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AN OVERVIEW ON CANCER CHRONOTHERAPY

Rachana Botla*, Syeda Nishat Fathima
Jayamukhi College of Pharmacy, Narsampet, Warangal-506332, Telangana, India

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ABSTRACT
The circadian clock is a complex biological circuitry that controls the daily rhythm of functions such as sleep, body temperature, and digestion. The master "clock" is an area in the brain that senses environmental cues (such as light) and communicates information to secondary clocks in other organs. The breaking of circadian tolerance or disbalance in the circadian clock results in the outbreak of several diseases. The prime factors that play in a disbalance circadian clock are artificial light during day or night, unbalanced diet, work-life balance, and unbalanced lifestyle. Defects or disruption in normal circadian functioning and altered levels of clock gene expressions can increase the risk of prostate cancers, breast cancers, ovarian cancers, colorectal cancers, endometrial cancers, non-Hodgkin's lymphoma, pancreatic cancers, osteosarcomas, head and neck squamous cell carcinomas, acute myeloid leukemia, and hepatocellular carcinomas. Chronotherapy for cancer involves optimal timing of drug delivery based on individual circadian times, which can improve treatment tolerability and efficacy of anti-cancer medications.

KEYWORDS: *Chronotherapy; Cancer; Biological clock*

INTRODUCTION
Circadian rhythm is the 24-hour internal clock in our brain that regulates cycles of alertness and sleepiness by responding to light changes in our environment. The daily light-dark cycle governs rhythmic changes in the behavior and/or physiology of most species. Studies have found that these changes are governed by a biological clock, which in mammals is located in two brain areas called the suprachiasmatic nuclei. The circadian cycles established by this clock occur throughout nature and have a period of approximately 24 hours. [1] At cellular level Disruptions in age, environment, or genetic mutation can have adverse effects on the cellular function and health of an organism. The circadian rhythm uses positive and negative molecular feedback loops as a mechanism to regulate their expression. There are several identified clock genes, BMAL1/BMAL2, CLOCK, CRY1/CRY2, and PER1/PER2/PER3, that regulate and control transcription and translation. Expression of these core clock genes inside the cell influence many signaling pathways which allows the cells to identify the time of day and perform appropriate function. Furthermore, phosphorylation of core clock proteins leads to degradation to keep the 24-hour cycle in sync. The presence of circadian rhythms in cells with and without nuclei indicate that the molecular clock is autonomous and external cues can be utilized for regulation. [2] Cancer is the second leading cause of death in the world today, killing millions of people every year [3]. According to reports, it is generally associated with disrupted circadian rhythms caused by various factors, including genetic, environmental, and internal factors. Defects or disruption in normal circadian functioning and altered levels of clock gene expressions can increase the risk of prostate cancers, breast cancers, ovarian cancers, colorectal cancers, endometrial cancers, non-Hodgkin's lymphoma, pancreatic cancers, osteosarcomas, head and neck squamous cell carcinomas, acute myeloid leukemia, and hepatocellular carcinomas. Chronotherapy against cancers are dependent on the effect that the circadian rhythm exerts on multiple cellular processes, such as cell cycle, DNA repair, proliferation and apoptosis, and drug metabolism, which are crucial molecular determinants of cellular pharmacokinetics and pharmacodynamics of cytotoxia/cytostatic drugs. Chronotherapy is a treatment strategy that searches for the optimal time for drug administration in accordance with the body biological clock, in order to promote the therapeutic effect of anti-cancer drugs.

Mechanism of Circadian Rhythm
The circadian pacemaker is the suprachiasmatic nucleus (SCN) of the hypothalamus. As the body transitions from light to dark, the body sends inputs to the retinohypothalamic pineal pathway. During the light cycle, axons from the retinal ganglionic cells deliver signals that activate the suprachiasmatic nucleus via cranial nerve II, the optic nerve. The SCN then delivers a signal via the inhibitory neurotransmitter GABA (gamma-amino-butyric acid) that inhibits the paraventricular nucleus. Axons subsequently send impulses through the intermediate lateral column to inhibit the superior cervical ganglion thus inhibiting the sympathetic nervous system. As a result, melatonin does not get released from the pineal gland into circulation. As night approaches, the departure of light signals the retinal ganglion cells to inhibit the suprachiasmatic nucleus activating the paraventricular nucleus which then sends

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axons through the intermediolateral nucleus (IML) to the superior cervical ganglion stimulating the sympathetic nervous system which induces sleepiness. The pineal gland is mobilized to secrete melatonin into circulation. [4]

Molecular design of the mammalian daily clock

The core molecular clock is comprised of positive regulators (Bmal1 and CLOCK) and negative regulators (cryptochrome (Cry 1/2) and period-Per1/2). The protein clock Bmal1 heterodimerizes with CLOCK/NPAS2 to initiate the transcription of target genes through E-boxes present in the promoter region of target genes, resulting in the expression of Per and Cry genes. Per and Cry dimerizes and translocates to the nucleus after being phosphorylated by casein kinase 1 epsilon (CK1ε) and casein kinase 1 delta (CK1δ), respectively, and repress their transcription. The Per and Cry proteins inhibit the expression of Bmal1 and CLOCK, creating the core negative feedback loop. In turn, CLOCK-Bmal1 generates another negative feedback loop that upregulates the negative transcription of REV-ERB proteins and negatively regulates Bmal1 transcription, and RORα binding to RORE elements increases the expression of Bmal1. Additionally, Per and Cry genes are regulated by proteins such as AMP-activated protein kinase (AMPK) and CK1ε/δ by phosphorylation and subsequent degradation. This phosphorylation targets Per genes for polyubiquitination by βTrCP and, similarly, Cry1/Cry2 are phosphorylated by the Fox- proteins, FBXL3 and FBXL21, directing them to ubiquitin-mediated proteasomal degradation. Collectively, these feedback loops trigger circadian oscillations and subsequently regulate the circadian expression of downstream clock-controlled genes (CCGs). [5]

Chronobiology of Cancer

Cell proliferation in rapidly renewing tissues follows a circadian rhythmic pattern. In 24-hour synchronized diurnally active human subjects, the proportion of cells going through the S-phase of the cell division cycle in tissues like bone marrow, intestinal mucosa, buccal epithelium, and skin may vary by 50% or more over a 24-hour span. In diurnally active human subjects, the probability of cells being in the S-phase in bone marrow, intestinal, and buccal epithelia is highest between 8:00 a.m. and 8 p.m. and lowest between midnight and 4:00 a.m.

On the molecular level, circadian clock proteins operate during normal S-phase progression and regulate DNA synthesis and repair. The circadian clock genes modulate the cell's sensitivity to genotoxic stress, which may form the basis for the circadian time-dependent changes in the effect of genotoxic agents, both in carcinogenesis and in chronochemo- or chronoradiotherapy. The circadian clock acts as a tumor suppressor at the systemic, cellular, and molecular level by controlling the expression of cell-cycle and tumor-suppressor genes at the transcriptional and posttranscriptional level. [6]

Mechanism of Circadian Rhythm in Cancer

The circadian clock plays an important role in tumorigenesis, tumor growth, metastasis, tumor immune escape, and other processes by regulating various biological functions, such as apoptosis and proliferation. The mechanisms may include the following: [7]

1. Tumour cells undergo a variety of biochemical reactions, including cell growth and senescence, cell proliferation and apoptosis, DNA damage repair process, and various metabolic processes; the circadian clock may affect tumour occurrence and development by regulating these reactions.
2. Cancer stem cells undergo tumorigenesis, development, and metastasis, and the circadian clock plays a crucial role in the stemness of self-renewal cancer cell subsets, such as acute myeloid leukemia and pleomorphic glioblastoma.
3. CLOCK components regulate the expression of angiogenic factors such as hypoxia-inducible factor 1α (HIF-1α), aryl hydrocarbon receptor nuclear translocator (ARNT), and vascular endothelial growth factor (VEGF) in cancer cells. Increased levels of these angiogenesis-promoting factors in the tumour microenvironment (TME) promote tumour development and metastasis.
4. CLOCK regulates the inflammation mediated by myeloid cells—a crucial cancer marker. For instance, in glioblastoma, CLOCK changes the microglial content of glioblastoma stem cells through transcriptional regulation of the chemokine olfactomedin-like 3. The infiltration of immune cells such as macrophages and neutrophils in renal clear cell carcinoma is associated with rhythmic changes in the expression of CLOCK-associated components (BMAL1, PER, etc.).
5. In addition, immune escape is an integral part of cancer progression. Changes in $CD8^+$ T cells often affect CLOCK expression in patients with glioblastoma multiforme.
6. The depletion of T cells and up-regulation of programmed death-ligand (PD-1) in patients with cancer may be associated with the widespread mutation and genomic instability of the CLOCK gene.

Targeting circadian rhythms in Cancer Treatment

Further insights into circadian rhythms and their related diseases have ignited growing interest in how these processes can be utilized to improve cancer prevention and treatment. Chronotherapeutic approaches for treatment of cancer can be categorised into three types: (1) training the clock: interventions to enhance or maintain a robust circadian rhythm in feeding-fasting, sleep-wake, or light–dark cycles; (2) drugging the clock: using small-molecule agents that directly target a circadian clock; and (3) clocking the drugs: optimizing the timing of drugs to improve efficacy and reduce adverse side effects [8]

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Applications of Chronotherapy in cancer

- The purpose of chronotherapy in anticancer medicine is to improve host tolerance and safety or tumour cytotoxicity.
- Chronotherapy in cancer is optimizing the administration time of anti-cancer treatment according to circadian rhythm and cellular phase to improve the efficacy against tumour cells while decreasing side effects on normal cells.
- Chronotherapy offers the opportunity to leverage existing treatments to extend patient survival and to increase their quality of life.
- Chronotherapy optimizes treatment timing based on the circadian rhythm of the individual patient, such that the treatment efficacy is maximized, and adverse effects are minimized.

Chronotherapy in Brest Cancer

Breast cancer growth is regulated by the circadian clock, with two daily peaks and clock-controlled genes. PER1 down-expression promotes tumor growth by enhancing the amplitude of these peaks. Vascular endothelial growth factor (VEGF) expression in malignant tumours is significantly increased and associated with poor prognosis. Circadian oscillation in hypoxic tumor cells and cancer cells implanted in mice controls VEGF transcription. Circadian variation of VEGF affects the pharmacological efficacy of antiangiogenic agents, with angiogenesis inhibitors showing the most repressive effect on tumour growth. The circadian rhythm plays a crucial role in the response to anticancer drugs in mice. Wild-type mice's sensitivity to cyclophosphamide (CY) treatment varies, with Clock mutant and Bmal1 knockout mice showing high sensitivity. However, mice with Cry1-/-Cry2-/- double knockouts show more resistance to CY. A recent study suggests a molecular relationship between circadian rhythm and oral drug absorption, with the expression of breast cancer resistance protein (BCRP) regulating oral drug absorption. The circadian clock-ATF4 pathway causes oscillation of BCRP function, causing a change in intestinal drug absorption. Understanding the difference in intestine absorption capacity between normal and cancer tissues can help predict the most favourable time for drug administration. [9]

Chronotherapy in Prostate Cancer

Chronotherapy has shown success in treating prostate cancer (PCa) and improving disease management. It can be applied to radiotherapy, as morning proton beam therapy for localized PCa significantly ameliorates worsening lower urinary tract symptoms compared to therapy around noon or late afternoon. Androgen deprivation therapy (ADT) is a common treatment for PCa patients, but most progress to castration-resistant PCa (CRPC). Circadian clock genes are involved in lipid metabolism regulation, and variants of circadian genes may be associated with varying serum sex steroid levels. ADT may aggravate circadian clock disruption and promote the progression of CRPC, making therapy targeting the circadian clock a new option for treating CRPC. Exogenous melatonin supplementation may resynchronize the circadian rhythm, providing a novel way in PCa management. Melatonin therapy inhibits tumor growth and reverses enzalutamide resistance in CRPC animal models with a disruption of circadian rhythm. It also inhibits PCa metastasis in both in vitro and in vivo models. Oral melatonin intake at human-achievable doses significantly inhibits PCa tumorigenesis in both in vitro and in vivo models. Other pharmaceutical agents that directly target the circadian clock might also be a new option. Longdaysin and KL001, small molecules that lengthen the circadian period and lead to PER1 degradation, have shown potential therapeutic potential when combined with chronotherapy. Circadian rhythm may also help in surveillance of PCa metastasis, as daily fluctuations in circulating tumor cell (CTC) count peaked during the nocturnal active phase in rodents. [10]

Chronotherapy in Glioblastoma

Temozolomide (TMZ), a standard treatment for Glioblastoma, has been studied for its potential to regulate toxicity in both humans and mice. TMZ has a short half-life in plasma and easily crosses the blood-brain barrier, so studies have explored administering it based on the circadian rhythm in humans and mouse Glioblastoma cells. The sensitivity of Glioblastoma cells to TMZ-induced DNA damage, apoptosis, and growth inhibition was most pronounced around the peak of BMAL1 expression in the morning for both humans and mice. However, the active phase of mice occurs during the lights-off period, so considerations for shifts in the endogenous CR need to be taken into account. Adapting TMZ administration to the peak of BMAL1 expression in Glioblastoma cells can enhance its efficiency. [11]

Chronotherapy in Colorectal Cancer

Chronotherapy consists of chemotherapy delivery according to circadian rhythms. These genetically based rhythms modulate cellular metabolism and cell proliferation in normal tissues. As a result, both the host tolerance and antitumor efficacy of 5-fluorouracil (5-FU) and oxaliplatin (L-OHP), like 30 other anticancer drugs, vary largely according to the dosing time in laboratory rodents. The transfer of this concept to the clinic is aimed primarily at increasing the dose-intensity of the therapy through adjustment of drug-delivery to 24h rhythms in host tolerance. A specific technology (programmable-in-time infusion pumps) enables administration of chronotherapy to fully ambulatory patients. Phase I-III clinical trials show chronotherapy significantly increases tolerance to high doses of cancer drugs and improves antitumor activity in patients with metastatic colorectal cancer. These safe conditions of drug-delivery led to the first demonstration of the high activity of the 5-FU-leucovorin-L-OHP protocol. Chronotherapy with these three drugs also allows surgical removal of previously unresectable liver and lung metastases. [12]

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Perspectives

Circadian disruption is an independent risk factor for cancer and has been classified as a carcinogen. As described herein, perturbations of the circadian clock strongly influence neoplastic transformation and tumor growth through alterations of multiple cancer regulatory pathways including cell cycle, apoptosis, DDR, and metabolism. While the robust link between circadian dysfunction and cancer is well established, mechanistic understanding is nascent. Therefore, it is imperative to continue to elucidate the mechanisms by which the mammalian circadian clock regulates cancer progression. [13]

CONCLUSION

Understanding the relationship between cancer and the circadian clock offers possibilities for new and effective cancer treatments and would help develop chronotherapeutic approaches to overcome cancer progression.

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