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Review

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

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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 CLOCK and 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 the 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; CLOCK; BMAL1; Cancer; Therapy

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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-hour 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 the transcriptional activators circadian locomotor output cycles kaput (CLOCK) and the 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 & Schibler, 2006). Upon accumulation in the cytoplasm, the PER and CRY proteins form heterodimeric complexes that translocate into the nucleus, where they suppress

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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 limb of the circadian oscillator and the commencement of subsequent 24-hour rhythmicity(Yoo et al., 2013). An auxiliary feedback loop involves the nuclear hormone receptor 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 et al., 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-hour 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 et al., 2024), and impaired immune surveillance (Curtis et al., 2014, Zhang et al., 2021). However, during malignant transformation, the normal oscillatory patterns of these circadian-regulated genes frequently become disrupted or completely lost in a tumor-type specific fashion (Huang et al., 2024, Grabe 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.

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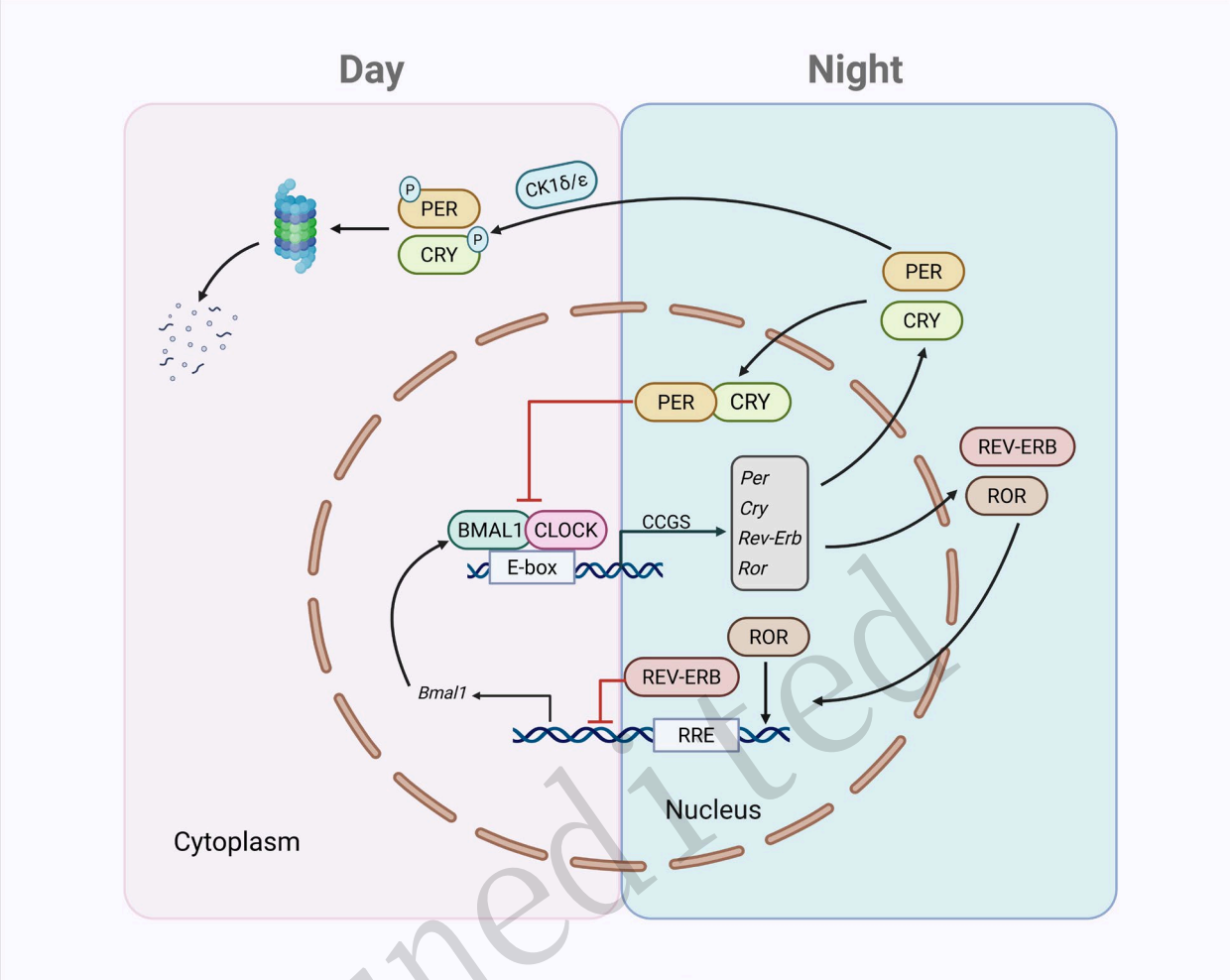

Fig. 1. Circadian gene TTFL model diagram. The CLOCK-BMAL1 heterodimers bind to E-box elements in CCGS to activate their transcription. Subsequently, PER and CRY proteins form heterodimers that suppress CLOCK-BMAL1-mediated transcription, establishing a negative feedback loop. Moreover, the stability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

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 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 AKT and suppressing the expression of pro-apoptotic genes Bax and 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-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 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 BRCA1 and 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 loop involving the tumor suppressor and checkpoint protein 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 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)

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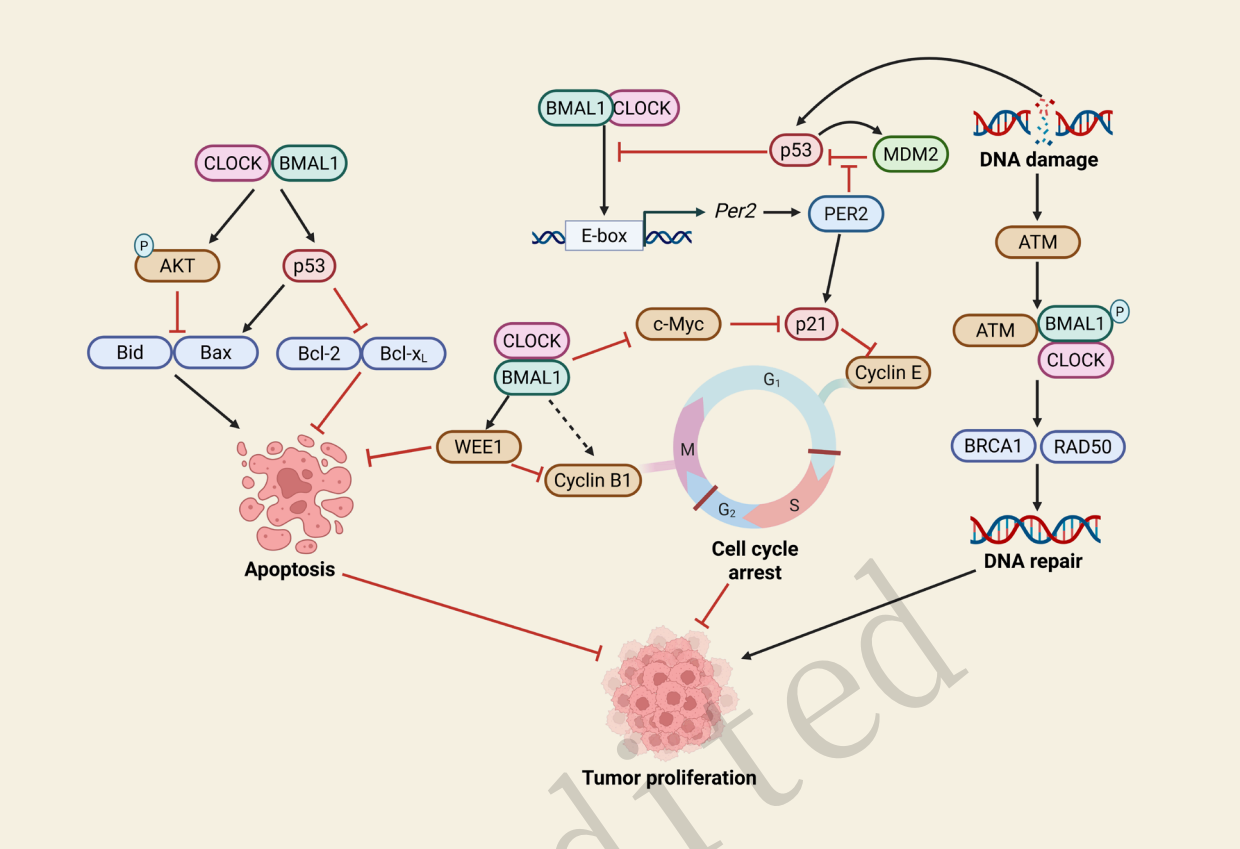

Fig. 2. Molecular mechanisms of CLOCK/BMAL1 in regulating the cell cycle, apoptosis, and DNA damage. CLOCK/BMAL1 exerts dual effects on tumorigenesis through its multifaceted regulation of cell cycle progression, apoptotic pathways, and DNA damage repair. CLOCK: circadian locomotor output cycles kaput,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

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4 Cell metabolism

Metabolic reprogramming represents a hallmark feature of cancer (Hanahan et al., 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 et al., 2016, Xu et al., 2021, Yip et al., 2021). Mounting evidence from the literature indicates that mammalian metabolism exhibits distinct circadian rhythmicity during cancer progression, where circadian disruption alters the oscillatory patterns in multiple metabolic processes, including glucose, glutamine, lipid, and nucleic acid metabolism (Wang et al., 2024). For instance, the disruption of BMAL1 alters hexokinase domain containing 1 (HKDC1) expression—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 that 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-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 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 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 tumor metabolic reprogramming. It elucidates 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 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 et al., 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 1-alpha (HIF1α). 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 A (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., 2024). Circadian dysregulation promoted lung metastasis in CRC-bearing mice, concomitant with the increased infiltration of pulmonary myeloid-derived suppressor cells (MDSC) and diminished $CD8^+$T cell efficacy (Liu et al., 2024). High CLOCK levels in glioblastoma 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 $LY6^{hi}$ 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 have 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, immune escape), indicating that the disruption of circadian cancer cell-TME crosstalk may represent a viable strategy to suppress tumor progression (Fig. 3).

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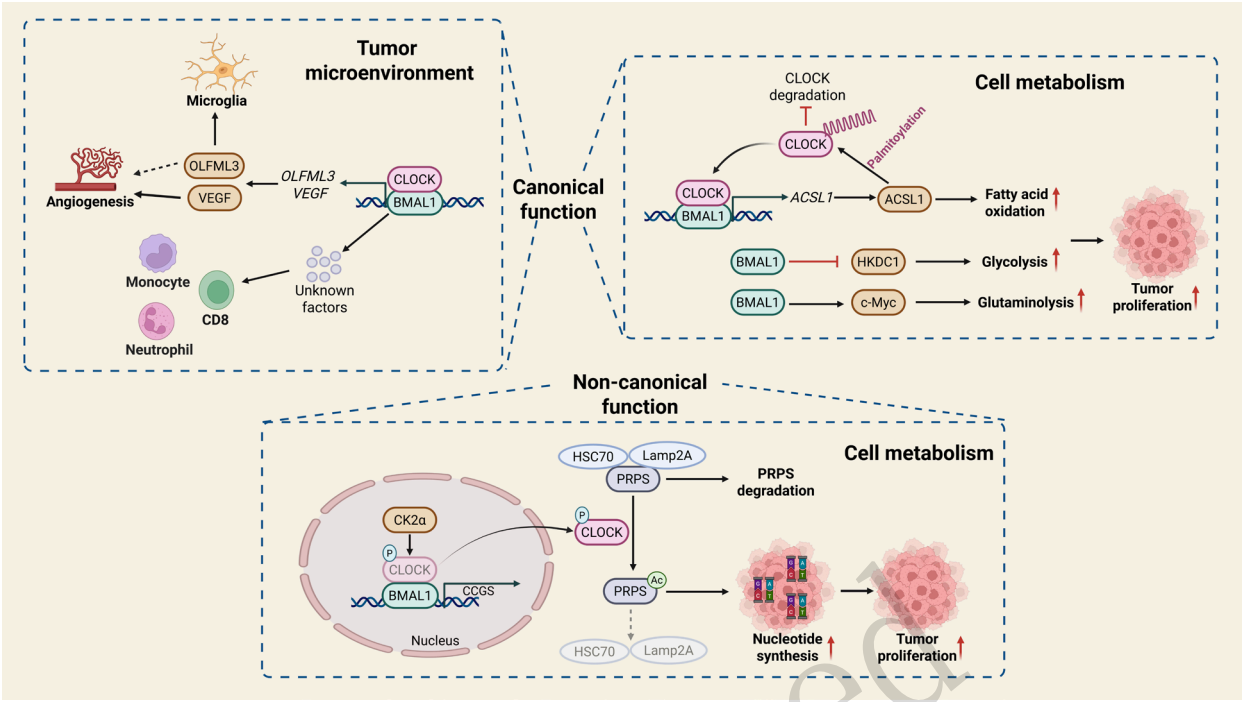

Fig. 3. Molecular mechanisms of CLOCK/BMAL1 in the TME and cell metabolism. The CLOCK/BMAL1 heterodimer exerts its canonical transcriptional functions in tumorigenesis by regulating both the TME and cellular metabolism. Furthermore, CLOCK can act as an acetyltransferase to regulate nucleotide metabolism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

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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 hours). Unlike traditional calorie-restricted diets, TRF maintains normal energy intake while enforcing temporal eating patterns (Longo et al., 2016, Queiroz et al., 2021, Li, 2022). A recent study reported that 6-h TRF-mimicking regimens suppressed core clock genes (eg., CLOCK) and exerted potent anti-tumor effects in 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. demonstrated that a glucose-restricted diet modulated cancer progression via circadian rhythm regulation by upregulating the energy-sensing factor AMPK, which enhanced BMAL1 expression and subsequently induced apoptosis in non-small cell lung cancer (NSCLC) (Wei et al., 2025).

Mounting evidence demonstrates 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. demonstrated that the combined administration of CRY agonist KL001 with REV-ERB agonists SR9009/SR9011 effectively suppressed CLOCK-BMAL1 transcriptional activity, inducing cell cycle arrest and apoptosis in GBM models (Dong et al., 2019). Similarly, Priscilla et al. confirmed that SHP1705, the first CRY activator is safe and well-tolerated in Phase I clinical trials, which exhibits potent inhibitory effects against glioblastoma stem cells (GSCs) when combined with novel REV-ERB agonist SR9065 (Chan et al., 2025). 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. reported that nobiletin ameliorated insulin resistance and lipid metabolic dysregulation in HCC cells through circadian clock reprogramming, exhibiting BMAL1-dependent mechanisms of action (Qi et al., 2018). Han et al. 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 (Han et al., 2025).

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 et al., 2017). Notably, a study based on a docking approach revealed that the 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 et al., 2021, Amiama-Roig et al., 2022). Temozolomide (TMZ) has demonstrated significant chronotherapeutic efficacy against GBM, with preclinical studies showing its DNA-damaging, pro-apoptotic, and anti-proliferative effects that 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, consistent with its established circadian regulation of DNA repair pathways (Damato et al., 2021). In addition, time-restricted administration of β-endorphin specifically during 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 the significant inhibition of tumor growth and reduction in cancer stem cell properties (Peng et al., 2024). As another critical aspect, the timing of immunotherapy administration also determines treatment efficacy. Both CAR-T cell therapy and 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

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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 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.

Table 1 Summary of chronotherapeutic approaches and agents

Therapy	Approach/agent	Cancer types	Potential effect	Potential mechanism	Reference
Chrononutritional intervention	TRF	Lung cancer	Inhibited proliferation Induced apoptosis Cell cycle arrest	Downregulating of core clock genes (eg., 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 gluco-lipid 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 cell and anti-PD-1 at ZT13	Melanoma	Inhibited proliferation	Higher ICM-1 and tumor immune cell infiltration at ZT13	Wang *et al*., 2024

CLOCK: circadian locomotor output cycles kaput, BMAL1: brain and muscle ARNT-like 1, TRF: time-restricted feeding, TMZ: temozolomide, ICM-1: intercellular adhesion molecule 1.

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

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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 patients' age, sex, genetic background, and chronotype (morning/evening preference) significantly influence therapeutic outcomes (Terzibasi-Tozzini et al., 2017, Lévi et al., 2024).

Addressing the aboves challenges demands a multipronged approach: (1) Developing next-generation wearable monitoring devices integrated with AI algorithms to establish dynamic, personalized therapeutic time-window prediction systems, as demonstrated by Kim et al.'s Approximation-based Least-Squares Method (ALSM) for the efficient extraction of physiological data from wearable time-series to assess circadian biomarker variations (Kim et al., 2023). Additionally, Leung et al. 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 (Leung et al., 2023). 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. 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., 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 transcriptional 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; (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 after 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.

7 Conclusions

The core circadian transcription factors CLOCK and BMAL1 exhibit complex and diverse regulatory roles

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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 tumor microenvironment. Particularly, the coordinated effects between circadian genes and metabolic pathways can explain how tumor cells adapt to nutrient fluctuations to sustain growth and influence treatment response, while 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 developing novel chronotherapy strategies. Building on these research 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, ultimately offering innovative therapeutic options to improve patient outcomes.

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Author contributions

All authors contributed substantially to this review by participating in literature research, content discussion, manuscript preparation, and critical revision prior to submission.

Compliance with ethics guidelines

All authors have no conflict of interest.

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

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