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Circadian Disruption as a Driver of Carcinogenesis: Advances in Mechanistic Understanding

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Abstract:

The circadian rhythm of organisms is regulated by the biological clock, a regular circadian rhythm is crucial for the physiological balance of the body and has an inhibitory effect on the development of many diseases, especially cancer. The relationship between circadian rhythm and cancer includes cell cycle regulation, hormone level changes, immune and inflammatory responses, as well as metabolic and oxidative stress regulation, indicating that maintaining a regular circadian rhythm is of great significance in preventing and treating cancer diseases. This article discusses the intricate relationship between circadian rhythm and cancer, and explores the way that circadian rhythm disorders are involved in tumorigenesis mechanisms and promote cancer progression. Maintaining a healthy circadian rhythm cycle includes avoiding exogenous factors (shift work, jet lag, artificial lighting, irregular sleep patterns) and early detection of endogenous factores (genetic factors). Mutations in clock control genes and epigenetics can promote tumor growth and also affect the efficacy of therapeutic drugs, leading to the need to regulate circadian rhythms and specific timing of administration to enhance the drug efficacy. The growth of tumors is mainly stimulated by DNA damage and decompensation of tumor suppressor genes, and then developed through immune and inflammatory responses, which are closely related to the components of the biological clock. At present, chronotherapy has been continuously explored and experimented as a highly promising cancer treatment method, and may be applied in clinical practice in the future.

Keywords: Circadian rhythm; Cancer; Metabolism; Melatonin; Chronotherapy.

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1. Introduction

Organisms exhibit periodic changes in behavior and physiology in order to adapt to the repeated environmental changes that occur every day. The circadian rhythm refers to the physiological alternation that occurs in an organism throughout a day. This rhythm is widely present in animals, plants, and microorganisms, and its molecular basis and physiological functions have become one of the research hotspots in many biomedical fields. The interconnection between circadian rhythms and different systems within an organism maintains its homeostasis inside their body. The molecular biological clock encoded by genes generates the circadian rhythm, and its components work together to produce periodic changes. Circadian rhythms influence many important body functions, including hormone secretion, sleep-wake and immune-inflammatory responses [1]. These regular regulations and fluctuations are controlled by the biological clock, which coordinates many genes expression to maintain normal physiological functions of the body [2]. In addition, the disruption of circadian clock genes can lead to dysfunction of autophagy in immune cells, increasing the risk of cancer diseases [3]. Therefore, maintaining the stability of circadian rhythm plays an irreplaceable role in the physiological health of organisms. However, nowadays, due to many social factors, circadian rhythm disorder is very common in modern life, such as shift work, jet lag, artificial lighting, etc., all of which are prominent features of Modern lifestyle [4]. Insufficient sleep is the most common type of circadian rhythm disorder, which can disrupt the circadian rhythm, cause metabolic disorders, immune dysfunction, and other pathological processes [5, 6]. Existing studies have shown that circadian rhythm disorder is closely related to the occurrence and development of various cancers (such as breast cancer, prostate cancer, colorectal cancer, etc.), and its mechanism involves cell cycle regulation, DNA damage and repair, immune inflammatory response, and other aspects. Multiple studies and evidence indicate a high relevance between cancer cell metastasis, tumor growth, and immune escape of cancer cells and sleep deprivation [7, 8]. Inverted sleep duration, fragmented sleep, and other types of circadian rhythm disorders are also major life factors causing many chronic diseases. In addition, many epidemiological and experimental studies have found that circadian rhythm disorders are associated with an increased risk of various types of cancer. Cancer is a group of heterogeneous and large size malignant tumors, defined as uncontrolled cells proliferation and their spread ability throughout the body [9]. Excluding genetic factors, environmental factors are one of the most important factors affecting the development of cancer diseases. Among them, daily routine has a strong impact on the development and risk of cancer, and irregular sleep patterns leading to disrupted circadian rhythms can increase the risk of various cancers. In a normal circadian cycle, immune systems secrete cytokines and maintain the normal functioning of cells. When the circadian rhythm veers from its regular functional pathway, cytokines start to be overproduced, leading to immune system disorders and subsequently triggering tumors. Enhancing the diagnosing ability in cancer and optimize treatment devices can be achieved by examining cytokines and cancer-related parameters [10]. Besides, irregular sleep cycle oscillations can affect melatonin production, which is straightly responsible for regulating the expression of specific clock control genes, thus to prevent the formation and development of tumor cells [11]. Exploring this particular relationship can improve treatment methods and provide new opportunities for cancer treatment. However, despite extensive exploration in both areas, there are significant vacancy in the understanding of the interaction and intricate relationship between circadian rhythms and cancer across different literature. There are also many differences in the comprehending of how circadian rhythm disorders lead to developing, progressing and treating cancer. Therefore, exploring the relationship between circadian rhythm disorders and the occurrence and development of cancer not only helps to reveal the molecular mechanisms of tumor occurrence, but also provides theoretical basis for formulating prevention strategies and optimizing treatment plans. This inconsistency highlights the necessity of elucidating the intricate relationship between circadian rhythm and cancer diseases, especially the molecular mechanisms and research progress of the impact of circadian rhythm disorders on cancer occurrence. However, existing research still lacks a systematic summary of the molecular mechanisms underlying different types of circadian rhythm disorders and their differenzial associations with cancer types.

2. The Physiological Basis and Regulatory System of Circadian Rhythm

There is a core set of circadian clock genes located in the nucleus of the suprachiasmatic nucleus (SCN) neurons in the circadian rhythm. It forms clock proteins through transcription and translation, which in turn inhibit the expression of clock genes, forming a negative feedback mechanism. This process is regular and periodic, forming a cyclic rhythm. Therefore, clock gene polymorphism is associated with sleep and wakefulness time. In this group of clock genes, there is a type of E-box gene that is activated and promoted by heterodimers formed by BMAL1

and CLOCK proteins. Clock proteins are expressed more abundantly at dusk and less at dawn, forming a periodic cyclic rhythm. The expression of E-box is promoted by BMAL1 and CLOCK proteins, but inhibited by other clock control genes (CCGs), including key regulators of cell cycle such as p21 and Wee1. The PER protein expressed by Per1/2/3 gene and the CRY protein expressed by Cry1/2 gene bind and phosphorylate, enter the nucleus through CK1 protein from the cytoplasm, bind to BMAL1 and inhibit clock protein synthesis, thus forming a negative feedback loop. This cycle takes about one day and is gradually degraded by PER and CRY. The E-box gene and clock gene re express clock proteins, and the cycle is restarted. These transcription translation feedback loops drive the 24-hour periodic expression of gene products, jointly participating in the cycle and regularity of cyclic rhythms, thereby producing rhythmic physiological functions (Figure 1) [4].

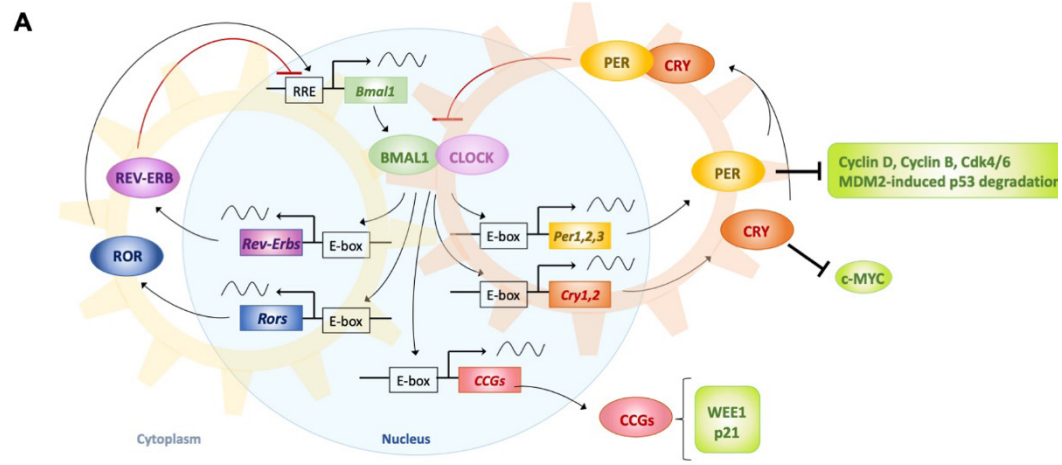

Fig. 1 Circadian Clock Feedback Loop and Cancer-Related Regulation [4]

The central clock integrates signals from the neuroendocrine pathways and autonomic nervous system, thus synchronizes with the light dark cycle from environment. In circadian rhythm, the immune system experiences a bidirectional change after activation, which is related to the balance of cytokines [12]. Th1 cytokines (such as IL-2, IFN γ, and IL-12) persist at night and are at higher levels during early sleep. Th cells producing IFN - γ/IL-4 moderately increase, leading to a peak in Th2 cytokine levels before waking up in the morning or during late sleep. Once this pattern is disrupted, cytokines become imbalanced, causing immune disorders tissue damage and chronic inflammation [13].

Melatonin is a pineal gland hormone with the highest blood levels at night and the lowest levels in the blood during the day. The mechanism of SCNrhythm production in controls its secreting level and mildly regulates the system. Melatonin also Feedback to the circadian oscillator that controles melatonin secretion (Figure 2) [14]. The circadian rhythm cycle could be synchronized by melatonin, thus melatonin has a hypnotic effect, such as inhibiting the driving force of circadian pacemakers for wakefulness, inducing sleep when the steady-state driving force of sleep is insufficient, causing a phase shift in the biological clock, and allowing the circadian rhythm stage with increased sleep tendency to occur at new and ideal times. Therefore, melatonin treatment can help treat diseases such as sleep delay syndrome and jet lag. Many abnormalities in circadian rhythms can affect the melatonin rhythm, thereby affecting the body health. Circadian rhythm is crucial for maintaining the homeostasis through the whole body. Keeping a good circadian rhythm is necessary for keeping the balance of general physiology and metabolism. Since the regulation of circadian rhythm, the stability of SCN and the clock gene network distributed in peripheral tissues is the basis for maintaining endocrine balance and immune function.

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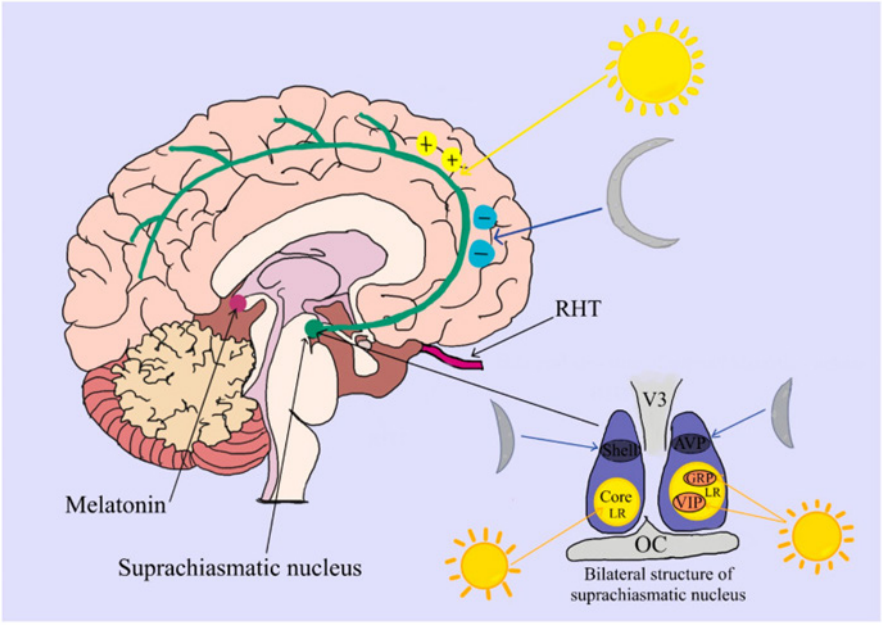

Fig. 2 Melatonin Secretion and Circadian Rhythm Regulation in the SCN [14]

3. Exogenous and Endogenous Triggers of Circadian Rhythm Disorder

Due to various social factors such as shift work, jet lag, artificial lighting, irregular sleep patterns, etc., the disrupted circadian rhythm has become a prominent feature of Modern life [4]. These factors are exogenous triggers for circadian rhythm disorders, and they are also the most influential type of trigger [15]. The fundamental orientation of these social factors is the irregularity of sleep and light cycles, which leads to disruption of circadian rhythms and subsequently endocrine disorders, resulting in imbalanced regulation of various hormones and ultimately causing diseases such as mental disorders, psychological disorders and cancer diseases. A case-control study designed by Fred Hutchinson Cancer Research Center showed that subjects who often stayed up at night had an increased risk of breast cancer [16]. Another independent cohort study of night shift workers and shift workers observed an increase in the prostate cancer incidence rate [17], endometrial epithelial malignancies [18] and non-Hodgkin's lymphoma [19]. Another factor, jet lag, arises from the difference between the body's biological clock and the light and dark cycles of the environment. Chronic and long-term jet lag among pilots and flight attendants can have more harmful effects than the people who experience brief jet lag in short period on their health. According to statistics, this group has a higher incidence rate of specific cancers, with skin cancer accounting for the highest proportion [20-23], followed by breast cancer [23, 24] and prostate cancer [20, 22]. To exclude the influence of cosmic radiation on cancer in aviation, another study calculated the data and shows that the prostate cancer's relative risk increased with the extention of long-haul flight hours but did not increase with estimated radiation dose [20]. This indicates that circadian rhythm disorder is a more significant influencing factor compared to radiation.

The endogenous triggers of circadian rhythm disorder are genetic factors, mainly including clock gene mutations and epigenetic abnormalities. The central clock in the nucleus of SCN neurons includes a series of clock genes, and the complex multi-level regulatory processes between genes jointly participate in the periodicity and regularity of the cyclic rhythm. If any gene or protein undergoes mutation or denaturation, the cyclic rhythm will become disrupted and no longer maintain regularity. Delayed sleep phase disorder is the most commonly diagnosed type of circadian sleep disorder [25]. Its clinical manifestation is a significant and sustained delay in the start and end time of sleep compared to the general social pattern, which is divided into congenital (hereditary) and acquired. The genetic and functional mechanisms of hereditary DSPD are strongly associated with mutations in the Cry1 gene. Cry1 acts a key regulator of circadian rhythm length, thus is the main transcriptional inhibitor in the negative feedback loop, which constitutes the core molecular clock. In general, Cry1 and the length of sleep cycles length have a positive correlation. In order to directly test whether the deletion of Cry1 exon 11 affects the biological clock, researchers did an expereiment, and the results showed that

the deletion of Cry1 exon 11 has a direct impact on the length of the circadian rhythm, which is consistent with DSPD symptoms [26]. Another well-known disease, familial advanced sleep phase syndrome (FASPS), is caused by mutations in the Per2 gene that result in early sleep cycle symptoms in patients. The patient became drowsy around 5pm, but became awake around 3am. This disease indicates that any mutation or denaturation of genes or proteins involved in regulating circadian rhythms can lead to changes in rhythm, not only forward or delayed, but also possibly prolonged or shortened cycles. Epigenetics refers to changes in the structure and function of genetic material caused by external environmental factors, such as DNA methylation and protein phosphorylation, without altering the genetic sequence. DNA methylation plays an significant role in Per2 gene regulation, and could lead to metabolic disorders if the methylation is dysfunctional [27-29]. The CpG methylation pattern in the Per2 gene is strongly associated with insulin resistance [30], which is one of the risk factors for type II diabetes. Bmal1 regulates the epigenetic state of enhancers, thus controls gene expression in response to inflammatory activation [31].

From this, it can be seen that there are many causes of circadian rhythm disorders, and the mechanisms and influencing processes are also very complex. Regardless of whether it is caused by external or internal factors, it is the central clock in the nucleus of SCN neurons - the clock control gene (CCG) - that is affected, thereby disrupting the circadian rhythm, causing damage to various functions in the body, and leading to a series of diseases and functional disorders, endangering human health and causing adverse effects [32].

4. Possible Mechanism of Circadian Rhythm Disorder Promoting Cancer Occurence

Cancer is a large class of heterogeneous malignant tumors. CCG, as a driving factor for circadian rhythm oscillations, exerts tumor suppressive effects in the human body [33]. However, if CCG is dysregulated, it can increase the susceptibility to cancer. The World Health Organization has defined circadian rhythm disorder as a possible carcinogenic substance. Research has shown that in certain human malignant tumors, key CCGs Per1/2/3, Cry1/2, Bmal1, and Clock can be dysregulated. Many cancers, including breast cancer, prostate cancer, pancreatic cancer, liver cancer, lung cancer, ovarian cancer and colorectal cancer, are closely related to the animal model of CCG genetic destruction [1] (Table 1). Therefore, restoring circadian rhythm may become one of the future treatment methods, while improving the prognosis, life, and status of cancer patients. To provide a more specific analysis and summary of the possible mechanisms by which circadian rhythm disorders promote cancer development, this article will elaborate on four aspects: cell cycle, hormone regulation, immune function, and oxidative metabolism.

Table 1. Summary of cancer types that may be affected by CCG dysregulation

Name of CCGs	Related cancers
Clock	Nephroblastoma, acute myeloid leukemia (AML)
Bmal1	Acute myeloid leukemia (AML), liver cancer, glioma
Cry1/2	Breast cancer, colorectal cancer, liver cancer
Per1/2/3	Glioma, breast cancer, prostate cancer, lung cancer, stomach cancer, colorectal cancer

4.1 Disruption of Gene Expression and Cell Cycle Regulation

Multiple studies have confirmed cells proliferation and cell cycle is regulated by BMAL1. Some scholars found that Bmal1 was down regulated in patients with pancreatic cancer (PC). To explore the mechanism of action of Bmal1 on PC, scholars used RNA seq to determine the sequence, and then analyzed the gene function and pathway enrichment. It was found that overexpression of Bmal1 led to significant reduction of PC proliferation and invasion and G2/M cell cycle stagnation. Conversely, low expression of Bmal1 would promote PC growth. In this experiment, Bmal1 was found to directly bind to the p53 gene promoter, thereby activating downstream tumor suppression pathways. Therefore, it proves a conclusion that BMAL1 exists as an anti-cancer gene in PC, and its anti-cancer effect is p53 dependent [33, 34]. In the central clock of the SCN, BMAL1 protein binds to CLOCK protein to form a dimer, which has been shown to regulate the expression of transcripts encoding the G2/M inhibitor Wee1, thus influence the cell cycle progression [35]. Given the role of Bmal in regulating the cell cycle, Per and Cry in CCG have inhibitory effects on the binding of BMAL to CLOCK. Therefore, PER and CRY are known as proteins that negatively regulate the biological clock,

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and their changes and abnormal expression also affect the regulation of the cell cycle. Similar to Bmal1, Per1/2 also interacts with p53, thus Per1/2 serves as a p53 dependent anti-cancer gene involved in combating cancer cell proliferation and invasion. In addition, PER1 and PER2 are also involved in the DNA damage response pathway, and their abnormal expression may lead to malignant transformation of cells by altering the cell cycle progression and checkpoint response to DNA damage [36]. Cry family genes play multiple roles in cancer types, and the mechanisms are very complex. The increased expression of Cry1 is associated with the progression of colorectal malignant tumors [37]. The survival rate of breast cancer patients is related to the high expression level of Cry2 [38]. A similar situation occurs in liver cancer, where low levels of Cry2 are straightly scaled to the short living time of liver cancer patients [39]. Follicular carcinoma and thyroid carcinoma is also associated with lower Cry2 levels [40]. Studies have shown that CRY2 plays a unique role in controlling DNA damage repair and genome stability [41].

4.2 Abnormal Hormone Regulation

From an endocrine perspective, circadian rhythms affect the hornones secretion such as melatonin, sex hormones and leptin, which play important roles in cell proliferation, diffusion, and death [42]. These hormonal rhythm changes can influence cell proliferation and apoptosis proportion, thereby facilitating the development of cancer. Melatonin, as a pineal gland hormone, is controlled by the rhythm of CCG expression, and its secretion amount and secretion time vary with the circadian rhythm. When melatonin binds to its receptor MT-1, cancer-related pathways are regulated. According to normal social norms, the level of melatonin in the blood is lowest during the day and reaches its peak at night. Melatonin has physiological effects such as aiding sleep and regulating body temperature, as well as regulating molecular pathways related to cell survival and inflammation. The disruption of circadian rhythm caused by artificial lighting, chronic jet lag, and other factors can disrupt the normal secretion rhythm of melatonin. An experiment has shown that exposure to nighttime light reduces the production of melatonin at night [4]. The level of melatonin will affect the estrogen receptor concentration of hormone dependent estrogen positive breast cancer, increase the production of estrogen, thus up regulating tumor metabolism, stimulating its growth, leading to a higher risk of breast cancer [4]. Androgens play an important role in both the normal development of the prostate and carcinogenesis. In normal prostate, CCG expression and androgen receptors exhibits diurnal oscillations. Per1 inhibits androgen receptors's transcriptional activity, so one of the triggers of prostate cancer is downregulation of clock genes. The results of some studies support that there have relationship between genetic differences in circadian rhythm genes and prostate cancer development. Therefore, excluding known prostate cancer risk factors such as aging, family history and ethnicity, circadian rhythm disorder may become a new risk factor. On the other hand, increasing evidence suggests that disturbances in circadian rhythms, particularly shortened sleep duration and prolonged wakefulness, can interfere with the hypothalamic feedback of satiety signals [43]. Leptin is a protein hormone with a wide range of biological effects, among which the most important one is to act on the metabolic regulatory center of the hypothalamus, exerting the effects of inhibiting appetite, reducing energy intake, increasing energy expenditure, and inhibiting fat synthesis. Once the satiety signal fed back by the hypothalamus is disrupted, leptin levels decrease and may be accompanied by changes in the amplitude of leptin circadian rhythms and an increase in ghrelin levels, leading to increased hunger in people with short sleep times and thus increasing calorie intake. Excessive calorie intake increases the risk of overweight and obesity, and numerous pieces of evidence have long shown that overweight is associated with an increased risk of cancer in at least 13 anatomical regions, including the esophagus, kidneys, liver, thyroid, breast, ovaries, and uterus. In addition, abnormal circadian rhythms of insulin and glucocorticoids have been shown to be associated with metabolic imbalances in various tumors [44].

4.3 Inflammation and Immune Dysfunction

During a normal sleep cycle, slow wave sleep (SWS) maintains cytokines derived from T helper 1 (Th1) and T helper 2 (Th2) cells, and the immune system exhibits a biphasic transition that supports antigen presentation processes (Figure 3) [13]. The disruption of sleep efficiency, duration and sleeping structure (SWS and rapid eye movement sleep) can lead to inflammatory responses in the body, including abnormal cellular inflammation, systemic inflammation, and inflammatory transcriptional activity [13]. Specifically, disruption of circadian rhythms leads to immune system dysfunction and abnormal activation of inflammatory responses, manifested by activation of soluble intercellular adhesion molecule (sICAM) regulated NF-κB inflammatory signaling, then inducting the inflammatory markers IL-6, TNF-γ, and C-reactive protein (CRP), indicating progression of inflammatory status and increased cancer risk [13]. The different stages of sleep, including slow wave sleep (SWS) and rapid eye movement (REM) sleep, induce varying degrees of nocturnal changes in the

activity of inflammatory cytokines. According to reports, levels of inflammatory cytokines peak in the early stages of SWS, but compared to wakefulness, IL-6 levels during SWS are lower than during REM [45]. Briefly, sleep interruption may lead to abnormal inflammatory response, up regulation of proinflammatory cytokines, and become a potential risk factor for many cancers, including breast cancer, ovarian cancer, brain cancer and colorectal cancer [13]. In addition, miRNA, as an endogenous RNA, has the function of regulating various biological activities, which relies on a regular circadian rhythm [46]. A large amount of data indicates that miRNA plays an significant role in the metabolic control of immune cells [1].

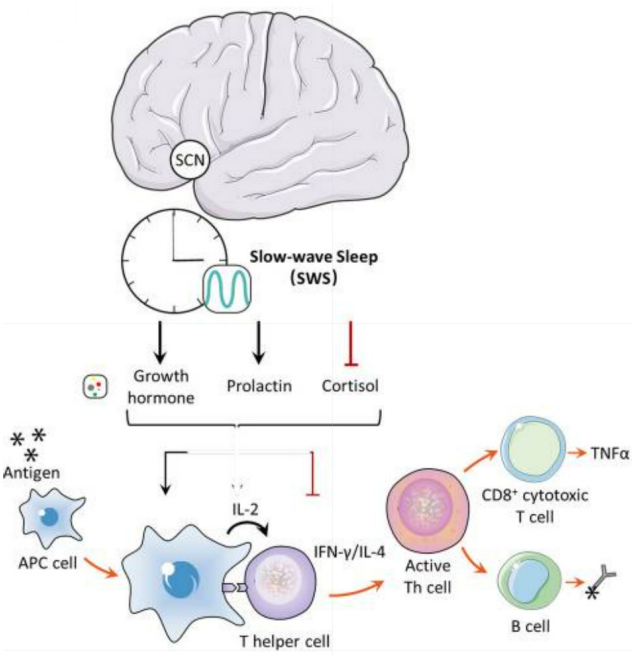

Fig. 3 Circadian Regulation of Immune Function [13]

4.4 Metabolic Disorders and Oxidative Stress

Trace amounts of miRNA are also involved in the energy metabolism process of the human body, especially in metabolising carbohydrates and fats, also in producing amino acids [47]. Cancer cells may prevent apoptosis and promote cell growth and survival by altering the metabolism way. Warburg effect is the most widespread study of metabolic phenotype of cancer cells, which resulted from miRNA dysregulation and makes glycolysis increasing [48, 49]. In addition, it was found that GLUT1 mRNA could inhibits glucose metabolism through multiple pathways. Accordingly, inhibiting GLUT1 reduces glycolysis, leading to cell death [50,51]. Leptin, which participates in the balance of circadian rhythm and hormone regulation, has lower secretion and blood levels due to disrupted circadian rhythm, leading to greater appetite and hunger, and soon afterward causing disturbances in blood lipid levels and triglyceride metabolism. The increased adipokines secretion and the release of macrophages from adipose tissue will increase the probability of chronic inflammation and stimulate DNA damage and oxidative stress in the body [52].

5. Conclusion

This article reviews the carcinogenic mechanisms of circadian rhythm disorder from four aspects: cell cycle, hormone levels, immune inflammation, and metabolic imbalance. Under normal physiological conditions, the regulatory system of circadian rhythm is maintained in the nucleus of SCN neurons by the interaction of the circadian clock gene CCG. So far, many epidemiological and animal experimental studies have confirmed that lifestyle factors such as night shift, jet lag, artificial light and so on, as exogenous incentives, significantly increase the risk of multiple cancers such as breast cancer, prostate cancer, colorectal cancer. Genetic factors including clock gene mutations and epigenetic abnormalities are as endogenous factors that also induce the development of various cancers. Analyzing the promoting effect of circadian rhythm disorder on cancer occurrence at the cellular level, this article introduces the mechanisms of promoting cancer cell proliferation and expansion from four sections: cell cycle regulation disorder, endocrine hormone regulation abnormality, immune response disorder and inflammatory response intensification, oxidative stress and metabolic disorder. By understanding these mechanisms and processes, cancer treatment methods may be able to prevent cancer development by regulating sleep cycles and improving circadian rhythm disorders. Chronotherapy, as an emerging cancer treatment method, is administered at appropriate times during the circadian cycle to ensure maximum effectiveness. However, chronotherapy is still in experimental and trial operation. By increasing interdisciplinary mechanism research, the impact of circadian rhythm on cancer development will have a better understanding, and then conduct long-term population tracking studies to collect more reliable data, which can help the clinical implementation of time therapy and further improve cancer treatment and prognosis. In the future, single-cell omics, multi omics, and artificial intelligence models can be used to deeply analyze the causal relationship between circadian rhythms and cancer progression, providing a basis for precision medicine.

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