The Connection Between Circadian Disruption and Cancer Risks

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Abstract

The circadian rhythm is an essential biological mechanism that uses the 24-hour geophysical cycle to regulate the body's physiological and behavioral processes. It operates on a complex molecular interaction system that coordinates gene expression, protein synthesis, and post-translational modifications. Disruption of this rhythm due to jet lag, shift work, and other unhealthy lifestyles has been linked to various health disorders, including cancer. Recent studies have suggested a strong association between circadian disruption and development cancers, such as breast cancer, lung cancer, and glioblastoma. Understanding the connection between circadian disruption and cancer and the mechanisms underlying this connection is essential for developing new cancer therapies. In this review, we provide an updated account of key circadian mechanisms and their regulations on human health. We examine the adverse impact of circadian disruption on health using lung cancer and glioblastoma as case studies. Finally, we also discuss the potentially promising cancer treatment of chronotherapy, which targets components of the circadian cycle. We believe that future research into circadian rhythm and cancer would encourage the progression into a new era of cancer medicine.

Keywords: Circadian rhythm, Cancer, Circadian disruption, Chronotherapy

Background

Every living organism on Earth has a routine cycle following environmental shifts between day and night. However, such daily rhythms are not triggered solely by external cues, such as the presence of sunlight. Rather, it is a self-sustaining rhythm regulated by a complex set of intrinsic biological mechanisms. It is generally believed that the endogenous timer, known as the circadian rhythm, has evolved for organisms to adapt and use the 24-hour geophysical cycle for maximum survival and competitive advantage. The circadian rhythm is an essential biological mechanism in that it regulates both physiological and behavioral processes, as well as the immune functions of the body. Disruption of this rhythm has been linked to various health disorders, including cancer. Recent studies have suggested a strong association between circadian disruption and cancer development. This literature review will examine the evidence linking circadian disruption to cancer and discuss potential mechanisms underlying this connection.

Regulation of Circadian Rhythms in the Human Body

Systemic Circadian Regulation, melatonin, and orexin

The circadian rhythm in the human body is controlled by an autoregulatory transcription-translation feedback loop that operates at two levels – systemic and cellular (Ruan et al. 2021). At the systemic regulatory level of the circadian clock, the suprachiasmatic nucleus (SCN) acts as a master pacemaker. The SCN is a small region in the brain's anterior hypothalamus that plays a crucial role in regulating sleep-wake cycles, hormone secretion, and metabolism throughout the body (Ruan et al., 2021). The SCN receives light input from the retina and synchronizes the body's internal clock to the external environment.

The SCN controls the circadian secretion of diffusible endocrine signals, including melatonin and orexin, through a complex network of signaling pathways. The SCN sends signals to the pineal gland to regulate melatonin secretion via sympathetic neurons. In contrast, the SCN sends signals to the lateral hypothalamus to regulate orexin secretion via glutamate and GABAergic neurons. Both melatonin and orexin convey circadian information from the SCN to peripheral tissues (Ruan et al., 2021).

Melatonin is a hormone that plays a vital role in regulating sleep-wake cycles. The SCN controls melatonin secretion from the pineal gland by directly innervating the gland's sympathetic neurons. In low-light conditions, the SCN induces the synthesis and release of melatonin by activating two melatonin receptors (M1 and M2) that inhibit neuronal firing and promote sleep at night (Ruan et al., 2021). By regulating the secretion rhythm, the SCN enables melatonin secretion to peak at night and decrease during the day. On the other hand, orexin is a neuropeptide that plays a crucial role in regulating wakefulness. The SCN regulates the secretion of orexin by directly innervating orexin neurons in the

lateral hypothalamus. When light is present, the SCN receives signals from light and activates the release of orexins, which bind to two orexin receptors (OX1R and OX2R) and activate the cortex, thus suppressing REM sleep, promoting the transition from NREM sleep to wakefulness and stabilizing wakefulness (Ruan et al. 2021). Opposite to the pattern of melatonin secretion, orexin expression is highest during the day and lowest at night. The secretion of melatonin and orexin occurs in an oscillating pattern, which allows the 24-hour sleep-wake cycle to be maintained.

Cellular Circadian Regulation

At the cellular level, circadian rhythm is regulated by a set of molecular mechanisms, even with the absence of such external cues as light. This review will emphasize the core loop of the mechanism, which involves a complex system of molecular interactions that coordinate gene expression, protein synthesis, and post-translational modifications.

The core loop of circadian regulation in humans consists of a feedback loop between two groups of genes – the positive elements and the negative elements. The positive elements include the transcription factors circadian locomotor output cycles kaput (CLOCK) and aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also known as BMAL1), which heterodimerize and bind to E-box elements in the promoter regions of genes encoding the negative elements, period circadian protein homologs 1, 2 and 3 (PER1, PER2, and PER3) and cryptochrome 1 and 2 (CRY1, CRY2) (Figure 1) (Takahashi et al., 2017). The negative elements are transcription factors that inhibit the activity of CLOCK-BMAL1 by forming complexes that repress their transcription. This feedback loop is modulated by several post-transcriptional and post-translational mechanisms. For example, CLOCK-BMAL1 activity is regulated by acetylation, which enhances its DNA-binding activity and its interaction with other transcriptional co-regulators (Figure 1). Additionally, the stability of PER and CRY proteins is regulated by phosphorylation and ubiquitination, which affect their degradation rates and their ability to inhibit the activity of CLOCK-BMAL1 (Figure 1) (Takahashi et al., 2017). As the protein levels of PERs and CRYs decline due to polyubiquitination and degradation during the night, the negative-feedback repression is suppressed, and the activity of CLOCK-BMAL1 transcription can be restored, starting a new cycle the next morning (Ruan et al. 2021). One core feedback cycle is approximately 24 hours long, thus regulating the circadian rhythm within the body.

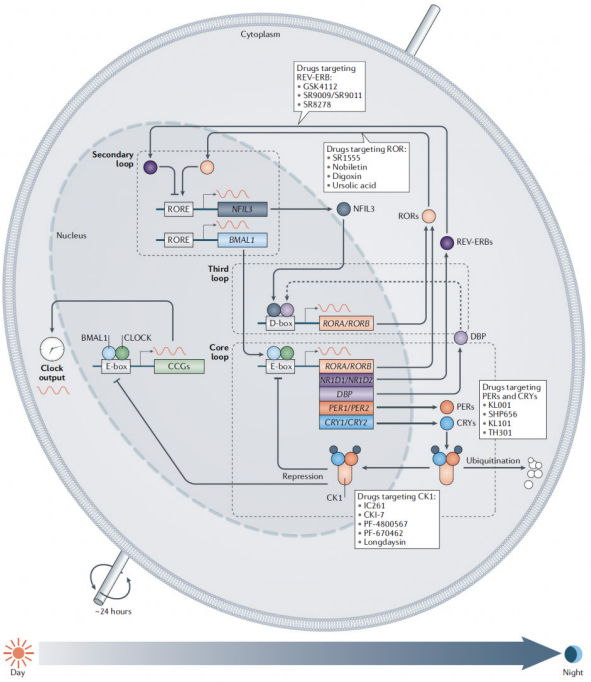

Figure 1. Cellular-level regulation of circadian rhythm (Ruan et al. 2021).

The circadian clock is also regulated by several other molecular pathways and feedback loops. In the secondary loop, two subfamilies of nuclear receptors, REV- ERBα and REV- ERBβ (encoded by genes NR1D1 and NR1D2), act as repressors, while RAR-related orphan receptors (RORs) α, β, and γ act as activators to regulate BMAL1 and other target genes during nighttime (Figure 1) (Takahashi et al., 2017). This regulation occurs through the ROR/REVERB-response element (RORE) promoter elements (Figure 1) (Ruan et al. 2021). In the third loop, the D-box, which is another vital circadian promoter element, is activated by D-box binding proteins (DBP) and repressed by E4 promoter-binding protein 4 (Figure 1) (E4BP4; also known as NFIL3). The ROR, NR1D, DBP, PER, and CRY genes are called core clock genes (CCGs) (Takahashi et al., 2017). The activation and suppression of the E-box, RORE, and D-box elements in the gene promoter regions of CCGs are responsible for their transcriptional regulation by the three loops of the circadian clock (Ruan et al., 2021).

Recent studies have shown that circadian regulation is not restricted to the central pacemaker in the SCN but also operates in peripheral tissues and organs. The peripheral cellular regulation of circadian rhythm in the human body is a complex and dynamic process that involves the interaction of multiple genes and proteins and is entrained by the SCN and responds to external cues such as light, food, and temperature (Ruan et al. 2021). The peripheral clocks regulate local physiological processes such as

metabolism, cell proliferation, and immune function and also communicate with the central pacemaker to ensure the coherence of circadian rhythms across the body. Therefore, understanding the molecular mechanisms of circadian regulation is essential for developing new therapies for circadian disorders such as sleep disorders, metabolic diseases, and even cancer.

Circadian Disruption and Cancer Risks

Diseases can be associated with circadian disruption in many ways. The World Health Organization states that disrupted circadian rhythmicity is a probable carcinogen. In modern society, unhealthy lifestyle such as shift-working is common and can disrupt circadian rhythm, enhancing the risks of many cancers. Several studies have investigated the association between circadian disruption and cancer risk. A prospective cohort study by Papantoniou et al. (2018) found that night shift work was associated with an increased risk of breast cancer. The study included 1,462 women with breast cancer and 1,567 healthy women as controls. The results showed that women who worked night shifts had a 30% higher risk of breast cancer compared to those who did not work at night. Another study by Travis et al. (2016) found that circadian disruption was associated with an increased risk of prostate cancer in men. In this study, the authors analyzed data from 2,790 men and found that those with a genetic predisposition to circadian disruption had a 40% higher risk of prostate cancer.

The mechanisms underlying the connection between circadian disruption and cancer are not fully understood. However, several hypotheses have been proposed. One hypothesis suggests that circadian disruption alters gene expression in cell division and DNA repair, leading to an increased risk of mutations and cancer development (Sancar et al., 2015). Another hypothesis suggests circadian disruption impairs immune function, making the body more susceptible to cancer (Dibner et al., 2010). In this review, we will examine circadian phase dissociation, caused by the alternation in the expression of circadian genes, sleep–wake cycles, and rhythms of key hormones, as being a risk factor of cancer, in which the overexpression or knockout of CCGs as a result of circadian disruption may aggravate cancer development.

Circadian Disruption and Lung Cancer Risks

Lung cancer is one of the leading causes of cancer deaths worldwide. The most prevalent lung cancer is the lung adenocarcinoma (LUAD) subtype of non-small cell lung cancer (NSCLC), with Kristen rat carcinoma (KRAS) being the most frequently mutated oncogene. Because the lung is under tight 24-hour circadian control, with the bronchiolar epithelial cells being key oscillators and regulators of lung respiratory functions, and because NSCLC is a cancer of epithelial origin, the disruption in circadian rhythm can lead to homeostatic dysregulation and increased cancer risks (Pariollaud et al., 2022).

A study by Pariollaud et al. (2022) found that chronic jet lag (CJL) greatly affected the expression of CCGs (BMAL1, CRY1, REV-ERBα) and WEE1 gene, a regulator of the G_2-M transition of the cell cycle, in CJL-affected mice, which experienced a 68% increase in tumor burden. This proves that circadian disruption impairs circadian clock components, leading to disrupted cell growth and uncontrolled cell proliferation, thus increasing tumorigenesis. The result of the study also shows that in CJL-affected mice, the gene heat shock factor 1 (HSF1) more readily activates the expression of heat shock proteins (HSPs) and the HSF1 cancer signature (HSFI-CaSig) network, which facilitates tumorigenesis and activates that facilitate malignant cell growth. An increase in HSF1 expression is also accompanied by a more robust expression of the BAG3 gene, which helps tumor cells evade apoptosis (Pariollaud et al., 2022). These findings suggest that the disruption in HSF1 signaling could be a key cause of circadian disruption and increased lung cancer risks. In addition, the study furthered into a potential treatment for NSCLC by using an HSF1 inhibitor (DTHIB) to stimulate the degradation of HSF1 protein, which successfully decreased the proliferation of lung cancer cells (Pariollaud et al., 2022). This result suggests the potential of new therapies against cancer that targets components of the circadian cycle.

Circadian Disruption and Glioblastoma Risks

Glioblastoma (GB) is a deadly form of brain cancer without existing effective treatments. Circadian disruption has emerged as a potential risk factor for GB. Several studies have investigated the relationship between circadian disruption and GB. In a study by Kettner et al., researchers found that shift work was associated with an increased risk of GB in humans. In another study by Jarabo et al. (2022), *Drosophila* with disrupted circadian rhythms were more likely to develop GB than those with normal circadian rhythms. The study shows that GB flies show disrupted circadian rhythms due to neurodegeneration by reduced neuronal insulin signaling and reduced synapse numbers (Jarabo et al., 2022). By adjusting the environmental signal to fit a 28-hour circadian cycle favored by GB, the researchers reduced circadian disruption caused by GB. They increased the survival length of the flies. This result suggests a potential link between circadian disruption and risks of GB, as well

as an innovative treatment potentially useful against GB by targeting the circadian rhythm.

Potential of Chronotherapy

Treatment options for cancer are constantly evolving. One potential treatment option that has emerged in recent years is chronotherapy, which involves administering medication by tailoring it to the patient's circadian rhythm, optimizing its efficacy, and minimizing side effects (Lévi et al., 2019). Additionally, chronotherapy may improve patient outcomes by synchronizing treatment with the body's natural rhythms. In a study by Sulli et al. (2018), the researchers modified the circadian cycle of mice with glioblastoma and successfully halted tumor growth. Specifically, they prolonged the production of REV-ERB proteins, which normally level up at night and inhibit the synthesis of essential nutrients, such as fat and recycled cell materials, required for cancer proliferation. Using two REV-ERB activators, SR9009 and SR9011, the team stopped cancer cells from developing while maintaining the normal function of other cells in the mice (Sulli et al., 2018). The study suggests that targeting circadian clock components can optimize cancer treatments' efficacy while minimizing side effects. Therefore, chronotherapy can be a potentially promising cancer treatment. However, further research is needed to fully understand the potential benefits of chronotherapy in cancer treatment.

Discussion

The evidence linking circadian disruption to cancer is growing. The studies discussed in this literature review suggest that circadian disruption may increase the risk of many deadly cancers, such as lung cancer and glioblastoma. While the mechanisms underlying this connection are not fully understood, several hypotheses have been proposed in which circadian disruption is correlated to dysregulation in the endogenous circadian clock at the molecular level that facilitates tumorigenesis (Ruan et al., 2019). It is important to acknowledge that adhering to a healthy circadian rhythm in everyday life may be a promising prevention strategy for reducing cancer risks. Furthermore, chronotherapy that targets components of the circadian cycle is emerging as an innovative and effective therapeutic strategy against cancer (Lévi et al., 2019). By modifying environmental cues, supplementing hormones as usual treatment, and correcting sleep-wake cycles, circadian rhythm may be restored, and cancer progression may be delayed or stopped. Nevertheless, current understandings are still insufficient to give a clear picture of circadian rhythm and cancer risks. Further research is needed to fully understand the link between circadian disruption and cancer and to develop strategies to mitigate this risk.

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