IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
Impact Factor: 7.67
Volume 5, Issue 2, March 2025

The Molecular Link Between Circadian Rhythms and Cancer: Implications for Therapeutic Interventions

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Abstract: *This review examines the molecular mechanisms connecting circadian rhythms to cancer progression and explores potential chronotherapeutic approaches. Circadian rhythms regulate key cellular processes including cell cycle progression, DNA damage repair, metabolism, and immune function. Disruption of these rhythms has been linked to increased cancer risk and poorer outcomes across multiple cancer types. This paper systematically analyzes the molecular crosstalk between core clock components (CLOCK, BMAL1, PER, CRY, REV-ERB, and ROR) and cancer-related pathways, presenting evidence for bidirectional regulation. Current therapeutic strategies targeting these connections are evaluated, including timed administration of existing treatments, small molecule modulators of clock components, and lifestyle interventions. The emerging field of chronotherapy demonstrates promising preclinical and clinical results, suggesting that time-of-day-based treatment approaches may significantly enhance efficacy while reducing toxicity. Future research directions and challenges in translating chronobiology to clinical oncology applications are discussed.*

Keywords: Circadian rhythm, Cancer, CLOCK, BMAL1, PER, CRY, Chronotherapy, Cell cycle

I. INTRODUCTION

Circadian rhythms, the endogenous approximately 24-hour oscillations in physiological and behavioral processes, evolved as an adaptation to Earth's rotation and consequent light-dark cycles (Takahashi, 2017). These rhythms are governed by a hierarchical system of molecular clocks, with the suprachiasmatic nucleus (SCN) of the hypothalamus functioning as the master pacemaker that synchronizes peripheral clocks throughout the body (Dibner et al., 2010). At the molecular level, circadian rhythms are generated by interconnected transcription-translation feedback loops involving core clock genes and their protein products.

Cancer, characterized by uncontrolled cell proliferation and invasion, involves dysregulation of many cellular processes that are normally under circadian control, including the cell cycle, metabolism, DNA repair, and apoptosis (Lamia, 2017). Epidemiological studies have established links between circadian disruption and increased cancer risk, with night shift work being classified as a probable carcinogen by the International Agency for Research on Cancer (IARC) (Straif et al., 2007). Additionally, cancer patients commonly experience severe circadian rhythm disruptions, which are associated with poorer quality of life and reduced survival (Innominato et al., 2014).

This paper examines the bidirectional relationship between circadian rhythms and cancer at the molecular level, exploring how circadian mechanisms influence cancer-related processes and how cancer progression disrupts circadian function. Furthermore, we discuss emerging therapeutic strategies that leverage circadian timing (chronotherapy) to improve treatment outcomes. Understanding these complex interactions may lead to innovative approaches for cancer prevention, diagnosis, and treatment.

Molecular Architecture of the Circadian Clock

The mammalian circadian system consists of a master clock in the SCN and peripheral clocks in virtually all cells throughout the body. The molecular machinery of these clocks comprises a set of core clock genes and proteins that form interconnected transcriptional-translational feedback loops (TTFLs) (Takahashi, 2017).

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Primary Feedback Loop

In the primary feedback loop, the CLOCK (or its paralog NPAS2) and BMAL1 (also known as ARNTL) proteins heterodimerize and bind to E-box elements in the promoters of target genes, including Period (PER1, PER2, PER3) and Cryptochrome (CRY1, CRY2). The resulting PER and CRY proteins form complexes that translocate back to the nucleus, where they inhibit CLOCK/BMAL1-mediated transcription, thereby suppressing their own expression and completing the negative feedback loop (Takahashi, 2017).

Secondary Feedback Loops

Secondary feedback loops involve nuclear receptors, particularly REV-ERBα/β and RORα/γ. CLOCK/BMAL1 activates transcription of REV-ERB and ROR genes. Their protein products compete for binding to ROR elements (ROREs) in the BMAL1 promoter, with REV-ERBs repressing and RORs activating BMAL1 transcription (Preitner et al., 2002).

Post-translational Modifications

Post-translational modifications (PTMs), including phosphorylation, ubiquitination, SUMOylation, and acetylation, regulate the stability, activity, and nuclear translocation of clock proteins. Key kinases involved include casein kinase 1 (CK1), glycogen synthase kinase 3β (GSK3β), and AMP-activated protein kinase (AMPK) (Hirano et al., 2016).

Table 1 summarizes the core components of the mammalian circadian clock and their primary functions.

Component	Function	Cancer-Related Interactions
CLOCK/NPAS2	Transcriptional activator, forms heterodimer with BMAL1	Regulates cell cycle genes, metabolism; overexpressed in several cancers
BMAL1 (ARNTL)	Transcriptional activator, partners with CLOCK/NPAS2	Suppresses cancer cell invasion; loss associated with increased cancer risk
PER1/2/3	Negative regulator, inhibits CLOCK/BMAL1 activity	Tumor suppressors; frequently downregulated in cancers
CRY1/2	Negative regulator, inhibits CLOCK/BMAL1 activity	Regulates DNA damage response; altered expression in various cancers
REV-ERBα/β	Represses BMAL1 transcription	Regulates metabolism and inflammation; potential therapeutic target
RORα/γ	Activates BMAL1 transcription	RORα has tumor-suppressive functions; RORγ promotes some cancers
CK1δ/ε	Phosphorylates PER proteins, regulating stability	Mutations affect circadian period; potential therapeutic target
GSK3β	Phosphorylates multiple clock proteins	Tumor suppressor in some contexts; therapeutic target

Circadian Regulation of Cancer-Related Processes

Cell Cycle Control

The circadian clock and cell cycle are intimately connected through multiple molecular mechanisms. Core clock proteins regulate the expression and activity of several cell cycle regulators, including cyclins, cyclin-dependent kinases (CDKs), and CDK inhibitors (Matsuo et al., 2003).

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CLOCK/BMAL1 directly regulates the transcription of cell cycle checkpoint genes such as WEE1 (G2/M checkpoint kinase), which displays robust circadian expression in many tissues (Matsuo et al., 2003). Additionally, the clock controls cyclin expression, with CLOCK/BMAL1 regulating Cyclin D1 expression and the PER2 protein interacting with cyclin D and CDK4 complexes (Kowalska et al., 2013).

The tumor suppressor p21, a critical CDK inhibitor, is regulated by PER2, which enhances its stability and activity (Gotoh et al., 2014). Furthermore, the p53 pathway, central to DNA damage response and cell cycle arrest, interacts bidirectionally with the circadian clock, with PER2 modulating p53 stability and transcriptional activity (Miki et al., 2013).

Table 2 highlights key cell cycle regulators under circadian control.

Cell Cycle Regulator	**Circadian Regulator**	**Phase of Cell Cycle**	**Effect of Circadian Disruption**
Cyclin D1	CLOCK/BMAL1, PER2	G1/S transition	Increased expression, accelerated G1/S
Cyclin E	REV-ERBα	G1/S transition	Dysregulated expression
Cyclin B1	CLOCK/BMAL1	G2/M transition	Premature activation, genomic instability
p21 (CDKN1A)	PER2	G1 arrest	Reduced expression, loss of checkpoint control
WEE1	CLOCK/BMAL1	G2/M checkpoint	Loss of G2/M checkpoint function
c-MYC	CRY, PER	Multiple phases	Overexpression, increased proliferation
MDM2	CRY2	p53 regulation	Enhanced p53 degradation
p53	PER2	Multiple checkpoints	Reduced activity, compromised DNA damage response

DNA Damage Response and Repair

The circadian clock system is intricately linked with DNA damage response (DDR) pathways, providing time-dependent regulation of genome maintenance (Sancar et al., 2010). Several key DNA repair proteins display circadian oscillations in expression or activity, allowing coordination of repair processes with periods of predicted DNA damage risk.

Nucleotide excision repair (NER), responsible for removing UV-induced DNA lesions, shows time-dependent efficiency with higher activity during the day in diurnal organisms (Kang et al., 2009). The key NER protein XPA demonstrates robust circadian oscillation controlled by the CLOCK/BMAL1 complex and modulated by the ataxia telangiectasia and Rad3-related (ATR) checkpoint kinase (Kang et al., 2010).

Additionally, CRY proteins, originally evolved from photolyase DNA repair enzymes, maintain interactions with DNA repair machinery. CRY1 participates in DNA damage checkpoint control through interactions with ATR and Chk1/Chk2 kinases (Papp et al., 2015). Similarly, PER proteins influence double-strand break repair, with PER1 interacting with ATM and Chk2 kinases (Gery et al., 2006).

Metabolism and Cancer

Circadian regulation of metabolism is increasingly recognized as a critical link between clock function and cancer development. The circadian clock controls key metabolic processes including glucose metabolism, lipid synthesis, and mitochondrial function, all of which can be dysregulated in cancer (Sulli et al., 2018).

CLOCK/BMAL1 regulates glucose metabolism through control of rate-limiting enzymes such as hexokinase, phosphofructokinase, and pyruvate kinase (Koike et al., 2012). Clock disruption can lead to a shift toward glycolysis,

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resembling the Warburg effect observed in many cancers. Similarly, circadian control of lipid metabolism, particularly through REV-ERBα/β and RORα, influences cancer cell membrane synthesis and signaling (Sulli et al., 2018).

The NAD^+-dependent deacetylase SIRT1, which links cellular metabolism to epigenetic regulation, demonstrates reciprocal regulation with the core clock component CLOCK and influences cancer-related processes including apoptosis and senescence (Chang & Guarente, 2013).

Immune Function and Tumor Surveillance

The immune system, crucial for tumor surveillance and elimination, exhibits strong circadian regulation. Immune cell trafficking, cytokine production, and effector functions all display time-of-day variations that can impact anti-tumor immunity (Scheiermann et al., 2013).

Natural killer (NK) cells, important for eliminating transformed cells, show circadian oscillations in number and cytotoxic activity regulated by the core clock through adrenergic signaling (Logan et al., 2012). T cell responses, including proliferation and cytokine production, are also under circadian control, with implications for cancer immunotherapy efficacy (Haspel et al., 2014).

Additionally, macrophage polarization between pro-inflammatory (M1) and tumor-promoting (M2) phenotypes is regulated by REV-ERBα, providing another link between circadian rhythms and tumor progression (Sato et al., 2014).

Clock Gene Dysregulation in Cancer

Altered Expression of Clock Genes in Various Cancers

Numerous studies have documented aberrant expression of clock genes across multiple cancer types. Table 3 summarizes these findings, highlighting the complex pattern of clock gene dysregulation in cancer.

Cancer Type	Upregulated Clock Genes	Downregulated Clock Genes	Clinical Correlations
Breast	CLOCK, BMAL2, CRY1	PER1, PER2, PER3, CRY2	PER downregulation associated with poorer prognosis
Colorectal	CLOCK, CRY1	PER1, PER2, PER3, BMAL1	PER loss correlates with liver metastasis
Lung	CRY1	PER1, PER2, PER3, BMAL1	PER1 methylation predicts poor survival
Prostate	CLOCK, BMAL1	PER1, PER2, CRY1	BMAL1 overexpression associated with metastasis
Pancreatic	BMAL1, CRY1	PER1, PER2	CRY1 overexpression correlates with tumor size
Liver	CLOCK, CRY1, CRY2	PER1, PER2, PER3	PER downregulation associated with portal vein invasion
Glioma	CLOCK, BMAL1	PER1, PER2	BMAL1 elevation correlates with higher grade
Leukemia	CRY1, CRY2	PER1, PER2, BMAL1	PER2 loss associated with poorer prognosis
Ovarian	CLOCK, CRY1	PER1, PER2, PER3	PER downregulation correlates with advanced stage
Skin	CLOCK, BMAL1	PER1, PER2, CRY2	PER1 methylation in melanoma progression

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A consistent pattern emerges across multiple cancer types: components of the positive limb of the circadian feedback loop (CLOCK, BMAL1) are frequently upregulated, while negative regulators (PER, CRY) are often downregulated. This pattern suggests a disruption of the normal feedback regulation in the molecular clock, potentially contributing to dysregulated cellular processes in cancer.

Epigenetic Silencing of Clock Genes

Epigenetic mechanisms, particularly promoter hypermethylation, contribute significantly to clock gene silencing in cancer. The PER family genes (PER1, PER2, PER3) exhibit promoter hypermethylation in breast, colorectal, endometrial, and lung cancers, correlating with reduced expression (Zhu et al., 2016). BMAL1 promoter methylation has been observed in hematological malignancies and breast cancer (Taniguchi et al., 2009).

Histone modifications also regulate clock gene expression, with alterations in these marks contributing to dysregulated expression in cancer. For example, decreased histone acetylation at the PER promoters, due to recruitment of histone deacetylases (HDACs), has been observed in certain cancer types (Kuo et al., 2011).

Genetic Alterations in Clock Genes and Cancer Risk

While somatic mutations in core clock genes are not among the most common driver mutations in cancer, germline polymorphisms in clock genes have been associated with cancer risk and outcomes.

Single nucleotide polymorphisms (SNPs) in PER1, PER2, PER3, CLOCK, and BMAL1 have been linked to increased susceptibility to breast, prostate, colorectal, and lung cancers, though the functional consequences of many of these variants remain to be fully elucidated (Zienolddiny et al., 2013).

The PER3 variable number tandem repeat (VNTR) polymorphism, which affects circadian preference and sleep regulation, has been associated with breast cancer risk, particularly in younger women (Zhu et al., 2005). Additionally, a functional polymorphism in the CLOCK gene (3111T/C) has been linked to breast cancer risk and altered hormone levels (Hoffman et al., 2010).

Cancer-Driven Disruption of Circadian Rhythms

Metabolic Perturbations

Cancer cells exhibit profound metabolic reprogramming, characterized by elevated glycolysis even under aerobic conditions (the Warburg effect), altered glutamine metabolism, and increased lipid synthesis (Pavlova & Thompson, 2016). These metabolic changes can directly impact the molecular clock, as many metabolic intermediates and cofactors serve as inputs to the circadian system.

The NAD^+/NADH ratio, which reflects cellular redox state and is often altered in cancer, influences the activity of SIRT1, which in turn regulates CLOCK, BMAL1, and PER2 through deacetylation (Chang & Guarente, 2013). Similarly, cancer-associated changes in AMP/ATP ratio affect AMPK activity, which phosphorylates CRY1 and promotes its degradation (Lamia et al., 2009).

Altered glucose metabolism in cancer can influence O-GlcNAcylation of clock proteins, affecting their stability and function. BMAL1 and CLOCK are subject to O-GlcNAcylation, linking glucose availability to circadian transcription (Li et al., 2013).

Inflammatory Signaling

Chronic inflammation, a hallmark of many cancers, disrupts circadian rhythms through multiple mechanisms. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, often elevated in the tumor microenvironment, can alter clock gene expression and desynchronize cellular clocks (Cavadini et al., 2007).

NF-κB signaling, activated in many cancers, interacts with the circadian clock bidirectionally. TNF-α-mediated NF-κB activation suppresses CLOCK/BMAL1-driven transcription, while CLOCK/BMAL1 can modulate the expression of NF-κB components (Spengler et al., 2012).

Additionally, STAT3 signaling, frequently constitutively activated in cancer cells, interacts with the circadian clock, with STAT3 directly regulating PER2 expression (Wang et al., 2010).

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Hypoxia and Circadian Disruption

Intratumoral hypoxia, resulting from abnormal vasculature and rapid growth, affects circadian function through hypoxia-inducible factor (HIF) signaling. HIF-1α interacts with the molecular clock in complex ways, with BMAL1 enhancing HIF-1α transcriptional activity and HIF-1α reciprocally affecting clock gene expression (Wu et al., 2017).

The PER2 promoter contains hypoxia response elements (HREs), allowing direct regulation by HIF-1α, while CRY1 can interact with and stabilize HIF-1α protein (Kobayashi et al., 2017). These interactions create a feedback loop between hypoxic signaling and circadian rhythm regulation that may contribute to tumor progression.

Chronotherapeutic Approaches in Cancer Treatment

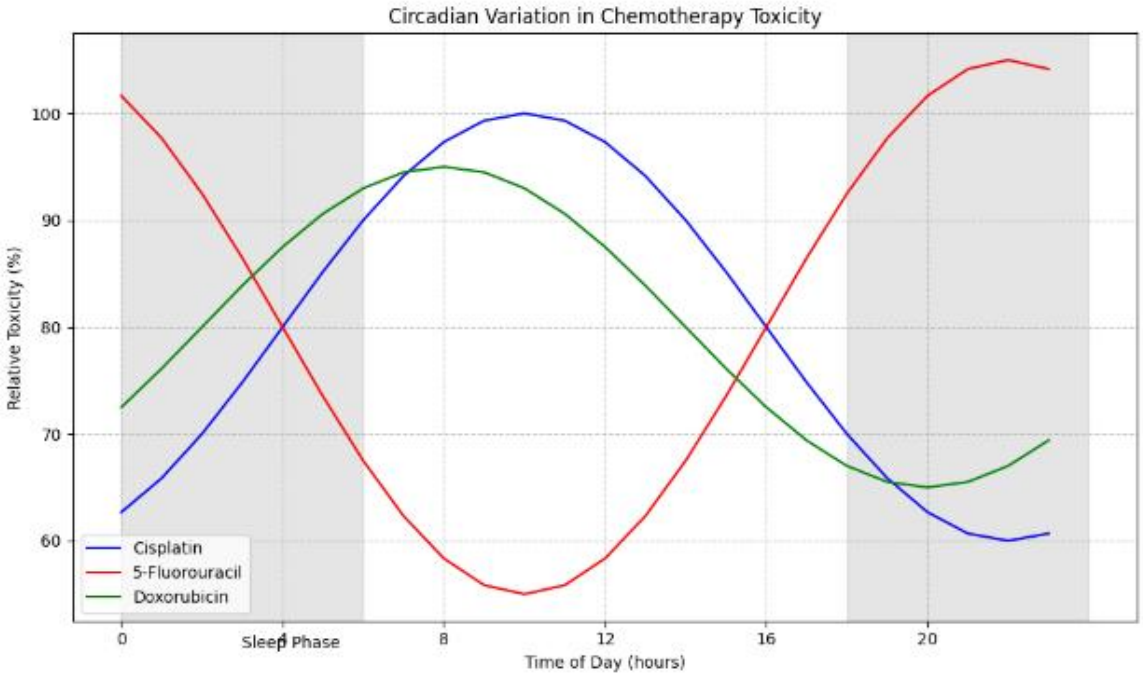
Timed Administration of Conventional Treatments

Chronotherapy—the timed administration of treatments according to biological rhythms—has shown promise in improving efficacy and reducing toxicity of conventional cancer therapies (Lévi et al., 2010).

Chronochemotherapy

Several chemotherapeutic agents demonstrate time-dependent efficacy and toxicity profiles. For example, 5-fluorouracil (5-FU) administration during the rest phase (night in humans) shows reduced gastrointestinal toxicity compared to administration during the active phase (Lévi et al., 1997). Similarly, platinum compounds, including cisplatin and oxaliplatin, exhibit circadian variations in nephrotoxicity and neurotoxicity, with reduced adverse effects when administered at specific times (Boughattas et al., 1989).

Figure 1 illustrates the relationship between administration time and drug toxicity for common chemotherapeutic agents.



Chronoradiotherapy

Radiotherapy efficacy and normal tissue toxicity also exhibit circadian variation. Cell cycle distribution, DNA repair capacity, and oxygen levels—all of which influence radiosensitivity—oscillate with circadian rhythms (Nishiyama et al., 2015). Early morning radiotherapy has been associated with reduced mucositis in head and neck cancer patients, potentially due to circadian variation in epithelial cell proliferation (Goyal et al., 2009).

Figure 2 shows the circadian variation in radiosensitivity and DNA repair capacity.

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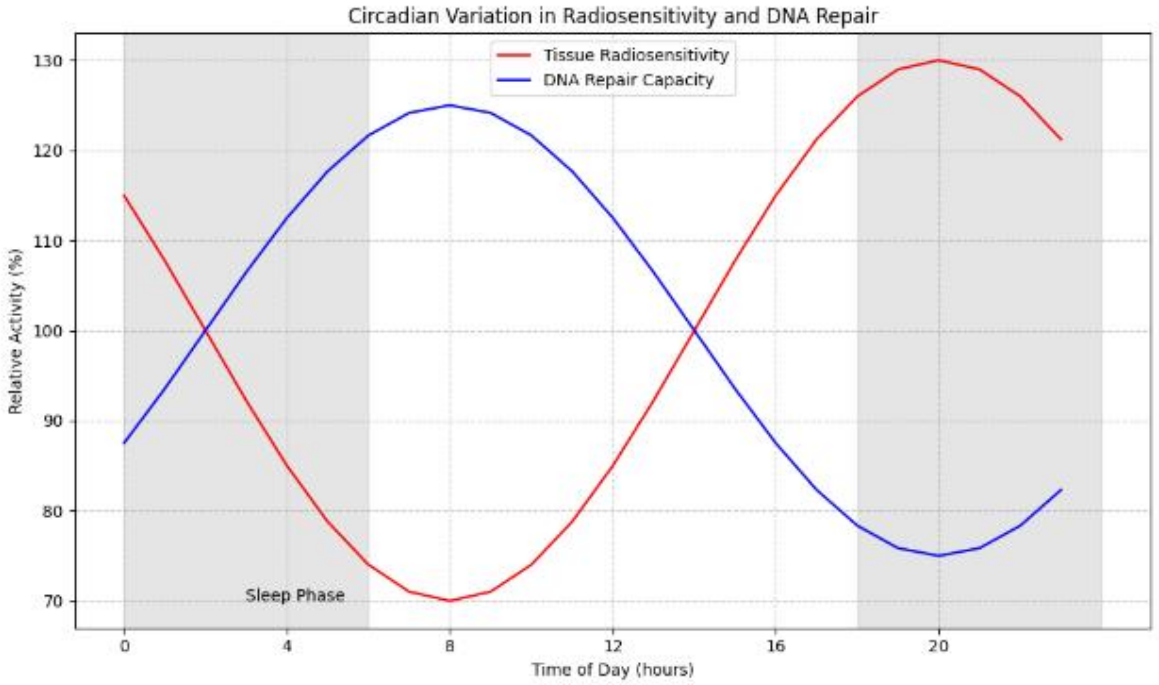

Chronoimmunotherapy

Emerging evidence suggests that the efficacy of immunotherapies, including immune checkpoint inhibitors, may depend on time of administration. Immune cell trafficking, cytokine production, and immune cell activity all display circadian rhythms that can influence tumor-immune interactions (Scheiermann et al., 2013).

T cell responses have been shown to vary throughout the day, with potential implications for adoptive T cell therapies and checkpoint inhibitor efficacy (Druzd et al., 2017). Similarly, macrophage polarization between pro-inflammatory and immunosuppressive phenotypes exhibits circadian regulation, potentially affecting tumor-associated macrophage function (Sato et al., 2014).

Clock-Targeting Compounds

Small molecules targeting specific components of the molecular clock have shown promise as potential cancer therapeutics. Table 4 summarizes current clock-modulating compounds with anti-cancer potential.

Compound	Target	Mechanism	Cancer Types	Stage of Development
SR9009	REV-ERB	Agonist	Breast, prostate, leukemia	Preclinical
SR9011	REV-ERB	Agonist	Glioblastoma, lung	Preclinical
KL001	CRY	Stabilizer	Liver, colon	Preclinical
CHRONO	PER2	Enhancer	Breast, pancreatic	Early preclinical
Core clock peptide (CCP)	CLOCK/BMAL1	Disruptor	Lymphoma, breast	Preclinical
SP2509	LSD1/BMAL1	Inhibitor	Prostate	Phase I clinical trials
VTP-50469	MLL1/CLOCK	Inhibitor	Leukemia	Phase I/II clinical trials

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KS15	CK1δ/ε	Inhibitor	Multiple myeloma	Preclinical
Longdaysin	CK1δ	Inhibitor	Leukemia	Preclinical

REV-ERB agonists SR9009 and SR9011 have demonstrated anti-cancer effects in multiple cancer models, inhibiting proliferation and inducing apoptosis through disruption of metabolic pathways (Sulli et al., 2018). Similarly, CRY stabilizer KL001 affects cell cycle progression and shows growth inhibitory effects in certain cancer models (Hirota et al., 2012).

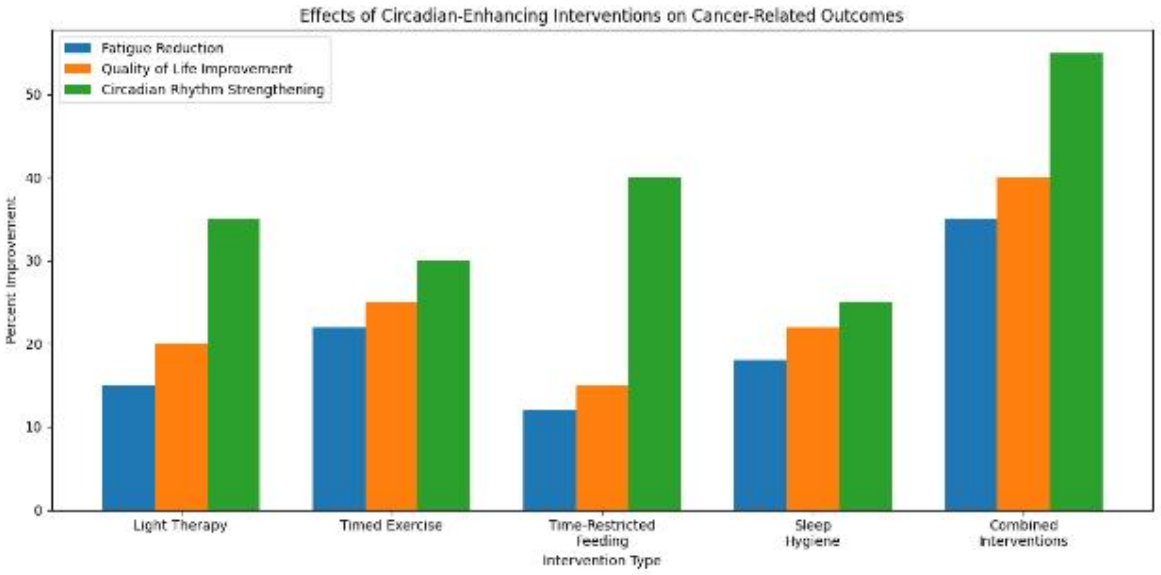
Lifestyle Interventions for Circadian Entrainment

Lifestyle interventions aimed at restoring or strengthening circadian rhythms represent a complementary approach to pharmacological chronotherapies. Such interventions include timed light exposure, meal timing, physical activity scheduling, and sleep hygiene improvements (Lévi et al., 2010).

Bright light therapy, particularly morning light exposure, can help entrain the master clock in the SCN and has been shown to reduce fatigue and improve quality of life in cancer patients (Johnson et al., 2018). Similarly, time-restricted feeding, limiting food intake to a consistent 8-12 hour window, may reinforce peripheral clock function and potentially impact tumor growth through metabolic mechanisms (Chaix et al., 2019).

Regular physical activity, particularly when consistently timed, strengthens circadian rhythms and may enhance anti-tumor immunity (Nakayama et al., 2019). Sleep hygiene interventions, aimed at improving sleep quality and regularity, can help maintain robust circadian rhythms and potentially influence cancer outcomes (Palesh et al., 2018).

Figure 3 illustrates the effect of circadian-enhancing interventions on cancer-related outcomes.



II. FUTURE DIRECTIONS AND CHALLENGES

Personalized Chronotherapy

Circadian timing varies between individuals due to genetic factors, age, sex, and environmental influences (Roenneberg et al., 2007). These differences, termed chronotypes, affect the optimal timing for therapeutic interventions. Future chronotherapeutic approaches will likely incorporate chronotype assessment and personalized timing strategies.

Wearable devices monitoring physiological parameters (temperature, activity, heart rate) can provide real-time information about an individual's circadian phase, potentially enabling personalized chronotherapy (Innominato et al., 2016). Additionally, molecular biomarkers of circadian phase, including plasma metabolites and salivary melatonin, may guide treatment timing decisions (Wittenbrink et al., 2018).

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Overcoming Circadian Disruption in Cancer

Cancer-associated circadian disruption presents a challenge for chronotherapeutic approaches. Strategies to restore or reinforce circadian rhythms may enhance the efficacy of both conventional and chronotherapeutic interventions.

Pharmacological approaches, including melatonin supplementation, REV-ERB agonists, and ROR modulators, can potentially resynchronize disrupted clocks (Lévi et al., 2010). Non-pharmacological interventions, such as scheduled light exposure, timed feeding, and physical activity, may complement drug-based approaches.

Integration with Precision Oncology

The future of chronotherapy lies in its integration with precision oncology approaches. Molecular profiling of tumors may reveal circadian gene expression patterns that can guide timing decisions. Additionally, pharmacogenomic factors influencing drug metabolism and toxicity often display circadian variation, providing opportunities for personalized chronotherapy (Zhang et al., 2018).

Chronotherapeutic approaches could be tailored based on tumor molecular subtypes, with different timing strategies for tumors with distinct circadian gene expression profiles. Similarly, host factors, including genetic polymorphisms in clock genes and chronotype, may inform individualized treatment schedules.

III. CONCLUSION

The molecular connections between circadian rhythms and cancer represent a complex and bidirectional relationship with significant implications for cancer prevention, diagnosis, and treatment. Circadian clocks regulate key cellular processes relevant to cancer, including cell cycle progression, DNA repair, metabolism, and immune function. Conversely, cancer development and progression often involve disruption of normal circadian function through genetic, epigenetic, and microenvironmental mechanisms.

Chronotherapeutic strategies, leveraging these molecular connections, show promise in enhancing treatment efficacy while reducing toxicity. Timed administration of conventional therapies, clock-targeting compounds, and circadian-enhancing lifestyle interventions represent complementary approaches that may improve outcomes for cancer patients.

Future advances in this field will likely involve more personalized chronotherapeutic approaches, incorporating individual chronotype assessment, real-time monitoring of circadian rhythms, and integration with molecular tumor profiling. Addressing the challenge of cancer-associated circadian disruption will be crucial for maximizing the potential of chronotherapy.

As our understanding of the molecular interface between circadian biology and cancer continues to deepen, chronotherapeutic approaches may become an integral component of cancer treatment strategies, potentially transforming therapeutic outcomes across multiple cancer types.

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IJARSCT
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International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.67
Volume 5, Issue 2, March 2025

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