thus, gaining a deeper understanding of the mechanisms behind circadian regulation of DNA damage response is crucial for developing strategies to prevent cancer and creating more effective yet less toxic treatments for patients receiving chemotherapy and radiation therapy (Fig. 2).

4 Cell metabolism

Metabolic reprogramming represents a hallmark feature of cancer (Hanahan, 2022). The alteration of tumor metabolism is a complex process wherein oncogene activation, tumor suppressor gene inactivation, and aberrant signaling pathway activation regulate the function of metabolic enzymes or regulatory proteins at multiple levels, including transcriptional and post-translational modifications. These changes subsequently modulate enzyme activity, subcellular localization, protein stability, or autophagic flux, ultimately driving the rewiring of metabolic pathways in cancer cells (Pavlova

and Thompson, 2016; Xu et al., 2021; Yip and Papa, 2021). Mounting evidence from the literature indicates that mammalian metabolism exhibits distinct circadian rhythmicity during cancer progression, where circadian disruption alters the oscillatory patterns of multiple metabolic processes, including glucose, glutamine, lipid, and nucleic acid metabolism (Wang Z et al., 2024). For instance, the disruption of BMAL1 alters the expression of hexokinase domain-containing 1 (HKDC1)—a key glycolytic enzyme responsible for glucose phosphorylation—resulting in time-dependent metabolic reprogramming characterized by enhanced glycolytic flux in CRC (Fuhr et al., 2018). The genetic ablation of BMAL1 promotes lung tumorigenesis by upregulating c-Myc and inducing metabolic reprogramming, which in turn enhances glutamine utilization (Papagiannakopoulos et al., 2016). Fatty acid oxidation (FAO) senses circadian disruption in sleep deficiency (SD)-accelerated lung tumorigenesis via the CLOCK/acyl-coenzyme A (CoA) synthetase long-chain family member 1 (ACSL1) axis. SD dysregulates CLOCK to overexpress ACSL1, generating palmitoyl-CoA that stabilizes CLOCK through *S*-palmitoylation, creating a feedforward loop that promotes cancer stemness (Peng et al., 2024) (Fig. 3).

Interestingly, a recent study revealed that the activation of insulin-like growth factor 1 receptor (IGF1R) promotes the casein kinase 2 (CK2)-mediated phosphorylation of CLOCK at S106, which results in the disassembly of the CLOCK-BMAL1 dimer, thereby suppressing downstream gene expression and disrupting circadian regulation in HCC cells. In addition, S106-phosphorylated CLOCK displays a conformational change and exposes its nuclear export signal, allowing a portion of CLOCK to translocate from the nucleus to the cytoplasm. Cytosolic CLOCK exerts a non-canonical function as a protein acetyltransferase by acetylating K29 of the nucleic acid synthesis rate-limiting enzymes phosphoribosyl pyrophosphate (PRPP) synthetase 1 (PRPS1) and PRPS2. This acetylation inhibits the degradation of PRPS1/2 via the heat shock cognate protein of 70 kDa (HSC70)-mediated

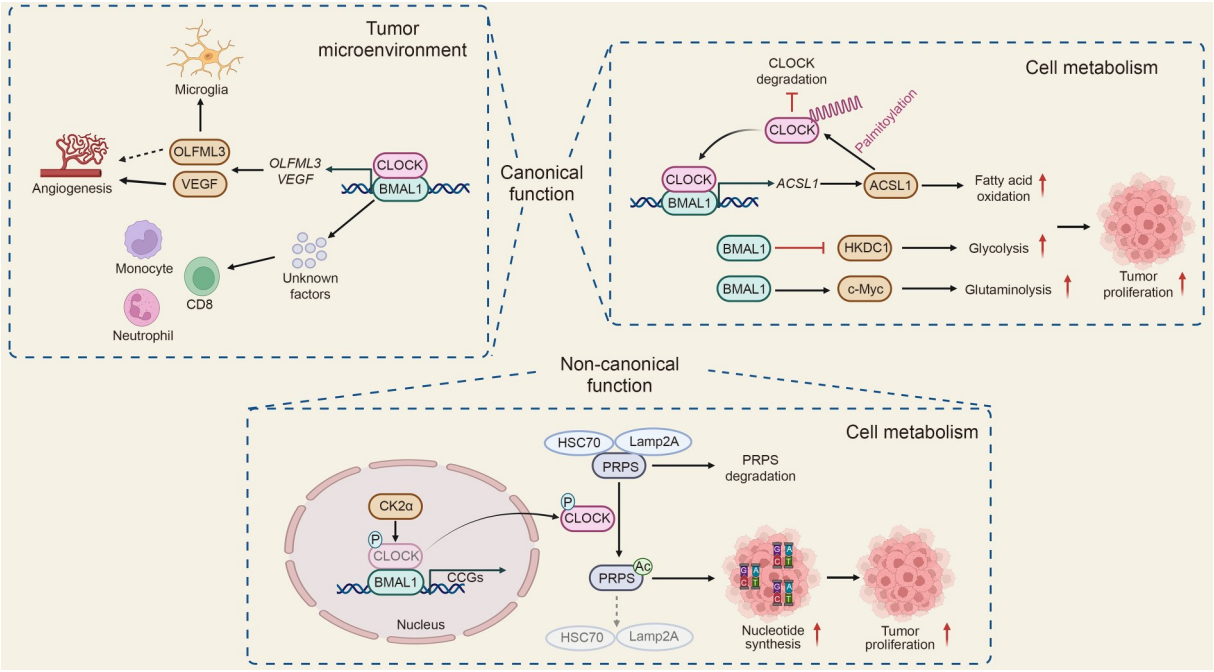

Fig. 3 Molecular mechanisms of circadian locomotor output cycles kaput (CLOCK)-brain and muscle ARNT-like 1 (BMAL1) in the tumor microenvironment (TME) and cell metabolism. The CLOCK-BMAL1 heterodimer exerts its canonical transcriptional functions in tumorigenesis by regulating both the TME and cellular metabolism. Furthermore, CLOCK can act as an acetyltransferase to regulate nucleotide metabolism in a non-canonical manner, thereby influencing tumor progression. OLFML3: olfactomedin-like 3; VEGF: vascular endothelial growth factor; CD8: cluster of differentiation 8; ACSL1: acyl-coenzyme A (CoA) synthetase long-chain family member 1; HKDC1: hexokinase domain-containing 1; c-Myc: cellular-myelocytomatosis viral oncogene; CK2*α*: casein kinase 2*α*; CCGs: clock-controlled genes; HSC70: heat shock cognate protein of 70 kDa; Lamp2A: lysosomal-associated membrane protein 2 isoform A; PRPS: phosphoribosyl pyrophosphate (PRPP) synthetase; Ac: acetylation. Created with BioRender.com.

lysosomal pathway, enhancing the protein stability of PRPS1/2 and accelerating de novo nucleotide synthesis in HCC cells, ultimately promoting HCC (Liu et al., 2023). This finding establishes a theoretical framework for understanding the crosstalk between circadian rhythms and metabolic reprogramming in tumors. These findings elucidate the molecular mechanisms by which oncogenic signals disrupt the formation of the CLOCK-BMAL1 complex, thereby interrupting the circadian rhythmic regulation. Furthermore, it uncovers the interconnection between the non-classical protein acetyltransferase function of the transcription factor CLOCK and the remodeling of tumor nucleotide metabolism (Fig. 3).

In summary, circadian genes orchestrate tumor metabolic reprogramming via both canonical and non-canonical mechanisms. This temporal governance not only rewires the energy acquisition and utilization pathways in cancer cells but also critically regulates their proliferative capacity, survival signals, and therapeutic susceptibility. Systematic investigations of the relationship between circadian genes and tumor metabolism can unveil new biomarkers and therapeutic targets, thereby providing innovative strategies for cancer treatment. Advances in this field may offer new hope for personalized medicine and improved patient outcomes.

5 Tumor microenvironment

The tumor microenvironment (TME) comprises a complex network of cells and extracellular components that collaboratively drive tumor growth, invasion, and metastasis (Quail and Joyce, 2013; Elhanani et al., 2023). Increasing evidence underscores that the circadian clocks regulate TME biology, including angiogenesis, tumor-promoting inflammation, and immune evasion (Xuan et al., 2021; Fortin et al., 2025). For example, the CLOCK-BMAL1 complex-driven expression of olfactomedin-like 3 (OLFML3) leads to the transcriptional upregulation of periostin (POSTN) mediated by hypoxia-inducible factor-1α (HIF-1α). Consequently, the secreted POSTN enhances tumor angiogenesis by activating the TANK-binding kinase 1 (TBK1) signaling pathway in endothelial cells (Pang et al., 2023). Additionally, the overexpression of CLOCK or BMAL1 increases the expression of vascular endothelial growth factor (VEGF) and facilitates angiogenesis and metastasis in CRC (Wang et al., 2017; Burgermeister et al., 2019).

Emerging evidence reveals the link between the circadian clock and immune function (Fortin et al., 2024; Zeng et al., 2024; Zhu et al., 2025). Circadian dysregulation promoted lung metastasis in CRC-bearing mice, concomitant with the increased infiltration of pulmonary myeloid-derived suppressor cells (MDSCs) and diminished cluster of differentiation 8-positive ($CD8^+$) T cell efficacy (Liu et al., 2024). High CLOCK levels in glioblastoma (GBM) stem cells (GSCs) enhanced chemokine OLFML3 production, thereby promoting the infiltration of immunosuppressive microglia into the GBM TME (Chen et al., 2020; Xuan et al., 2022). The myeloid cell-specific deletion of BMAL1 was shown to promote inflammation by inducing the expression of monocyte-attracting chemokines and disrupting the trafficking of $LY6C^{hi}$ monocytes (Nguyen et al., 2013). Moreover, genetic knockout of *BMAL1* in a CRC model increases the infiltration of neutrophils and monocytes while substantially depleting $CD8^+$ T cells, suggesting the presence of an immunosuppressive role of the circadian clock (Fortin et al., 2024). Genomic mutation analyses revealed that the core circadian regulators CLOCK and BMAL1 are functionally linked to immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Circadian rhythm disruption may lead to elevated expression of these immunosuppressive checkpoints, which can contribute to T cell exhaustion—a state of T cell dysfunction caused by chronic activation (Wu et al., 2019).

Altogether, the existing data demonstrate that cancer cell clock components serve as essential regulators of TME hallmarks (angiogenesis, inflammation, and immune escape), indicating that the disruption of circadian cancer cell–TME crosstalk may represent a viable strategy to suppress tumor progression (Fig. 3).

6 Treatment strategies

As mentioned above, the multifaceted roles of core circadian genes *CLOCK* and *BMAL1* across various cancer types have been increasingly elucidated, not only establishing a causative link between circadian disruption and malignant progression but also highlighting promising molecular targets for innovative

anti-neoplastic interventions. Current therapeutic strategies targeting CLOCK/BMAL1 primarily fall into three categories: chrononutritional interventions, chronopharmacological modulation, and chronotherapy optimization (Sulli et al., 2018; Amiama-Roig et al., 2022) (Table 1).

Time-restricted feeding (TRF) is an emerging chrononutritional intervention that aligns nutrient availability with endogenous circadian rhythms by restricting daily food intake to a defined window (typically ⩽12 h). Unlike traditional calorie-restricted diets, TRF maintains normal energy intake while enforcing temporal eating patterns (Longo and Panda, 2016; Queiroz et al., 2021; Li, 2022). A recent study reported that 6-h TRF-mimicking regimens suppressed core clock genes (e.g., *CLOCK*) and exerted potent anti-tumor effects on lung adenocarcinoma via inhibiting cell proliferation, inducing cell apoptosis, and causing cell cycle arrest (Fang et al., 2024). Additionally, glucose restriction has emerged as a significant chrononutritional intervention in cancer progression. Wei et al. (2025) demonstrated that a glucose-restricted diet modulated cancer progression via circadian rhythm regulation by upregulating the energy-sensing factor adenosine monophosphate-activated protein kinase (AMPK), which enhanced BMAL1 expression and subsequently induced apoptosis in non-small cell lung cancer (NSCLC).

Mounting evidence has demonstrated that the chronopharmacological modulation of circadian genes exerts significant anti-tumor effects across multiple cancer types. Building upon the TTFL framework, the indirect regulation of CLOCK and BMAL1 through other circadian components represents a promising therapeutic strategy. Dong et al. (2019) demonstrated that combined administration of CRY agonist KL001 with REV-ERB agonist SR9009/SR9011 effectively

Table 1 Summary of chronotherapeutic approaches and agents

Therapy	Approach/agent	Cancer type	Potential effect	Potential mechanism	Reference
Chrononutritional intervention	TRF	Lung cancer	Inhibited proliferation; induced apoptosis; cell cycle arrest	Downregulating the expression of core clock genes (e.g., *CLOCK*)	Fang et al., 2024
	Glucose restriction	NSCLC	Induced apoptosis	Upregulating BMAL1 expression	Wei et al., 2025
Chronopharmacological modulation	KL001, SR9009/SR9011	GBM	Induced apoptosis; cell cycle arrest	Downregulating CLOCK-BMAL1 transcription	Dong et al., 2019
	SHP1705, SR9065	GSCs	Inhibited proliferation	Downregulating CLOCK-BMAL1 transcription	Chan et al., 2025
	Nobiletin	HCC	Ameliorated glucolipid metabolic disorders	Upregulating BMAL1 expression	Qi et al., 2018
	Clock-NVs	Melanoma, breast cancer, CRC	Inhibited proliferation; enhanced tumor immunity	Upregulating BMAL1 expression	Han et al., 2025
	CCM	Osteosarcoma	Suppressed inflammation in macrophage	Impairing BMAL1 transcriptional activity	Pu et al., 2025
Chronotherapy optimization	Administration of TMZ in the morning	GBM	Induced DNA damage; inhibited proliferation; induced apoptosis	Peak BMAL1 in the morning	Damato et al., 2021
	Administration of β-endorphin at ZT8	Lung cancer	Inhibited proliferation	Downregulating CLOCK expression	Peng et al., 2024
	Administration of CAR-T and anti-PD-1 at ZT13	Melanoma	Inhibited proliferation	Higher ICM-1 and tumor immune cell infiltration at ZT13	Wang C et al., 2024

TRF: time-restricted feeding; Clock-NVs: clock-modulated nanovesicles; CCM: core circadian modulator; TMZ: temozolomide; CAR-T: chimeric antigen receptor-T cell; Anti-PD-1: anti-programmed death-1; NSCLC: non-small cell lung cancer; GBM: glioblastoma; GSC: GBM stem cell; HCC: hepatocellular carcinoma; CRC: colorectal cancer; CLOCK: circadian locomotor output cycles kaput; BMAL1: brain and muscle ARNT-like 1; ICM-1: intercellular adhesion molecule-1.

suppressed CLOCK-BMAL1 transcriptional activity, inducing cell cycle arrest and apoptosis in GBM models. Similarly, Chan et al. (2025) confirmed that SHP1705, the first CRY activator identified in phase I clinical trials, is safe and well-tolerated; SHP1705 has potent inhibitory effects on GSCs when combined with novel REV-ERB agonist SR9065. Furthermore, ROR agonists such as nobiletin, as a naturally occurring bioactive compound in citrus fruits, display notable anticancer properties (He et al., 2016; Ma et al., 2020). Qi et al. (2018) reported that nobiletin ameliorated insulin resistance and lipid metabolic dysregulation in HCC cells through circadian clock reprogramming, exhibiting BMAL1-dependent mechanisms of action. Han et al. (2025) innovatively developed clock-modulated nanovesicles (Clock-NVs), encapsulating ROR agonist SR1078 within tumor cell membrane-derived vesicles. These Clock-NVs reprogrammed the TME by converting detrimental reactive oxygen species (ROS) into circadian-enhancing oxygen signals. Mechanistically, Clock-NVs restore tumor circadian rhythms through the HIF-1α/BMAL1 axis, concurrently triggering BMAL1-mediated tumor cell apoptosis while enhancing dendritic cell antigen presentation and mitochondrial metabolism. These dual chrono-immunotherapeutic effects yielded 60% primary tumor regression when combined with adoptive T-cell therapy and achieved complete (100%) prevention of tumor recurrence with anti-PD-L1 treatment, demonstrating particular efficacy against chemotherapy-resistant senescent tumors.

An alternative chronopharmacological approach involves direct targeting of the CLOCK/BMAL1 complex using small molecules to disrupt its structural integrity and alter circadian rhythmicity. CLOCK and BMAL1, along with their paralogs, are members of the mammalian basic helix-loop-helix PER-ARNT-SIM (bHLH-PAS) family (Huang et al., 2012). Structural analyses have resolved the architecture of their bHLH-PASA-PASB domains, providing a foundation for targeted intervention (Wu et al., 2016; Wu and Rastinejad, 2017). Notably, a study based on a docking approach revealed that the CLOCK-binding small molecule (CLK8) binds selectively to the bHLH domain of CLOCK. This interaction destabilizes the CLOCK-BMAL1 heterodimer, inhibits CLOCK nuclear import, and amplifies circadian oscillations by reinforcing the negative feedback loop, without altering periodicity (Doruk et al., 2020). Complementing these findings, recent work identified the core circadian modulator (CCM) as a BMAL1-directed ligand that engages the PASB domain. CCM binding induces allosteric changes that tune the transcriptional output by BMAL1. Biochemical and cellular validation confirmed the high specificity of CCM for BMAL1, enabling the precise manipulation of BMAL1-CLOCK activity. Functionally, CCM dose-dependently tunes PER2-Luc rhythms and suppresses macrophage inflammatory and phagocytic responses (Pu et al., 2025), highlighting its therapeutic potential in tumor treatment.

Chronotherapy optimization refers to the strategic temporal coordination of drug administration with endogenous circadian rhythms to enhance treatment effectiveness and reduce side effects (Sancar and van Gelder, 2021; Amiama-Roig et al., 2022). Temozolomide (TMZ) has demonstrated significant chronotherapeutic efficacy against GBM, with preclinical studies showing that its DNA-damaging, pro-apoptotic, and anti-proliferative effects peak during phases of maximal BMAL1 expression in both human and murine GBM cells (Slat et al., 2017). This mechanistic insight was clinically corroborated by a retrospective analysis revealing superior overall survival in GBM patients receiving morning TMZ administration compared to evening dosing. The observed chronotherapeutic benefit strongly supported the pivotal role of BMAL1 in mediating cellular responses to TMZ-induced DNA damage, which is consistent with its established circadian regulation of DNA repair pathways (Damato et al., 2021). In addition, time-restricted administration of β-endorphin specifically at ZT8 (mid-active phase), but not at ZT20 (resting phase) or via continuous osmotic pump delivery, effectively rescued SD-induced circadian disruptions in β-endorphin, CLOCK, and ACSL1 expression, leading to a significant inhibition of tumor growth and a reduction in cancer stem cell properties (Peng et al., 2024). As another critical aspect, the timing of immunotherapy administration also determines treatment efficacy. Both chimeric antigen receptor-T cell (CAR-T) therapy and anti-programmed death-1 (anti-PD-1) treatment exhibited significantly enhanced tumor suppression when administered at ZT13 (active phase) compared to ZT1 (rest phase) in melanoma mouse models. Mechanistically, this chronotherapeutic effect stems from the circadian regulation of intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells, which peaks during nocturnal

phases in a BMAL1-dependent manner. The genetic ablation of BMAL1 disrupts the diurnal expression pattern of ICAM-1, consequently impairing the rhythmic infiltration of tumor-infiltrating lymphocytes (TILs). Importantly, this circadian regulation of immune cell trafficking is conserved in human cancers, where clinical observations revealed distinct diurnal fluctuations in both the quantity and antitumor phenotypes of tumor-infiltrating $CD4^+$ and $CD8^+$ T cells, with peak cellular abundance and enhanced effector functions occurring during the early afternoon hours corresponding to the human active phase (Wang C et al., 2024).

Collectively, the above findings establish a transformative framework for rhythm-based interventions in oncology, underscoring the pivotal role of circadian biology in shaping innovative cancer treatment paradigms. By harnessing the mechanistic insights from circadian gene regulation, researchers are poised to develop novel therapeutic approaches that not only potentiate the efficacy of existing treatments but also mitigate their adverse effects. These advances compellingly demonstrate the need to integrate circadian principles into both cancer research and clinical practice, paving the way for more precise and personalized oncological care. As research continues to unravel the intricate interplay between circadian rhythms and cancer biology, the chronotherapeutic strategies emerging along this pursuit hold revolutionary potential to redefine the cancer treatment landscape, offering new promise for enhanced patient outcomes.

7 Future perspectives

Circadian rhythm regulation has a revolutionary potential in cancer therapeutics, yet its clinical translation faces multifaceted challenges requiring systematic solutions. At the molecular level, a core dilemma lies in the marked tissue-specific heterogeneity of clock gene regulation, posing significant challenges for developing strategies that target tumor tissue specifically without disrupting normal physiological rhythms. Current research reveals that the same circadian gene may exert diametrically opposite effects across different TMEs, or even within distinct regions of the same tumor. Another major obstacle is the absence of reliable dynamic monitoring tools: the current clinical landscape lacks standardized biomarker systems for the real-time tracking of patients' circadian phases, severely constraining personalized chronotherapeutic planning. In drug development, circadian modulators face precision limitations, typically affecting both malignant and healthy tissues indiscriminately. Besides, the intricate spatiotemporal interaction networks between tumor cells and their microenvironment (e.g., circadian fluctuations in immune cell infiltration) introduce additional complexity to treatment design. Individual variability presents another critical challenge, as patient age, sex, genetic background, and chronotype (morning/evening preference) significantly influence therapeutic outcomes (Terzibasi-Tozzini et al., 2017; Lévi et al., 2024).

Addressing the above challenges demands a multipronged approach: (1) Developing next-generation wearable monitoring devices integrated with artificial intelligence (AI) algorithms to establish dynamic, personalized therapeutic time-window prediction systems, as demonstrated by Kim et al. (2023)'s approximation-based least-squares method (ALSM) for the efficient extraction of physiological data from wearable time-series to assess circadian biomarker variations. Additionally, Leung et al. (2023) employed a computational model of the molecular network regulating cell cycle progression phases, performing numerical simulations to investigate the effects of circadian control on cell cycle dynamics. Their work enables the prediction of optimal timing for phase-specific anticancer drugs and underscores the need to better characterize cellular heterogeneity and synchronization for effective chronopharmacology protocols. (2) Creating intelligent tumor-targeted drug delivery systems for precise, rhythm phase-specific drug release. Notably, Kamal et al. (2025) innovatively combined AI with molecular communication technology to develop a smart targeted delivery system featuring bidirectional bio-network interfaces. This breakthrough system significantly enhances tumor cell drug response rates while minimizing adverse effects on healthy cells, realizing the vision of personalized therapy with "right time, right location, exact dose" precision (Kamal et al., 2025). (3) Conducting large-scale multicenter trials focusing on circadian-adapted regimens for shift workers and special populations. (4) Advancing fundamental research to elucidate dosing–time effects on pharmacokinetics/pharmacodynamics and the clock gene–epigenetic crosstalk.

Notably, core clock genes possess important non-canonical functions beyond traditional circadian regulation. *CLOCK*, for instance, not only functions as a transcription factor but also demonstrates acetyltransferase activity, directly promoting tumor nucleotide metabolism through PRPS1/2 acetylation—a paradigm-shifting discovery revealing the multifaceted roles of circadian genes in tumor biology (Liu et al., 2023). However, research on these non-canonical functions faces substantial challenges: first, their intricate interplay with oncogenic pathways (e.g., IGF1R-CK2) forms sophisticated regulatory networks; second, the dynamic equilibrium between canonical and non-canonical functions remains unclear (e.g., CLOCK's nuclear vs. cytoplasmic role switching); third, translating these findings into clinical strategies presents significant uncertainties. Future research should prioritize: (1) mechanistic studies to delineate non-canonical functions in tumor metabolic reprogramming, cell cycle regulation, and apoptosis resistance; (2) developing novel therapeutics targeting non-canonical activities, particularly CLOCK acetyltransferase inhibitors; (3) exploring chrono-metabolic combination strategies that integrate conventional chemotherapy with circadian-targeted agents; and (4) establishing dynamic monitoring systems for the simultaneous assessment of canonical and non-canonical functions. These advances may pioneer new therapeutic avenues, especially for metabolically dysregulated tumors, potentially yielding multidimensional chronotherapeutic strategies to overcome tumor heterogeneity and treatment resistance. Interdisciplinary collaboration will be pivotal in establishing circadian modulation as a cornerstone of precision oncology, ultimately delivering more effective, tailored cancer therapies.

It is also worth emphasizing that simple behavioral adjustments in daily life can effectively mitigate the detrimental effects of environmental disruption on circadian rhythms, thereby contributing to disease prevention or supporting cancer treatment. For instance, nocturnal exposure to short-wavelength light, particularly blue light, can disrupt endogenous rhythmicity and delay melatonin release. Limiting or filtering such light is beneficial for maintaining circadian stability. For individuals who work at night or use electronic devices in the dark, wearing blue light-blocking glasses may reduce circadian interference. The use of blackout curtains in the bedroom can also help create an environment conducive to rhythm synchronization. Furthermore, maintaining a consistent sleep–wake routine, optimizing the sleep environment for darkness and tranquility, and engaging in moderate physical activities such as walking, Tai Chi, or aerobic exercise can improve sleep quality and reinforce robust circadian regulation in cancer patients.

8 Conclusions

The core circadian transcription factors CLOCK and BMAL1 exhibit complex and diverse regulatory roles in tumor biology, demonstrating unique tissue-specific expression patterns across different cancer types. Beyond maintaining their canonical circadian regulatory functions, the CLOCK protein has been found to possess novel functional characteristics such as atypical acetyltransferase activity, providing new perspectives for understanding tumorigenesis and progression. In-depth investigations of the interactions between CLOCK/BMAL1 and other cancer-related signaling pathways are crucial for elucidating their regulatory mechanisms within the TME. Particularly, the coordinated effects between circadian genes and metabolic pathways can explain how tumor cells adapt to nutrient fluctuations to sustain growth and influence the treatment response, whereas the circadian regulation of immune responses suggests that integrating chronobiology with immunotherapy may enhance antitumor efficacy. A more comprehensive understanding of circadian gene regulatory networks, especially their non-canonical functions, will not only deepen our knowledge of cancer biology but, more importantly, provide a theoretical foundation for the development of novel chronotherapy strategies. Building on these findings, future clinical applications may include designing treatment regimens based on the body's natural rhythms, optimizing drug administration timing to improve efficacy while reducing toxicity, and guiding personalized therapy through circadian biomarkers. As our understanding of circadian regulatory networks in cancer continues to deepen, rhythm-based intervention strategies will bring new breakthroughs in cancer treatment, promoting the integration of precision medicine and chronotherapy and ultimately offering innovative therapeutic options to improve patient outcomes.

Acknowledgments

This work was supported by the Ministry of Science and Technology of the People's Republic of China (Nos. 2020YFA0803300 and 2021YFA0805600), the National Natural Science Foundation of China (Nos. 92157113, 82072630, 82173114, 82072903, 82272872, 82002811, 82188102, and 82030074), the Zhejiang Natural Science Foundation Key Project (Nos. LD22H160002 and LD21H160003), the Zhejiang Natural Science Foundation Discovery Project (No. LQ22H160023), and the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (No. 2019R01001), China.

Author contributions

Yuli SHEN wrote the entire manuscript. Yuqian ZHAO designed and prepared the figures. Xue SUN, Guimei JI, Daqian XU, and Zheng WANG critically revised the manuscript and corrected errors. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Yuli SHEN, Yuqian ZHAO, Xue SUN, Guimei JI, Daqian XU, and Zheng WANG declare that they have no conflicts of interest.

This review does not contain any studies with human or animal subjects performed by any of the authors.

References

Alhopuro P, Björklund M, Sammalkorpi H, et al., 2010. Mutations in the circadian gene *CLOCK* in colorectal cancer. *Mol Cancer Res*, 8(7):952-960. https://doi.org/10.1158/1541-7786.MCR-10-0086

Amiama-Roig A, Verdugo-Sivianes EM, Carnero A, et al., 2022. Chronotherapy: circadian rhythms and their influence in cancer therapy. *Cancers*, 14(20):5071. https://doi.org/10.3390/cancers14205071

Boivin DB, Boudreau P, 2014. Impacts of shift work on sleep and circadian rhythms. *Pathol Biol*, 62(5):292-301. https://doi.org/10.1016/j.patbio.2014.08.001

Burgermeister E, Battaglin F, Eladly F, et al., 2019. Aryl hydrocarbon receptor nuclear translocator-like (ARNTL/BMAL1) is associated with bevacizumab resistance in colorectal cancer *via* regulation of vascular endothelial growth factor A. *eBioMedicine*, 45:139-154. https://doi.org/10.1016/j.ebiom.2019.07.004

Chan P, Nagai Y, Wu QL, et al., 2025. Advancing clinical response against glioblastoma: evaluating SHP1705 CRY2 activator efficacy in preclinical models and safety in phase I trials. *Neuro-Oncol*, 27(7):1772-1786. https://doi.org/10.1093/neuonc/noaf089

Chen PW, Hsu WH, Chang A, et al., 2020. Circadian regulator CLOCK recruits immune-suppressive microglia into the GBM tumor microenvironment. *Cancer Discov*, 10(3):371-381. https://doi.org/10.1158/2159-8290.CD-19-0400

Cho H, Zhao X, Hatori M, et al., 2012. Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature*, 485(7396):123-127. https://doi.org/10.1038/nature11048

Cotta-Ramusino C, McDonald ER III, Hurov K, et al., 2011. A DNA damage response screen identifies RHINO, a 9-1-1 and TopBP1 interacting protein required for ATR signaling. *Science*, 332(6035):1313-1317. https://doi.org/10.1126/science.1203430

Curtis AM, Bellet MM, Sassone-Corsi P, et al., 2014. Circadian clock proteins and immunity. *Immunity*, 40(2):178-186. https://doi.org/10.1016/j.immuni.2014.02.002

Damato AR, Luo JQ, Katumba RGN, et al., 2021. Temozolomide chronotherapy in patients with glioblastoma: a retrospective single-institute study. *Neuro-Oncol Adv*, 3(1):vdab041. https://doi.org/10.1093/noajnl/vdab041

Dong Z, Zhang GX, Qu M, et al., 2019. Targeting glioblastoma stem cells through disruption of the circadian clock. *Cancer Discov*, 9(11):1556-1573. https://doi.org/10.1158/2159-8290.CD-19-0215

Doruk YU, Yarparvar D, Akyel YK, et al., 2020. A CLOCK-binding small molecule disrupts the interaction between CLOCK and BMAL1 and enhances circadian rhythm amplitude. *J Biol Chem*, 295(11):3518-3531. https://doi.org/10.1074/jbc.RA119.011332

Duong HA, Robles MS, Knutti D, et al., 2011. A molecular mechanism for circadian clock negative feedback. *Science*, 332(6036):1436-1439. https://doi.org/10.1126/science.1196766

Elhanani O, Ben-Uri R, Keren L, 2023. Spatial profiling technologies illuminate the tumor microenvironment. *Cancer Cell*, 41(3):404-420. https://doi.org/10.1016/j.ccell.2023.01.010

Fagiani F, di Marino D, Romagnoli A, et al., 2022. Molecular regulations of circadian rhythm and implications for physiology and diseases. *Signal Transduct Target Ther*, 7:41. https://doi.org/10.1038/s41392-022-00899-y

Fang GF, Chen QY, Li JL, et al., 2024 The diurnal transcriptome reveals the reprogramming of lung adenocarcinoma cells under a time-restricted feeding-mimicking regimen. *J Nutr*, 154(2):354-368. https://doi.org/10.1016/j.tjnut.2023.11.033

Farshadi E, Yan J, Leclere P, et al., 2019. The positive circadian regulators CLOCK and BMAL1 control G2/M cell cycle transition through Cyclin B1. *Cell Cycle*, 18(1):16-33. https://doi.org/10.1080/15384101.2018.1558638

Fortin BM, Pfeiffer SM, Insua-Rodríguez J, et al., 2024. Circadian control of tumor immunosuppression affects efficacy of immune checkpoint blockade. *Nat Immunol*, 25(7):1257-1269. https://doi.org/10.1038/s41590-024-01859-0

Fortin BM, Mahieu AL, Fellows RC, et al., 2025. The diverse roles of the circadian clock in cancer. *Nat Cancer*, 6(5):753-767. https://doi.org/10.1038/s43018-025-00981-8

Fuhr L, El-Athman R, Scrima R, et al., 2018. The circadian clock regulates metabolic phenotype rewiring via HKDC1 and modulates tumor progression and drug response in colorectal cancer. *eBioMedicine*, 33:105-121.

https://doi.org/10.1016/j.ebiom.2018.07.002

Gaucher J, Montellier E, Sassone-Corsi P, 2018. Molecular cogs: interplay between circadian clock and cell cycle. *Trends Cell Biol*, 28(5):368-379. https://doi.org/10.1016/j.tcb.2018.01.006

Gotoh T, Vila-Caballer M, Santos CS, et al., 2014. The circadian factor Period 2 modulates p53 stability and transcriptional activity in unstressed cells. *Mol Biol Cell*, 25(19):3081-3093. https://doi.org/10.1091/mbc.E14-05-0993

Grabe S, Ananthasubramaniam B, Herzel H, 2024. Quantification of circadian rhythms in mammalian lung tissue snapshot data. *Sci Rep*, 14:16238. https://doi.org/10.1038/s41598-024-66694-7

Han ZY, Zhang C, An JX, et al., 2025. Directly evolved nanovaccines modulate disrupted circadian rhythm and enhance cancer immunotherapy. *Adv Mater*, 37(34):2502602. https://doi.org/10.1002/adma.202502602

Hanahan D, 2022. Hallmarks of cancer: new dimensions. *Cancer Discov*, 12(1):31-46. https://doi.org/10.1158/2159-8290.CD-21-1059

He BK, Nohara K, Park N, et al., 2016. The small molecule nobiletin targets the molecular oscillator to enhance circadian rhythms and protect against metabolic syndrome. *Cell Metab*, 23(4):610-621. https://doi.org/10.1016/j.cmet.2016.03.007

Huang LH, Huang CY, Liu YW, et al., 2024. Circadian rhythm disruption in hepatocellular carcinoma investigated by integrated analysis of bulk and single-cell RNA sequencing data. *Int J Mol Sci*, 25(11):5748. https://doi.org/10.3390/ijms25115748

Huang N, Chelliah Y, Shan YL, et al., 2012. Crystal structure of the heterodimeric CLOCK: BMAL1 transcriptional activator complex. *Science*, 337(6091):189-194. https://doi.org/10.1126/science.1222804

Jiang WL, Zhao SL, Jiang XH, et al., 2016. The circadian clock gene *Bmal1* acts as a potential anti-oncogene in pancreatic cancer by activating the p53 tumor suppressor pathway. *Cancer Lett*, 371(2):314-325. https://doi.org/10.1016/j.canlet.2015.12.002

Kamal IR, El-Atty SMA, El-Zoghdy SF, et al., 2025. Intelligent deep learning model for targeted cancer drug delivery. *Sci Rep*, 15:19068. https://doi.org/10.1038/s41598-025-96149-6

Kiessling S, Beaulieu-Laroche L, Blum ID, et al., 2017. Enhancing circadian clock function in cancer cells inhibits tumor growth. *BMC Biol*, 15:13. https://doi.org/10.1186/s12915-017-0349-7

Kim DW, Mayer C, Lee MP, et al., 2023. Efficient assessment of real-world dynamics of circadian rhythms in heart rate and body temperature from wearable data. *J Roy Soc Interface*, 20(205):20230030. https://doi.org/10.1098/rsif.2023.0030

Leung C, Gérard C, Gonze D, 2023. Modeling the circadian control of the cell cycle and its consequences for cancer chronotherapy. *Biology*, 12(4):612. https://doi.org/10.3390/biology12040612

Lévi FA, Okyar A, Hadadi E, et al., 2024. Circadian regulation of drug responses: toward sex-specific and personalized chronotherapy. *Annu Rev Pharmacol Toxicol*, 64:89-114. https://doi.org/10.1146/annurev-pharmtox-051920-095416

Li MD, 2022. Clock-modulated checkpoints in time-restricted eating. *Trends Mol Med*, 28(1):25-35. https://doi.org/10.1016/j.molmed.2021.10.006

Liu JL, Xu X, Rixiati Y, et al., 2024. Dysfunctional circadian clock accelerates cancer metastasis by intestinal microbiota triggering accumulation of myeloid-derived suppressor cells. *Cell Metab*, 36(6):1320-1334.e9. https://doi.org/10.1016/j.cmet.2024.04.019

Liu T, Wang Z, Ye LG, et al., 2023. Nucleus-exported CLOCK acetylates PRPS to promote de novo nucleotide synthesis and liver tumour growth. *Nat Cell Biol*, 25(2):273-284. https://doi.org/10.1038/s41556-022-01061-0

Longo VD, Panda S, 2016. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metab*, 23(6):1048-1059. https://doi.org/10.1016/j.cmet.2016.06.001

Ma YR, Ren X, Patel N, et al., 2020. *Nobiletin*, a citrus polymethoxyflavone, enhances the effects of bicalutamide on prostate cancer cells via down regulation of NF-κB, STAT3, and ERK activation. *RSC Adv*, 10(17):10254-10262. https://doi.org/10.1039/c9ra10020b

Miki T, Matsumoto T, Zhao ZY, et al., 2013. p53 regulates *Period2* expression and the circadian clock. *Nat Commun*, 4:2444. https://doi.org/10.1038/ncomms3444

Mure LS, Le HD, Benegiamo G, et al., 2018. Diurnal transcriptome atlas of a primate across major neural and peripheral tissues. *Science*, 359(6381):eaao0318. https://doi.org/10.1126/science.aao0318

Negrini S, Gorgoulis VG, Halazonetis TD, 2010. Genomic instability — an evolving hallmark of cancer. *Nat Rev Mol Cell Biol*, 11(3):220-228. https://doi.org/10.1038/nrm2858

Nguyen KD, Fentress SJ, Qiu YF, et al., 2013. Circadian gene *Bmal1* regulates diurnal oscillations of Ly6C^{hi} inflammatory monocytes. *Science*, 341(6153):1483-1488. https://doi.org/10.1126/science.1240636

Ortega-Campos SM, Verdugo-Sivianes EM, Amiama-Roig A, et al., 2023. Interactions of circadian clock genes with the hallmarks of cancer. *Biochim Biophys Acta Rev Cancer*, 1878(3):188900. https://doi.org/10.1016/j.bbcan.2023.188900

Pang LZ, Dunterman M, Xuan WJ, et al., 2023. Circadian regulator CLOCK promotes tumor angiogenesis in glioblastoma. *Cell Rep*, 42(2):112127. https://doi.org/10.1016/j.celrep.2023.112127

Papagiannakopoulos T, Bauer MR, Davidson SM, et al., 2016. Circadian rhythm disruption promotes lung tumorigenesis. *Cell Metab*, 24(2):324-331. https://doi.org/10.1016/j.cmet.2016.07.001

Patke A, Young MW, Axelrod S, 2020. Molecular mechanisms and physiological importance of circadian rhythms. *Nat Rev Mol Cell Biol*, 21(2):67-84. https://doi.org/10.1038/s41580-019-0179-2

Pavlova NN, Thompson CB, 2016. The emerging hallmarks of cancer metabolism. *Cell Metab*, 23(1):27-47.

https://doi.org/10.1016/j.cmet.2015.12.006

Peng F, Lu JX, Su KY, et al., 2024. Oncogenic fatty acid oxidation senses circadian disruption in sleep-deficiency-enhanced tumorigenesis. *Cell Metab*, 36(7):1598-1618.e11. https://doi.org/10.1016/j.cmet.2024.04.018

Pu H, Bailey LC, Bauer LG, et al., 2025. Pharmacological targeting of BMAL1 modulates circadian and immune pathways. *Nat Chem Biol*, 21(5):736-745. https://doi.org/10.1038/s41589-025-01863-x

Qi GY, Guo R, Tian HY, et al., 2018. Nobiletin protects against insulin resistance and disorders of lipid metabolism by reprogramming of circadian clock in hepatocytes. *Biochim Biophys Acta Mol Cell Biol Lipids*, 1863(6):549-562. https://doi.org/10.1016/j.bbalip.2018.02.009

Qu M, Zhang GX, Qu H, et al., 2023. Circadian regulator BMAL1::CLOCK promotes cell proliferation in hepatocellular carcinoma by controlling apoptosis and cell cycle. *Proc Natl Acad Sci USA*, 120(2):e2214829120. https://doi.org/10.1073/pnas.2214829120

Quail DF, Joyce JA, 2013. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*, 19(11):1423-1437. https://doi.org/10.1038/nm.3394

Queiroz JDN, Macedo RCO, Tinsley GM, et al., 2021. Time-restricted eating and circadian rhythms: the biological clock is ticking. *Crit Rev Food Sci Nutr*, 61(17):2863-2875. https://doi.org/10.1080/10408398.2020.1789550

Ripperger JA, Schibler U, 2006. Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian *Dbp* transcription and chromatin transitions. *Nat Genet*, 38(3):369-374. https://doi.org/10.1038/ng1738

Sancar A, van Gelder RN, 2021. Clocks, cancer, and chronochemotherapy. *Science*, 371(6524):eabb0738. https://doi.org/10.1126/science.abb0738

Sancar A, Lindsey-Boltz LA, Kang TH, et al., 2010. Circadian clock control of the cellular response to DNA damage. *FEBS Lett*, 584(12):2618-2625. https://doi.org/10.1016/j.febslet.2010.03.017

Schrader LA, Ronnekleiv-Kelly SM, Hogenesch JB, et al., 2024. Circadian disruption, clock genes, and metabolic health. *J Clin Invest*, 134(14):e170998. https://doi.org/10.1172/JCI170998

Shi D, Fang GF, Chen QY, et al., 2023. Six-hour time-restricted feeding inhibits lung cancer progression and reshapes circadian metabolism. *BMC Med*, 21:417. https://doi.org/10.1186/s12916-023-03131-y

Slat EA, Sponagel J, Marpegan L, et al., 2017. Cell-intrinsic, Bmal1-dependent circadian regulation of temozolomide sensitivity in glioblastoma. *J Biol Rhythms*, 32(2):121-129. https://doi.org/10.1177/0748730417696788

Sulli G, Manoogian ENC, Taub PR, et al., 2018. Training the circadian clock, clocking the drugs, and drugging the clock to prevent, manage, and treat chronic diseases. *Trends Pharmacol Sci*, 39(9):812-827. https://doi.org/10.1016/j.tips.2018.07.003

Terzibasi-Tozzini E, Martinez-Nicolas A, Lucas-Sánchez A, 2017. The clock is ticking. Ageing of the circadian system: from physiology to cell cycle. *Semin Cell Dev Biol*, 70:164-176. https://doi.org/10.1016/j.semcdb.2017.06.011

Wang C, Zeng Q, Gül ZM, et al., 2024. Circadian tumor infiltration and function of $CD8^+$ T cells dictate immunotherapy efficacy. *Cell*, 187(11):2690-2702.e17. https://doi.org/10.1016/j.cell.2024.04.015

Wang YP, Qian RZ, Sun N, et al., 2015. Circadian gene hClock enhances proliferation and inhibits apoptosis of human colorectal carcinoma cells in vitro and in vivo. *Mol Med Rep*, 11(6):4204-4210. https://doi.org/10.3892/mmr.2015.3247

Wang YP, Sun N, Lu C, et al., 2017. Upregulation of circadian gene 'hClock' contribution to metastasis of colorectal cancer. *Int J Oncol*, 50(6):2191-2199. https://doi.org/10.3892/ijo.2017.3987

Wang Z, Ma LN, Meng Y, et al., 2024. The interplay of the circadian clock and metabolic tumorigenesis. *Trends Cell Biol*, 34(9):742-755. https://doi.org/10.1016/j.tcb.2023.11.004

Wei T, Cheng Y, Ge JR, et al., 2025. The pro-apoptotic effect of glucose restriction in NSCLC via AMPK-regulated circadian clock gene Bmal1. *Cancer Sci*, 116(8):2101-2112. https://doi.org/10.1111/cas.70098

Wu DL, Rastinejad F, 2017. Structural characterization of mammalian bHLH-PAS transcription factors. *Curr Opin Struct Biol*, 43:1-9. https://doi.org/10.1016/j.sbi.2016.09.011

Wu DL, Su XY, Potluri N, et al., 2016. NPAS1-ARNT and NPAS3-ARNT crystal structures implicate the bHLH-PAS family as multi-ligand binding transcription factors. *eLife*, 5:e18790. https://doi.org/10.7554/eLife.18790

Wu YC, Tao BR, Zhang TY, et al., 2019. Pan-cancer analysis reveals disrupted circadian clock associates with T cell exhaustion. *Front Immunol*, 10:2451. https://doi.org/10.3389/fimmu.2019.02451

Xu DQ, Shao F, Bian XL, et al., 2021. The evolving landscape of noncanonical functions of metabolic enzymes in cancer and other pathologies. *Cell Metab*, 33(1):33-50. https://doi.org/10.1016/j.cmet.2020.12.015

Xuan WJ, Khan F, James CD, et al., 2021. Circadian regulation of cancer cell and tumor microenvironment crosstalk. *Trends Cell Biol*, 31(11):940-950. https://doi.org/10.1016/j.tcb.2021.06.008

Xuan WJ, Hsu WH, Khan F, et al., 2022. Circadian regulator CLOCK drives immunosuppression in glioblastoma. *Cancer Immunol Res*, 10(6):770-784. https://doi.org/10.1158/2326-6066.CIR-21-0559

Yip HYK, Papa A, 2021. Signaling pathways in cancer: therapeutic targets, combinatorial treatments, and new developments. *Cells*, 10(3):659. https://doi.org/10.3390/cells10030659

Yoo SH, Mohawk JA, Siepka SM, et al., 2013. Competing E3 ubiquitin ligases govern circadian periodicity by degradation of CRY in nucleus and cytoplasm. *Cell*, 152(5):1091-1105. https://doi.org/10.1016/j.cell.2013.01.055

Zeng YE, Guo ZC, Wu MQ, et al., 2024. Circadian rhythm regulates the function of immune cells and participates in the development of tumors. *Cell Death Discov*, 10:199. https://doi.org/10.1038/s41420-024-01960-1

Zeng ZL, Luo HY, Yang J, et al., 2014. Overexpression of the circadian clock gene *Bmal1* increases sensitivity to oxaliplatin in colorectal cancer. *Clin Cancer Res*, 20(4):1042-1052. https://doi.org/10.1158/1078-0432.CCR-13-0171

Zhang CF, Chen LP, Sun L, et al., 2023. BMAL1 collaborates with CLOCK to directly promote DNA double-strand break repair and tumor chemoresistance. *Oncogene*, 42(13): 967-979. https://doi.org/10.1038/s41388-023-02603-y

Zhang R, Lahens NF, Ballance HI, et al., 2014. A circadian gene expression atlas in mammals: implications for biology and medicine. *Proc Natl Acad Sci USA*, 111(45):16219-16224. https://doi.org/10.1073/pnas.1408886111

Zhang Z, Zeng PH, Gao WH, et al., 2021. Circadian clock: a regulator of the immunity in cancer. *Cell Commun Signal*, 19:37. https://doi.org/10.1186/s12964-021-00721-2

Zhou L, Zhang Z, Nice E, et al., 2022. Circadian rhythms and cancers: the intrinsic links and therapeutic potentials. *J Hematol Oncol*, 15:21. https://doi.org/10.1186/s13045-022-01238-y

Zhu YF, Zheng Y, Dai RY, et al., 2025. Crosstalk between circadian rhythm dysregulation and tumorigenesis, tumor metabolism and tumor immune response. *Aging Dis*, 16(4): 2073-2099. https://doi.org/10.14336/AD.2024.0533