

The role of circadian rhythm in breast cancer, lung cancer, and colorectal cancer

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Abstract. Circadian rhythm is a biological rhythm system with a self-regulating function and a 24-hour cycle that is synchronized with the alternation of day and night and is driven by circadian clock genes and clock-control genes. The circadian clock governs and controls processes like immune, metabolism, endocrine, cell division and proliferation, apoptosis, and sleep, allowing cells, tissues, and organs to carry out different living activities in an organized and coordinated way. The root cause of tumors is gene mutations that cause the body to lose its normal regulation of cell growth. According to studies, cancer and problems of biological rhythm are tightly linked. Related epidemiological studies are related to the occurrence and inhibition of tumors by circadian rhythms the molecular mechanism of action has become a hot issue. In this paper, combined with relevant research at home and abroad, we focus on the specific association between circadian rhythm and the high occurrence of breast cancer, lung cancer, and colorectal cancer in three populations, as well as the part circadian clocks play at the molecular level in tumor development and progression, and discuss the timing of cancer. Therapeutics is a novel therapeutic field that has the potential to increase efficacy and minimize negative effects. A sounder theoretical foundation for the identification, management, and prognosis of clinical cancers will be made possible by the clarification of the circadian clock in cancer.

Keywords: Circadian rhythms, circadian clock, cancers, cancer therapy.

1. Introduction

Circadian rhythm refers to the phenomenon that under the periodic drive of circadian clock genes and clock-controlled genes, the body's physiology, metabolism, behavior, and other life activities show a regular oscillation phenomenon with a period of approximately 24 hours, and is regulated by the circadian clock as an endogenous oscillator. In mammals, the circadian clock consists of the central clock and the peripheral clock. The core circadian clock is housed in the hypothalamic suprachiasmatic nucleus (SCN). The major function of the SCN clock is to communicate retinal light information to peripheral clock systems, allowing internal body rhythms to be synchronized with external day and night cycles on a regular basis. This information is derived from the retinohypothalamic tract (RHT) [1].

Cell-autonomous regulatory feedback loops are a common feature of the circadian rhythm systems in species on Earth. The molecular clock oscillator in mammals is responsible for regulating the expression of several clock-controlled genes (CCGs), including signaling genes, metabolic genes, and epigenetic regulators, is composed of an autoregulatory feedback loop that switches between the CLOCK/BMAL1 transcriptional activator complex and its activators (ROR), repressors (PER/CRY, REV-ERB), or activators and activators (ROR). This molecular mechanism exists in the brain and peripheral organs, forming a circadian network throughout the body.

Circadian clocks govern several physiological processes in complex multicellular organisms and sustain equilibrium by establishing circadian cycles. Therefore, circadian rhythm disorders can easily lead to the occurrence of various diseases, including endocrine disorders, metabolic syndrome, and tumors. Numerous studies have demonstrated a link between cancer development and its progression and circadian rhythms. Cancer incidence and mortality are quickly growing globally, becoming the leading cause of death in each country and posing a significant barrier to extending life expectancy. The number of new cases of cancer worldwide is expected to reach 28.4 million by 2040[2]. The hallmark of tumorigenesis is the disruption of cellular and tissue homeostasis, resulting in rapid and

uncontrolled proliferation, heightened metabolic requirements, triggering of immune evasion, opposition to apoptosis, anticancer drug resistance, and the creation of an inflammatory environment that supports tumors [3]. Components of the circadian clock either directly or indirectly control the expression of genes in distinct cell types, and maintain the homeostasis of the body by affecting the daily rhythm of cells, including cell cycle, aging, autophagy, protein folding, DNA damage repair, redox control, and nutrition metabolism, among other things. These mechanisms are dysregulated when circadian rhythms are disturbed, which leads to a cellular environment that encourages carcinogenesis [4]. In addition, many clock proteins interact with proteins involved in cancer-related pathways, which are also implicated in cancer development.

Combined with recent domestic and foreign research, this article will focus on three high-incidence cancers—breast cancer, lung cancer, and colorectal cancer, including their epidemiological studies, causes, circadian rhythm disturbances, the role of circadian clock genes in carcinogenesis and how to use the clock to treat cancers.

2. Circadian rhythm and breast cancer

2.1. Factors affecting the occurrence of breast cancer

As a malignant tumor, breast cancer refers to the abnormal proliferation of breast epithelial cells caused by a variety of carcinogenic causes, with exorbitant morbidity and death, men and women are both at risk, but it is more common in women, and the incidence increases with age [5]. According to studies, there are numerous factors that are linked to breast cancer. Breast cancer risk is increased by genetic factors, and in women, a family history of the disease is typically present [6]. High-fat, high-calorie, or bad eating habits based on meat and seafood are important factors for the body to present an acidic body and cause breast cancer. An unhealthy lifestyle, long-term mental stress, long-term hormonal drug stimulation, age, multiple abortions, birth status, etc. can all induce breast cancer.

2.2. Epidemiological association between circadian rhythm disorder and breast cancer

The association between breast cancer and circadian clock abnormalities has been supported by some epidemiological data. Breast cancer risk is increased for women who work irregular shifts, such as nurses who perform extended night shifts in hospitals [7]. The risk increases with age and Increased weekly night shift hours. This was also demonstrated by the fact that mice that were simulated shift work developed significantly more mammary tumors than their littermates reared on a normal light/dark cycle [8]. The mammalian SCN's circadian pacemaker activity is disrupted by nighttime illumination, which ultimately affects the body's overall circadian rhythms [8]. One reason has to do with the production of melatonin: In human breast cancer cells, melatonin has anticancer effects, increases genomic stability, and can resist metastasis. Melatonin is released rhythmically from the pineal gland, but nocturnal light inhibits its production. Moreover, lowered melatonin levels at night may intensify the effects of estrogen, raising the risk of breast cancer. Another reason for changes in microRNA (miRNA) levels: Circadian rhythm disturbances have a major impact on miRNA variations, some of which are correlated with the expression of proteins involved in breast cancer, like NF-kB and Stat3. Losing the daily rhythm also had a boost to tumor growth: Animal experiments showed that tumors in mice with disrupted SCN grew much faster than controls.

2.3. Circadian clock genes' impact on breast cancer

Breast epithelial cells have been found to contain several circadian clock genes, and the expression of these genes exhibits a circadian rhythm that is regulated by the microenvironment of the cell and the stage of tissue development. The risk of breast cancer will rise because of circadian clock gene expression disturbance [8]. Some circadian clock genes are related to cell cycle control and apoptosis. PER1 and PER2 inhibit breast cancer by inducing apoptosis. Compared with normal breast, the expression of Per gene in breast cancer cells is reduced, which may be caused by the methylation of the Per promoter region. Furthermore, by altering cell metabolism, circadian clock genes can also

activate and disseminate cancer cells. Cellular switches SIRT1 and AMPK, which regulate metabolism, alter cellular function in response to a metabolic condition. In both cases, the biological clock is involved. The SIRT1 and AMPK signaling pathways may be directly impacted by clock disruption, impairing breast cell growth and apoptosis. The estrogen receptor (ER) gene is also regulated by PER1, and PER2 interacts with ER to repress estrogen-mediated transcription of ER target genes. Loss of ER expression is linked to an aggressive tumor phenotype. Breast cancer can also result from ER transcriptional activity dysregulation. Moreover, a current study revealed that matrix metalloproteinase 9 (MMP9), a factor mediating both local and distant tumor invasion and metastasis, is upregulated when BMAL1 is overexpressed, promoting breast cancer cells to invade and spread [9].

3. Circadian rhythm and colorectal cancer

3.1. Factors influencing colorectal cancer incidence

Colorectal cancer (CRC) is the world's third most common and second most fatal malignancy. There are some variations across different locations and populations, but colorectal cancer incidence and mortality are rising globally. Studies have found that colon cancer has a higher incidence rate in young people, which may be related to young people's exposure to more risk factors, such as lack of exercise, unhealthy diet, alcohol, obesity, smoking, etc. [10]. In addition, 10%-20% of colorectal cancer patients have a positive family history [11]. Inactivating mutations or deletions of the APC and TP53 tumor suppressor genes by the causative events in most CRCs [12], the occurrence of CRC often carries an activating mutation (Krasmut) of the KRAS gene, which drives the invasion and metastasis of colorectal cancer [13].

3.2. Association of circadian rhythm genes with the occurrence and progression of colorectal cancer

Before the identification of a molecular clock, the circadian rhythmic activity of the gut led to the inference of a circadian clock in the gut [14]. For example, colon activity is minimal during sleep but significantly increases upon awakening. Mucosal enzymes and gut microbiota also exhibit rhythmicity. Circadian clock genes have a significant impact on gut physiology, according to existing research. Colonic epithelial cells express Per1-2, Cry1, CLOCK, BMAL1, and REV-ERB and display circadian cycles. Per2 and BMAL1, which are found in the myenteric plexus and epithelial cells, are crucial for coordinating gastrointestinal functions like cell migration and proliferation, and BMAL1 can control the function of the intestine drug disposal system.

Circadian rhythm disruption mostly results in anomalies of the Per, Cry, ARNT1 (BMAL1), and CLOCK genes, which may impact colon cancer progression [14]. Per1-3 has tumor suppressor properties, its expression is downregulated in tumor tissues of colorectal cancer patients and regulates CRC progression by interfering with the cell cycle. Low levels of Cry2, which prevent colon tumor growth, were found in CRC tissues, whereas high levels of Cry1 are linked to lower patient survival. The major elements of the circadian clock system are CLOCK and its heterodimer BMAL1. Its altered expression in CRC tumor tissues correlates with clinicopathological characteristics and controls the proliferation of colorectal cancer cells by influencing metabolism and cell cycle.

4. Circadian rhythm disorder and lung cancer

4.1. Lung cancer causes and mechanisms

Globally, lung cancer is the primary cause of cancer patient mortality. They can be split into two groups from a histological perspective: 85% of lung cancer cases are non-small cell lung cancer (NSCLC), while 15% of lung cancer cases are small cell lung cancer (SCLC). Despite significant advances in diagnostic and therapeutic techniques, the NSCLC and SCLC survival rates remain low.

Smoking has a strong correlation with mortality and incidence of lung cancer[15], Nicotine (NNK) in tobacco is a strong carcinogen, has a high affinity for the lung, and mainly causes adenoma and adenocarcinoma. NNK can cause DNA damage through a variety of methods, ultimately cause gene mutations, including mutations of proto-oncogenes (such as RAS, MYC, ERB-B, etc.) and tumor suppressor genes (such as P53, Rb, etc.), causing the disorders of normal cell differentiation, growth, apoptosis, and other processes, which ultimately results in malignancies like lung cancer. Pahn are also important lung carcinogens in tobacco. In addition, tobacco also contains a large number of unstable oxidants and free radicals, which cause damage to biological macromolecules such as DNA, RNA, proteins, and fats. About 10-15% of lung cancers occur in never-smokers, which can be explained by other risk factors including lung infections, chronic lung disease, occupational and environmental exposure, and lifestyle choices. One important factor is genetics. Mutations in the TP53 tumor suppressor gene, EGFR variants especially T790M, ATM variants in the breast and pancreatic cancer susceptibility genes, and SFTPA1 and SFTPA2 mutations all increase the risk of cancer[16].

4.2. Circadian rhythm disorder and lung cancer

Studies have found that the biological clock has a certain relationship with the occurrence of lung cancer. Night shift workers have an increased risk of lung cancer, according to epidemiological studies [17]. In lung tissue, a total of 271 genes are regulated to varying degrees or involved in the etiology of several tumor types, and their expression shows rhythmic oscillations. Some of these genes are potential therapeutic targets and tumor biomarkers for lung cancer [18]. Many clock genes and clock-controlled transcription factor genes showed signs of circadian regularity in their expression [19]. It can be shown that the circadian clock controls lung tissue and is necessary to maintain the normal function of the lungs. Utilizing a lung cancer genetically engineered mouse model (GEMM), Papagiannakopoulos et al. found that circadian rhythm disturbances can promote lung tumorigenesis, and loss of core clock components *Per2* or *Bmal1* leads to proliferation, increased c-Myc levels, and increased metabolic activity. This accelerates tumor growth and alters immune function [20]. Hua H et al. discovered that the circadian rhythm gene *mPer2* may be crucial in the suppression of tumors by causing apoptotic cell death, which was ascribed to increased pro-apoptotic signaling and diminished anti-apoptotic activities [21]. Using a model of mice exposed to chronic circadian rhythm disruption (CJL), Pariollaud et al. demonstrated that the expression of heat shock factor 1 (HSF1) target genes was increased by CJL, thereby increasing the risk of Kras mutation-driven lung cancer [22].

5. Application of circadian clock in tumor therapy

Sulli et al. categorized interventions that exploit circadian rhythms to prevent or treat disease into three categories[23]: (a) interventions that maintain robust circadian rhythms during sleep-wake, eat-fasting, or light-dark cycles (training clocks), (b) adjusting the time of dose to increase effectiveness and decrease negative side effects, and (c) employ tiny molecule medications that specifically target the circadian clock or regions that are strongly associated to it. A phase III randomized clinical trial and meta-analysis assessing the importance of chronotherapy observed that treatment modalities incorporating circadian rhythms were five-fold more tolerable and two-fold more effective for the drugs studied than usual regimens, which demonstrated that the circadian clock could constitute a new therapeutic option.

5.1. Training clocks

According to research, preserving a healthy circadian rhythm by following regular daily eating and sleeping schedules may dramatically lower the chance of developing cancer [24]. Good sleep hygiene, cognitive behavioral therapy, and sleep drugs like melatonin have all been used for years by sleep researchers and medical professionals to treat issues like insomnia, sleep deprivation, and

prolonged sleep latency. Enhancing sleep strengthens at least one key output of circadian rhythms and may indirectly improve other components of daily rhythms, which benefits quality of life. Light is thought to be a major contributor to circadian rhythm disruption. Light at night can inhibit the secretion of melatonin and sleep motivation, which can promote sleep, thereby delaying falling asleep or affecting sleep quality. Therefore, blocking blue light at night becomes an important way to improve sleep. The timing of food intake has a greater impact on the peripheral circadian clock than light exposure [25], as a result, to keep healthy circadian rhythms in peripheral organs, time-restricted feeding (TRF) has become a behavioral intervention option.

5.2. Clocking drugs

Just as most biological functions are affected by changes in circadian rhythms, pharmacodynamics, and pharmacokinetics are also affected by these circadian rhythms. Pharmacokinetics consists of four phases: drug absorption, distribution, metabolism, and excretion, known as the ADME process. They exhibit circadian rhythms and express distinct drug-metabolizing enzymes and transporters. Different administration times can affect the ADME process and may alter the action and efficacy of the drug. Chemotherapy is one of the main methods to treat tumors. Studies have so far found a connection between chronotherapy and chemotherapy and identified the appropriate chronotherapy-appropriate chemotherapy medications. Ballesta et al. discovered that a drug's efficacy, side effects, and prognosis might all possibly be improved by timing it to the correct phase of the circadian cycle in cancer patients [26]. Hrushesky et al. showed that the timing of delivery had a significant impact on the chemotherapeutic efficacy and toxicity of doxorubicin and cisplatin in patients with advanced ovarian cancer by administering them at various times [27]. Oxaliplatin, fluorouracil, and folinic acid are less toxic and more pronounced with chronotherapy in metastatic colorectal cancer [28] as well as in other types of cancer including metastatic endometrial, bladder, and renal cell carcinoma Effect [29]. Additional instances include research on cisplatin-based chronotherapy, which can lessen the negative effects of chemotherapy in non-small cell lung cancer, such as leukopenia or neutropenia (grade 3 or 4) and the incidence of gastrointestinal adverse effects were (grade 2) significantly reduced [30]. In addition, a study developed a new mathematical model that combines the core clock network with the drug mathematical model to optimize the dosing time of irinotecan in colorectal cancer, which can be used to predict the optimal Timing of medication to support individualized treatment planning [31].

Clock gene expression, including those of BMAL1, CLOCK, PER, and CRY is also influenced by circadian rhythms in radiation therapy, another type of cancer treatment. Clock genes coordinate molecular activities and generate circadian rhythms that influence radiation therapy over 24 hours [32]. It makes cells more sensitive to treatment during certain periods. Stupp et al. discovered that the longevity of cultured brain tumor cells was significantly impacted by chronological exposure to a DNA-damaging chemical like temozolomide and radiation [33]. Akgun et al.'s study of patients with rectal cancer demonstrated that time-modulated radiation, whether used alone or in combination with other drugs [34], can improve the therapeutic effect.

5.3. Drugging clocks

Several metabolic or signaling pathways are frequently damaged in chronic disorders like cancer; the ideal medication would either promote or inhibit one of these afflicted pathways. There are currently two types of clock drugs: One category is those that can alter the core circadian clock genes' activity directly (such as ROR, REV-ERB, and CRY) or target core circadian clock gene regulators. ROR γ is highly expressed in metastatic castration-resistant prostate cancer (CRPC) tumors, and the expression of the androgen receptor (AR) is activated by ROR γ . In vivo, ROR antagonists stop the development of AR-expressing tumors and reestablish the sensitivity of drug-resistant tumors to Enzalutamide (ENZ), an androgen signaling inhibitor currently used to treat prostate cancer [35]. Numerous REV-ERB agonists identified in various studies have demonstrated anti-cancer effects against various types of tumors and may influence the formation of glioblastoma in vivo [36,37].

Moreover, studies conducted in vitro have demonstrated that pharmacological suppression of CRY lowers the growth of cancer cells [38]. The second class of medicines' target proteins is non-specific for clock components and is capable of phosphorylating or destroying clock elements in additional target proteins. These compounds include targeting casein kinase 1 ϵ , casein kinase 1 δ , and the F-box protein Fbxw7. An important target for antitumor therapy is the casein kinase 1 family, which includes two members (CK1 and CK1) that are considered to have essential functions in the circadian clock mechanism's control and are found in high concentrations in a range of tumor forms, including leukemia, breast cancer, pancreatic cancer, and ovarian cancer [39]. The ubiquitination and degradation of REV-ERB are encouraged by Fbxw7. In vitro and xenograft tumor growth was inhibited by forcing nuclear retention of Fbxw7 utilizing a particular inhibitor of nuclear export (SINE) [40].

6. Summary

The biological clock establishes regular patterns in various living activities to ensure body homeostasis. Tumor genesis and development are influenced by disruption of the circadian rhythm and changes to the core circadian clock. The finding of a link between cancer and the circadian clock gives rise to new possibilities for cancer treatment and prevention, as well as future directions for lifestyle interventions, diagnostic markers, genetic testing, chronotherapy, and, ultimately, new therapies that specifically target the clock's components. It has a great prospect for clinical applications. However, the future study must address several important issues, including: Is there a specific kind of tumor or stage at which circadian disruption is no longer a concern? What diagnostic standards are used to assess the effectiveness and prospective application of clock medications in cancer? The molecular mechanism of the effect of circadian rhythm on tumors also needs to be further studied.

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