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The Influence of Circadian Rhythm on Cancers

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Abstract: Circadian rhythms, which are intrinsic 24-hour biological cycles, regulate essential physiological processes that significantly impact health and are intricately associated with cancer development. Modern lifestyle disruptions can disturb circadian rhythms, affecting key tumorigenesis pathways like cell cycle regulation, DNA damage response, and metabolic processes. Core circadian proteins BMAL1 and CLOCK significantly influence cancer progression. Specifically, BMAL1 has been shown to activate oncogenic signaling pathways. Chronotherapy is a novel treatment that synchronizes the delivery of treatment with circadian biology. It shows outstanding promise in enhancing cancer treatment efficacy while reducing side effects. Clinical trials indicate that optimal temporal administration of chemotherapeutic and immunotherapeutic agents can significantly reduce drug toxicity and improve treatment outcomes. Despite implementation challenges, recent technological advances and deeper circadian insights are enabling personalized treatment development. This study highlights the therapeutic potential of synchronizing cancer therapies with circadian rhythms to improve outcomes.

Keywords: Cancer, Circadian clocks, Circadian rhythms, Chronotherapy

1. Introduction

Circadian rhythms are 24-hour internal cycles regulating physiological processes like sleep, hormone release, and metabolism [1]. The biological clock, mainly in the hypothalamus, controls it and significantly impacts health [2, 3]. Think of it as the conductor of an orchestra, making sure that every instrument plays in harmony. However, modern life disrupts these rhythms through shift work, artificial light, and erratic schedules, which have far-reaching implications, particularly for the development of cancer [4]. Essentially, when the conductor loses control, the orchestra descends into disharmony. On a cellular level, such an episode can have adverse consequences. Circadian rhythm disruptions, caused by genetics, environment, or lifestyle, may result in sleep disorders, metabolic syndrome, and cardiovascular disease [5]. Increasing evidence associates circadian rhythm disruption with higher cancer risk [4]. The IARC classifies shift work with circadian disruption as a potential carcinogen. It follows that the body's complex timing mechanisms are not just related to feeling tired or energetic, but to something more basic: preventing cellular chaos. At a molecular level, the circadian clock plays a major role by managing important processes that are involved in the formation of tumors. It precisely regulates critical biological processes, including cell cycle control, DNA damage response, programmed cell death, and metabolic regulation [6]. As a consequence, this disruption facilitates the survival of malignant cells. The circadian rhythm protein BMAL1 serves as a pivotal regulator in cancer progression, modulating multiple signaling pathways that may either

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stimulate or suppress tumorigenesis. Specifically, BMAL1 activates oncogenic pathways, including the c-Myc pathway, which governs cellular proliferation and division [7, 8]. BMAL1 additionally activates the Wnt/β-catenin signaling pathway, which is intricately linked to enhanced tumorigenesis and metastatic progression. Furthermore, BMAL1 modulates the activity of p53, a renowned tumor suppressor protein. The aberrant regulation of BMAL1 can diminish p53 functionality and impair cellular capacity to respond to DNA damage [4].

The encouraging development lies in the fact that elucidating these intricate interrelationships between circadian rhythms and oncogenesis paves the way for novel therapeutic strategies. Chronotherapy is a treatment strategy based on the biological principles of circadian rhythms that aims to optimize the timing of drug therapy in order to increase its efficacy and minimize side effects. The best thing to do is work with your body's natural rhythms, not against them. Chronotherapy seeks to optimize patient outcomes by strategically administering chemotherapy, radiation therapy, and other therapeutic modalities during specific circadian phases when malignant cells exhibit heightened vulnerability while minimizing toxicity to healthy tissues [8]. Clinical investigations have demonstrated that chronotherapy, as a method to align the treatment with the natural rhythms of the human body, has yielded encouraging outcomes. This method has been found to enhance the efficacy of a multitude of chemotherapy agents by optimizing therapeutic indicators. Moreover, it has succeeded in mitigating the severity of adverse reactions commonly associated with such treatments, thereby significantly enhancing the quality of life for patients. For instance, targeting BMAL1's regulatory influence on key signaling pathways such as Akt/mTOR and Wnt/β-catenin may provide a strategic approach to suppress tumorigenesis [9]. Similarly, augmenting the tumor-suppressive functions of Rev-ERBα/β constitutes an additional promising therapeutic approach. Nevertheless, the clinical translation of chronotherapeutic strategies continues to encounter significant implementation challenges. Patient compliance with precisely timed treatment schedules, healthcare system constraints, and interindividual variability in circadian rhythms all pose logistical hurdles [10]. However, as technology advances and our understanding of circadian biology deepens, personalized chronotherapy approaches are becoming increasingly feasible. Ultimately, research on circadian rhythms and cancer is a compelling reminder that our biology is interconnected. Research shows that optimal health is not only about what we do but also when we do it. As we continue to unravel the intricacies of the body clock, we may find new strategies to prevent and treat cancer, paving the way for a future where treatments are not only effective but also in sync with natural rhythms. This systematic review endeavors to comprehensively delineate the contemporary advancements in chronotherapeutic research within the field of oncology through a meticulous analysis of findings derived from randomized controlled trials pertaining to both chemotherapeutic and radiotherapeutic interventions.

2. Molecular mechanisms linking circadian dysfunction to cancer

The complex link between circadian rhythms and cellular processes is becoming a key area of cancer research. As organisms evolved to synchronize with the 24-hour circadian rhythm, our physiological processes became regulated by an endogenous biological clock that orchestrates fundamental cellular functions, encompassing cell cycle regulation, DNA repair mechanisms, and metabolic homeostasis. However, modern lifestyles often disrupt these rhythms, leading to a state of circadian misalignment that has profound implications for health, particularly in the context of cancer [11, 12]. A more comprehensive elucidation of these molecular interconnections is consequently imperative for the formulation of efficacious strategies in both cancer prevention and therapeutic interventions [11]. The perturbation of circadian rhythms may precipitate aberrant cellular proliferation, heightened genomic instability, and diminished apoptotic responsiveness. As such, the interplay between circadian dysfunction and cancer is complicated, and the influence of circadian clock genes is a necessary

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condition for understanding. The regulatory impact of the circadian clock on cell cycle progression and DNA repair mechanisms constitutes a fundamental determinant in the preservation of genomic stability [12]. Clock genes, including BMAL1, PER, and CRY, serve as pivotal regulatory elements in cell cycle checkpoint control, guaranteeing the precise execution of DNA replication and cellular division processes. BMAL1 and CLOCK form a heterodimer that activates PER and CRY genes. PER and CRY proteins then accumulate and inhibit CLOCK and BMAL1 transcription, creating a negative feedback loop. Disruptions to this intricate system can result in uncontrolled proliferation and genomic instability, both hallmarks of cancer [12]. The protein p53, which suppresses tumors and is vital for coupling circadian and cell-cycle oscillators, is also affected by circadian dysregulation [11]. The Bmal1 gene exhibits anti-oncogenic potential through its activation of the p53 tumor suppressor pathway [13]. The dysregulation extends to apoptosis and autophagy, key cellular processes that maintain cellular health. Apoptosis, or programmed cell death, eliminates damaged or unwanted cells, while autophagy involves the degradation and recycling of cellular components. The circadian clock regulates both pro-apoptotic and anti-apoptotic (BCL-2) pathways, and dysfunctional circadian control can lead to resistance to programmed cell death, a characteristic of cancer cells. Moreover, circadian rhythms influence autophagy, the altered regulation of which is implicated in cancer progression. Metabolism, another critical area, is also governed by the circadian clock, influencing glucose metabolism, lipid synthesis, and oxidative stress [14]. In normal cells, metabolic processes are tightly controlled by the circadian system, but tumor cells often exhibit aberrant circadian clock function, disrupting these metabolic rhythms [14]. This misalignment can promote the Warburg effect, characterized by aerobic glycolysis in cancer cells, which facilitates rapid proliferation and survival [12]. Key metabolic regulators, including SIRT1 and AMPK, significantly contribute to this regulatory mechanism [11, 15]. In essence, AMPK activation exerts antitumor effects by negatively modulating the Warburg effect [15].

3. Circadian disruption as a risk factor for cancer

Epigenetic changes, like DNA methylation and histone modifications, are important ways to control gene expression without changing the actual DNA sequence [13]. The circadian clock influences these epigenetic processes, and aberrant clock gene expression can lead to epigenetic instability [16]. Studies have demonstrated significant alterations in DNA methylation patterns in cancer, indicating that DNA methylation at clock genes may serve as a critical terminal modification. Furthermore, shift work and exposure to artificial light have been shown to induce epigenetic modifications, which may potentially influence the expression patterns of oncogenes and tumor suppressor genes [17]. Shift work and light pollution represent significant lifestyle factors contributing to circadian disruption and increased cancer risk. Epidemiological evidence increasingly links night shift work to an elevated risk of breast, prostate, and colorectal cancers [11]. The suppression of melatonin, a hormone with tumor-suppressive properties, is a key factor in this association. Nocturnal light exposure, a prevalent condition among shift workers, significantly diminishes melatonin production, thereby potentially impairing its anticancer properties. Shift work is frequently accompanied by confounding variables, indicating the necessity for further comprehensive studies to substantiate the correlation between shift work and elevated cancer risk. Furthermore, disruptions in circadian hormone rhythms, such as cortisol, insulin, and leptin, also contribute to cancer risk [11]. Cortisol circadian rhythms, for instance, have been identified as a potential prognostic indicator in both lung and breast cancer. The complex nature of cancer is further complicated by the existence of genetic mutations in circadian clock genes. Mutations in genes like BMAL1, PER2, and CRY1 have been associated with increased tumorigenesis. The ClockΔ19/+ mutation, for instance, has been demonstrated to synergize with p53 mutations. Additionally, polymorphisms in circadian clock genes may function as potential biomarkers for cancer risk; however, the mechanistic implications of these polymorphisms require

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further elucidation [11]. It has been demonstrated that genetic variations in circadian clock genes are significantly correlated with an elevated risk of breast carcinoma. Furthermore, genetic mutations can induce profound circadian rhythm disruptions, which may exert a substantial influence on tumorigenic processes.

The immune system, under circadian control, plays an important role in maintaining immune surveillance. Disruption of circadian rhythms can result in immune dysregulation, adversely affecting T-cell activity, natural killer (NK) cell function, and cytokine secretion. The core circadian regulators Bmal1, Clock, and Cry have been shown to modulate the activity of NF-κB, a pivotal regulator of inflammatory responses. Furthermore, the perturbation of physiological cytokine oscillations, induced by oncogenic transformation, may significantly influence the tumor microenvironment and adjacent tissues [11]. Chronic circadian disruption can promote pro-inflammatory states, which contribute to tumor progression. These findings underscore the pivotal role of circadian rhythm maintenance in optimizing immune function and preventing cancer. The burgeoning comprehension of the circadian clock's involvement in oncogenesis is unveiling novel therapeutic avenues.

4. Circadian-based cancer therapies

Chronotherapy, an innovative cancer treatment approach, leverages our body's 24-hour circadian rhythms. These rhythms regulate key biological processes, including cell division and immune function. The therapy targets chemotherapy timing to maximize cancer cell vulnerability and normal cell resilience [18]. The premise is straightforward: aligning drug delivery with the body's internal clock reduces toxicity, boosts efficacy, and enhances patient outcomes. This personalized approach marks a major advancement in cancer care, moving from a uniform model to a more tailored understanding of individual biological rhythms. Chronotherapy's efficacy relies on synchronizing treatment with the body's circadian rhythm, which regulates crucial cellular functions including drug metabolism, DNA repair, and cell cycle [18]. Drug-metabolizing enzymes, including cytochrome P450, show circadian variations, affecting drug plasma levels and efficacy. DNA repair activity also fluctuates daily, peaking when cells are less active. By utilizing these cycles, physicians can schedule chemotherapy to enhance drug metabolism, minimize toxicity, and maximize the effect on cancer cells. Timing is indeed crucial in cancer treatment. Clinical trials strongly support chronotherapy's benefits. A study on non-small cell lung cancer patients with brain metastasis revealed longer median survival for those receiving radiotherapy before 12:30 h compared to evening treatment. Research also reveals sex-specific responses, with irinotecan better tolerated in mornings for men and afternoons for women with metastatic colorectal cancer [18]. These findings emphasize the need to consider individual chronotypes and gender differences in treatment design. However, implementing chronotherapy faces practical challenges, including hospital scheduling, patient compliance, and accurate circadian rhythm assessment. Notably, breast cancer patients receiving afternoon radiotherapy experienced less skin toxicity than morning recipients, highlighting the biological clock's role in treatment outcomes.

Chronotherapy aims to optimize treatment timing, but a more direct approach targets clock genes like BMAL1, CLOCK, PER, and CRY to disrupt cancer progression. These genes control the circadian clock and affect tumorigenesis-related processes like cell cycle regulation, DNA repair, and metabolism [18, 19]. By directly modulating the activity of these genes, researchers hope to restore normal circadian function and inhibit tumor growth and metastasis. It’s a bold approach, attempting to rewire the very circuitry of cancer cells. Inhibiting BMAL1 and CLOCK shows promise as a cancer therapy. These core clock genes control proteins regulating cell cycle, DNA repair, and apoptosis [19]. BMAL1 suppression in nasopharyngeal carcinoma reduces proliferation and increases radiosensitivity, indicating therapeutic potential. Deletion of BMAL1 has also been shown to protect from tumor initiation and progression in a cutaneous squamous tumor model [20]. But, as always,

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there are caveats. Clock genes promote tumor growth based on cancer cell status or type. BMAL1 silencing significantly increased apoptosis and caused mitotic and morphological abnormalities in malignant pleural mesothelioma (MPM) cells [20]. Manipulating CRY proteins, key components of the circadian clock, also presents a therapeutic strategy. PER1 interacts with the checkpoint kinase Chk1 and regulates the expression of the p16-INK4A gene, which serves as a critical inhibitor of CDK/cyclin complexes. Experimental evidence demonstrates that c-Myc expression is transcriptionally regulated and suppressed by the CLOCK/BMAL1 complex, while its stability is modulated by PER1. CRY1 promotes p53 degradation in bladder cancer cells by facilitating its binding to MDM2, enhancing drug sensitivity. Further research is required to explore the therapeutic potential of targeting clock genes in cancer.

Melatonin, produced by the pineal gland, plays a crucial role in cancer prevention and treatment. Beyond regulating sleep, it demonstrates tumor suppression, circadian regulation, immune modulation, and anti-proliferative effects. Its low toxicity makes it a promising adjuvant therapy to boost conventional treatments' efficacy and reduce side effects. Melatonin has been shown to regulate a wide range of cellular processes relevant to cancer development and progression. Melatonin selectively targets cancer cells while protecting normal cells by restoring circadian rhythm and reducing chemotherapy toxicity [20]. It acts as an antioxidant, scavenging free radicals and protecting DNA. Studies show melatonin's anticancer effects stem from receptor-independent mechanisms like antioxidant activity, apoptosis regulation, tumor metabolism modulation, immune enhancement, angiogenesis suppression, and circadian rhythm maintenance. Melatonin's multifaceted mechanisms and low toxicity make it a promising cancer therapeutic. It shows efficacy against breast, prostate, and colorectal cancers. In breast cancer, it suppresses cell proliferation and migration by downregulating miR-24. In prostate cancer, it inhibits growth in both androgen-dependent and independent cells, with blue light enhancing its effects by reducing tumor growth rates and metabolic activities. In colorectal cancer, it dose-dependently decreases cancer cell proliferation and migration. However, assessment challenges persist due to varying measurement methods and circadian fluctuations.

Lifestyle and behavioral changes are essential for comprehensive cancer prevention and treatment [20]. Improving glucose metabolism and insulin sensitivity while reducing inflammation, all cancer risk factors, is achieved through time-restricted eating (TRE), which syncs metabolism with circadian rhythms to lower cancer risk. A Fred Hutchinson Cancer Research Center study revealed that morning exercisers have lower prostate and breast cancer risks compared to evening exercisers. Aligning peripheral clocks with the central circadian rhythm enhances glucose metabolism and insulin sensitivity while reducing inflammation—all of which are critical factors in lowering cancer risk. As de Cabo and Mattson noted, time-restricted eating's full potential could decrease metabolic dysfunction, lower cancer risk, improve treatment response, and enhance survivors' life quality and longevity. Irregular sleep patterns disrupt the internal clock, causing adverse health effects. Improving sleep hygiene and light exposure aids cancer prevention. Human cancer xenograft studies indicate daytime blue light enhances melatonin's nighttime tumor growth inhibition in prostate, liver, and breast cancers. Melatonin also reduces chemotherapy toxicity by restoring circadian rhythms. A meta-analysis links low melatonin levels with higher cancer incidence in patients exposed to nighttime light. This approach represents the future of cancer care [20].

The integration of chronotherapy, clock gene targeting, melatonin, and lifestyle interventions marks a paradigm shift in cancer care. Sulli et al. categorized chronotherapeutic approaches into three types: training, drugging, and clocking the clock. Recognizing circadian rhythms' impact on cancer biology enables a shift from conventional to personalized strategies. Current chronotherapy applications in cancer treatment are promising, cost-effective, and clinically feasible [19]. Although more research is needed to understand circadian regulation mechanisms, existing evidence is strong.

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5. Conclusion

In summary, the complex interplay between circadian rhythms and oncogenesis is indisputable. Disruptions to the circadian clock, caused by genetic mutations or environmental factors, increase the risk of malignancies like prostate, breast, and colorectal cancer. These disturbances affect cell proliferation, DNA repair, immune regulation, and endocrine homeostasis, promoting tumorigenesis. Core clock genes regulate downstream targets involved in hormonal and metabolic processes. As Chen Huang noted, "CLOCK and tumorigenesis mechanisms" are key research areas. Longitudinal studies on circadian gene expression across cancer subtypes are essential. Additionally, investigating circadian clock genes' role in cancer stem cell properties may reveal new therapeutic targets. Sulli et al. highlighted critical questions: "Do core clock gene alterations drive tumorigenesis via circadian rhythms?" and "Can circadian clock modifications promote metastasis, and how?" Addressing these questions will improve cancer prevention and treatment.

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