CHAPTER 4

CIRCADIAN RHYTHM AND CARCINOGENESIS

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INTRODUCTION

The circadian clock is closely associated with cell proliferation, cell survival, DNA damage response, DNA repair, angiogenesis, and metastasis (1). Circadian rhythm disorders resulting from shift work, chronic jet lag and time-restricted feeding/ calorie restriction are called "carcinogens" and are associated with different types of cancer (2). Recently, specific studies have been conducted to understand the mechanistic relationship between them. Although the molecular regulation mechanism of clock elements such as Clock, Bmal1, Per and Cry is precise, their molecular mechanism in the pathogenesis of cancer has not yet been clarified.

MOLECULAR BASIS OF RHYTHM

Circadian rhythm refers to regular fluctuations in biochemical, physiological, and behavioral rhythms in mammals and many life forms over a cycle of approximately 24 hours. This internal control mechanism is called the circadian rhythm; it predicts and adapts to upcoming changes in the light/dark cycle (3-5). The circadian clock has a significant role in several important diseases such as metabolic syndrome, obesity and cancer. It is generally accepted that the circadian clock consists of two parts, one in the suprachiasmatic nucleus (SCN) in the hypothalamus and the other in the peripheral tissues and organs. The master clock (SCN) in the hypothalamus with light; in peripheral tissues, it is regulated by both nutrients and messenger signals from the SCN (6-8). The mammalian circadian clock consists of feedback (negative) and feedforward (positive) cycles involving transcription, translation, and posttranslational events. The positive elements in this network are Bmal1 (Brain and muscle ARNT-Like 1) and Clock (Circadian locomotor output cycles hood) genes; It regulates the expression of these genes during the day by binding to the E-box promoter regions of genes involved in negative regulation such as Per1 and Per2 (Period) and Cry (Cryptochrome) (9-12).

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At night, the transcription inhibitor complex is formed by Per and Cry proteins and transferred from the cytoplasm to the nucleus, where they bind to Bmal1 and Clock and suppress their own gene expression. Rev-erbα (NR1D1) and Rev-erbβ (NR1D2), which are known as nuclear hormone transcriptional repressors and have two subgroups, are controlled by Bmal1 and provide a negative feedback loop to control gene expression in tissues (Figure 1) (13-14). This control mechanism is also realized through the promoter region of Rev-erbα/β. When the Rev-erbα/β proteins reach a certain level, they bind to the promoter of Bmal1 and suppress their expression (15). Rev-erbα is the primary form of this family of nuclear receptors and is highly abundant in the SCN (suprachiasmatic nucleus). It is also known that Rev-erbα/β shows strong circadian oscillation in the SCN, gene expressions peak between ZT (zeitgeber time) 6-9, and regulate glucose, lipid metabolism and inflammatory response (16-18).

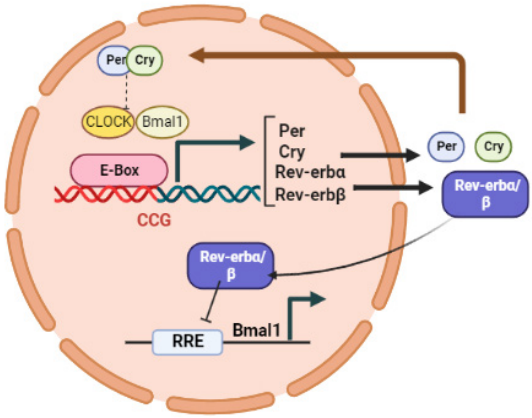

Figure 1: The molecular basis of the mammalian circadian clock (19) is drawn from the relevant source. The circadian clock consists of positive (Bmal1, CLOCK) and negative (Per, Cry) regulatory networks. Circadian transcription factors regulate the expression of these genes by binding to the E-box region in the promoter of clock-controlled genes (CCG). The transcription of the central clock genes Per and Cry are also regulated in the same way. The Per/Cry heteroprotein then migrate to the nucleus, where they bind to the promoter of Bmal1/Cry and repress their own transcription. The CLOCK/Bmal1 heterodimer likewise stimulates the transcription of Rev-erbα/β, while Rev-erbα/β inhibits Bmal1 on the ROR element (RRE).

THE RELATIONSHIP OF CLOCK GENES WITH TUMOROGENESIS

Different clock genes are associated with different types of cancer. Although healthy and cancerous tissues are controlled by the same clock genes in the or-

ganism (20), the daytime expressions of these genes in cancerous tissue change and diverge from the current rhythm in healthy tissue (21). It has been reported that central circadian genes such as Bmal1, Clock, Cry, Per have an important role in carcinogenesis (22). For example, Per 1 expression is increased by radiation and is required for radiation-induced apoptosis (23-24). Bmal1, Cry2 increase is associated with adenocarcinoma. In addition, studies have shown that Cry2 has a deficient expression in the TNM stage of the tumor which shows that Cry2 plays a negative role in the development and progression of adenocarcinoma (25).

Several epidemiological studies indicate that circadian rhythm disturbances are associated with an soaring risk of cancers (for example prostate, overian, breast, colon, liver, lung, pancreatic and lung) . In addition, circadian rhythm disorders reduce the effectiveness of cancer treatments and increase the early death rate in cancer patients. Furthermore, blind individuals who are free of light entertainment have a lower overall risk of cancer (26-27). Accelerating the growth of malignant tumors as a result of disruption of circadian rhythms in the suprachiasmatic nucleus (SCN) ablated mice suggested that the circadian clock may play an important role in the endogenous control of tumor progression (28). Circadian gene mutant animal models have revealed disruption of major clock genes thus, increased tumorigenesis (29). Some studies suggest that CLOCK and BMAL1 have tumor-suppressive roles (30). In humans, single nucleotide polymorphisms (SNPs) are associated with increased cancer susceptibility. Suppression of BMAL1 expression increases metastasis in lung, prostate cancers in vivo and in vitro. The tumor suppressor properties of BMAL1 are hypothesized to occur through the regulation of PI3K-AKT signaling pathway. For example, the component of the AKT pathway, ribosomal S6 protein kinase 1 (S6K1), influences tumorigenesis by both the translation machinery of BMAL1 and by stimulating protein synthesis by phosphorylating BMAL1. While Bmal1 $^{-/+}$ heterozygous mice were prone to lymphoma, Clock and Bmal1 expressions were increased in diseases such as colorectal cancer and acute myeloid leukemia (31). In addition, circadian rhythm is disrupted in CLOCK mutant mice, the expressions of metabolic genes are changed, chromatin remodeling, DNA damage response and tumor suppression are observed. In addition to CLOCK/BMAL1, CRY and Per genes are also involved in tumor suppression. There is convincing evidence that polymorphisms in the Per1, Per2, and Per3 core circadian genes are frequently found in human cancers, resulting in decreased expression of these genes and that oncogenic MYC suppresses the clock (32). In the absence of both Per1 and Per2 alleles, increased spontaneous and radiation-induced tumorigenesis was observed in many animal

models compared to normal-type mice. In addition, Per2 inactivating mutations increase the risk of neoplastic development. Cell proliferation over β-catenin and c-Myc increases in the human colon cancer model, especially when the Per2 gene is suppressed. Per1, on the other hand, directly interacts with ATM and regulates tumor suppressor effect and tumorigenesis, including TP53 and CHK2. This interaction is observed in cancer cells where there is overexpression of Per1 in the presence of DNA damage and in cancer cells induced by DNA damage. It has been noted that Per1 expression decreased in breast cancer, lymphoma, glioma, colon cancer and liver cancer. It has been reported that if Per1 expression is suppressed, it suppresses apoptosis by reducing the sensitivity to X-rays in U343 glioma cells (24, 33). Therefore, Per 1 and 2 are clearly considered to have tumor-suppressive effects. Similarly, in the absence of alleles of Cry1 and/or 2 in mice, spontaneous or radiation-induced tumorigenesis is increased compared to normal-type mice. Bloking of Cry2 expression directly associated with tumor formation (26). In addition, this clock gene is a central clock gene that has been associated with the incidence and progression of many carcinomas, as well as its role in cancer resistance (30). Mice lacking the circadian Per2 gene have an increased incidence of cancer and tumor growth (34). Increasing evidence has shown that BMAL1, Cry2, and ROR-α levels are significantly associated with the diagnosis of adenocarcinoma. NPAS2 is associated with survival in cancer patients, suggesting that NPAS2 and Timeless may be involved in the transcriptional mechanism of the circadian clock in adenocarcinoma and squamous cell carcinoma, respectively (30). The potential of using circadian clock genes as biomarkers in the pathogenesis of cancer is still in the experimental stage, and studies in this area may provide valuable data for diagnosis.

CIRCADIAN CONTROL OF THE CELL CYCLE

Cell proliferation is the hallmark of cancer. Studies since the early 20th century have shown that there may be a relationship between the mammalian circadian clock and the phases of cell division. From cyanobacteria to eukaryotes, the circadian rhythm actually acts as an additional checkpoint in the cell division cycle. However, it is not yet clear how this mechanism occurs in mammalian cells. Some studies suggest that cell division occurs in a specific phase of the circadian cycle (35). Studies have shown that circadian clock components suppress or stimulate the transcriptional and posttranscriptional control of cell cycle progression by the time of day. Therefore, each phase of the cell cycle is potentially influenced by the circadian clock, by cyclin/cyclin-dependent kinases and cyclin-dependent kinase

inhibitors (1).

c-Myc, Cyclin-D1 and Wee-1, are expressed rhythmic dependent manner. Wee-1 encodes a kinase that regulates entry into mitosis and phosphorylates the CDC2/Cyclin-B1 complex, directly regulated by the CLOCK/BMAL complex. Circadian mutant mice showed impaired cell cycle control in vivo (34). For example, G1 phase Rev-erbα and RORα/γ suppress the transcription of the cyclin-dependent kinase regulator, thereby suppressing cell cycle progression. In contrast, NONO, a clock CDK inhibitor p16, induces cell senescence in a Per-dependent manner at the G1-S transition. In addition, Per1 and Tim interact with G1-S transition ATM (ataxia-telangiectasia-mutated) and Checkpoint 2 to stop the cell cycle. In the G1/S phase transition, the cyclin D1 gene is suppressed by PER1, and therefore, PER1 overexpression inhibits cellular growth. On the other hand, c-MYC is inhibited by the transcription factor PER2 and PER2 gene mutation increases the levels of cyclin A, cyclinD1, MDM2, c-MYC, β-catenin and cyclin E, stimulates proliferation and shortens the cell cycle (1). It has been reported that clock elements have positive and negative effects in the similar paradigm G2-M transition. Cry1 stimulates cell proliferation by inhibiting WEE, G2-M regulatory kinase stimulates mitotic entry. Circadian control of key checkpoints is responsible for maintaining the physiological homeostasis of G2-M checkpoints. In the light of all the data, we can say that circadian factors in G1-S and G2-M transitions reveal different effects depending on the phase of the circadian rhythm. Considering all the studies, the effect of the clock-cell cycle relationship on tumor formation is quite complex, and we can say that the clock is effective in tumor development, but more studies are needed in this area (26).

CLOCK AND CANCER METABOLISM

The molecular clock and metabolic pathways relationship is essential for maintaining physiological homeostasis in healthy cells. The regulation of metabolic circadian clock defined by mammalian red blood cells manage by the redox cycle of peroxiredoxin/thioredoxin/NADPH enzymes. This complex drives the metabolism of H_2O_2 in various tissues. NADPH is a critical cofactor in the cancer-causing metabolite and circadian regulated mechanism. The reorganization of energy metabolism associated with cancer predominantly uses glycolytic activity despite aerobic conditions, causing more NADPH formation, lowering TCA activity and increasing fatty acid synthesis. Recent studies have revealed that these processes are associated with the circadian clock. For example, the increase in melatonin levels under light exposure impaired the Warburg effect in the prostate and breast

cancer xenograft model, thus reducing the development of these cancers. In addition, the alteration of the pentose phosphate pathway that produces NADPH is under tight circadian regulation. In the light of previous findings, we can say that circadian disorders cause cancer development by affecting metabolic adaptation. Again, according to these findings, the determination of nutritional conditions improves metabolic diseases even if a high-fat diet is fed. The effect of the circadian clock on metabolism affects lipogenesis, bile acid synthesis, cardiovascular diseases and inflammation. For example, chronic jet lag disrupts the circadian rhythm and causes hepatocellular carcinoma. Interestingly, BMAL1, Cry1 and Cry2 knockout mice disrupt the transcriptional and metabolic rhythms, respectively, with effects such as shortening, lengthening, and separation. The relationship between metabolism and circadian rhythm is bidirectional. In other words, disruptions in nutritional rhythm also affect circadian rhythm (36). With transcriptional regulations and posttranslational modifications, the circadian clock combines metabolism and nutrient signaling essential for tumorigenesis (26). In addition, the interaction between the oncogenic bHLH transcription factor MYC and CLOCK has been shown to correlate with glycolytic genes, possibly facilitating cancer progression in MYC-induced cancers such as neuroblastoma. The reciprocal communication between CLOCK-BMAL1 and HIF-1α represents an additional node for co-regulation of circadian and metabolic pathways in HIF-dependent cancers (37).

SIRT1 has fundemental roles in metabolism. This molecule is resposible of deacetylating many proteins and regulating gene expression through histone deacetylation. SIRT1 deacetylates p53 and thus inhibits its activity, resulting in reduced apoptosis after genotoxic stress (38). SIRT1 also interacts with hypermethylation in cancer 1 (HIC1), an epigenetically silenced tumor suppressor. SIRT1 is upregulated in tumors lacking HIC1 and intervents apoptosis by deacetylating p53. It is clear that SIRT1 can promote or prevent cancer depending on the specific function of its substrate (39). With the studies to be done in this field in the near future, it may be possible to control tumorigenesis by regulation of SIRT1 expression.

DNA DAMAGE REPAIR AND RESPONSE

Cell proliferation and DNA damage repair controled by circadian clock. Clock disturbances disrupt responses of DNA damage repair and cell cycle checkpoints and causes cancer formation by stimulating intrinsic apoptosis (40). One hour or more after apoptosis is activated, a very characteristic and irreversible fragmen-

tation of DNA begins at a single-stranded nick. Studies have shown that clock genes regulate; DNA repair, DNA damage control and apoptosis in healthy and cancerous cells. It is known that there are polymorphic sequences in circadian clock genes in many cancer types. Although healthy and cancerous tissues are controlled by the same clock genes in the organism, the expression of these genes during the day varies. DNA damage G1/S phase and G2/M phase checkpoints are under the influence of circadian rhythm genes. Period 1 naturally upregulates c-Myc, cyclin D1, Cyclin E1, cyclinB1 and CDK1, and the induced p53 pathway ATM and Rad 3 related kinase (ATR), which causes Chk2 phosphorylation and inhibits G1/S and G2/M switching, enabling apoptosis. Circadian genes act similarly to p53 by blocking the replication mechanism of cells in response to DNA damage.

Impaired DNA damage response leads to many cancer phenotypes, and there is ample evidence that the circadian clock is associated with DDR (DNA damage response). In Cry1-/- and Cry2 -/- mice, UVB radiation suppresses the circadian rhythm of the nucleotide excision repair gene XPA. In addition, time-restricted feeding changed the amplitude and phase of the circadian clock in the epidermis, impaired sensitivity to UVB-induced DNA damage and expression of XPA, and prevented refinement. Other members of the molecular clock, TIM, PER1, and PER2, also play a central role in DDR. As a result of radiation-induced DSBs, PER1 interacts directly with ATM/CHK2. Overexpression of Per1 activates Myc-mediated apoptosis as a result of radiation-induced DSBs, while down-regulation of Per2 resists radiation-induced apoptosis as it inhibits CHK2 activation. TIM also has DDR function, such that there is a need to identify different circadian clock components involved in the modulation of CHK1 and ATR in the single-stranded DNA strand and the DDR in the double-stranded DNA strand. The positive circadian component, BMAL1, is also a precursor to DDR. Bmal1 knockout abolished radiation-induced p53 activation and released cells from the retention state (26). It is accepted that clock genes maintain the repair of DNA damage in humans. Indeed, it has been reported that both pancreatic carcinoma and osteosarcoma xenografts grow faster in animals with suprachiasmatic core lesions (41).

In mice undergoing partial hepatectomy, nocturnal liver regeneration and nocturnal mitosis were significantly increased with CLOCK and BMAL1 directly controlling Wee1 mRNA. In addition, PER1 ataxia telangiectasia mutated (ATM) interacts with serine/threonine kinase to regulate CHK-2 (checkpoint kinase 2) dependent DNA damage response. Moreover, mice with Per2 frame deletion were

prone to radiation-induced tumorigenesis, and their expression was impaired, including many genes in the cell cycle and genes directly regulated by Bmal1, such as cMyc in the DNA damage response (35). Briefly, circadian clock protect cells aganist the destroying effect of DNA damage by activating microenvironmental and systemic homeostasis (42).

CHRONOTHERAPY

Many metabolic pathways associated with the circadian clock have been used in cancer treatment (43). For example, the chemotherapeutic agent cisplatin, when used day or night, creates markedly different outcomes in patients suffering different cancer types. We also show that the cisplatin toxic/therapeutic ratio will be achieved with chronotherapy. Moreover, optimal dosing timing of extra-chemotherapeutic drugs improves treatment outcomes in cancer progressing. The mechanism of many anticancer drugs can be restricted due to their side and toxic effects on normal cells. However, chronotherapeutics aim to increase the effectiveness of cancer chemotherapeutics, minimize the toxic and undesirable side effects, and increase the life expectancy and drug tolerance of cancer patients. Bmal1 knockout mice are more sensitive to the time of administration of chemorein. Cry1 $2^{-/-}$ knockout mice are more resistant to chemotherapeutics than normal mice (26, 44). In addition, radiotherapy, which is frequently used in cancer treatment, aims to prolong survival and reduce side effects in cancer types (31). Performing radiotherapy at the appropriate circadian time will reduce its side effects (inflammation, leukopenia, skin rash, healthy organ damage, sleep disturbance, fatigue) as well as increase the effectiveness of the treatment and increase the quality of life (31, 45). In addition, radiation chronotherapy is associated with the circadian clock. Therefore, these mechanisms related to the circadian clock can cause changes in response to radiotherapy during the day (23, 46).

Since metformin changes the NAD^+/NADH ratio, it inhibits mitochondrial complex 1 and impairs respiration. NAD^+ dependent regulation of mammalian sirtuins in cancer treatment shows the importance of the clock mechanism. In addition, the circadian clock provides cyclic regulation of NAD^+ and plays a critical role in the NAMPT-NAD salvage pathway by controlling the activity of NAMPT (nicotinamide phosphoribosyl transferase). Therefore, future pharmacological interventions, particularly clock function reinstatement strategies, should be attempted.

In addition, melatonin, a circadian hormone, is frequently used in the clinical laboratory in order to both increases the effectiveness of chemotherapeutics

and reduce their toxic effects in cancer treatment. Melatonin protects reproductive system in mice by minimizing mitochondrial damage caused by glutathione in the ovaries. Melatonin also works in combination with 5-fluorouracil (5-Fu) by suppressing cell proliferation in colon cancer. Finally, melatonin inhibits epithelial-mesenchymal transition (EMT) by increasing E-cadherin expression and decreasing migration/invasion capacity in breast cancer cell culture. Clinical findings similarly increased the 5-year survival of metastatic NSCLC patients by adding melatonin to the combination of cisplatin and etoposide (2).

REV-ERBs is an effective strategy to strike to cancer without side effect to normal cells. There are some REV-ERBs agonist commercialy avaliable and affecting metabolic level of nutrients which are necessary for cancer cells (32). Several clinical trials examining various chemotherapy agents have shown promising results in reducing toxicity and improving treatment efficacy in time dependent manner (41).

Circadian control of the cell cycle; the timing of surgery is obviously of practical significance for the administration of radiation therapy and cell cycle inhibitor drugs for cancer treatments (34). Clearly, some scientists explain the practical difficulty of applying tumor chronotherapy as follows: The observed cancer-prone phenotypes may be due not to disturbed circadian rhythms but to the "clock-independent" (pleiotropic) functions of these genes. In addition, there are opinions that circadian clock disturbance is the result of tumor carcinogenesis, not the causative factor of tumor carcinogenesis. Therefore, many questions still remain to be clarified in the field of tumor chronotherapy (47). Providing additional mechanistic explanation into the relationships between cancer progression and circadian clock disturbances is of increasing importance which could lead to the identification of new prognostic markers and therapeutic targets (29).

CONCLUSION

The molecular circadian rhythm is an crucial system required to regulate fundamental cellular processes such as the cell cycle and DNA damage repair, so circadian rhythm distrubition can cause rapid proliferation and dramatic impairment in cellular metabolism, which may set out cancer progression. However, issues such as whether clock disruption initiates tumorigenesis or whether some cancer-related genes operate independently of rhythm and rhythmic control of cancer cell signaling are not yet clear. Thus, although there are increasing examples of circadian clock disruption in various cancers, and also many types of cancers whose circadian clock is still functional. The worldwide increase in cancer incidence increases the need to identify new prognostic markers and therapeutic

targets for specific cancers.

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