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CIRCADIAN CLOCK AND ITS ROLE FOR INDUCING OR PREVENTING CANCER WITH A VIEW ON CHRONOTHERAPY FOR CANCER TREATMENT

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ABSTRACT

The circadian clock is well known as a master regulator of mammalian physiology that regulates crucial biological processes in our body to maintain homeostasis and behaviors. We know that perturbation of the clock rhythmicity can change these crucial systems and can cause various diseases. In recent years, circadian rhythm disruption has been identified as an independent risk factor for cancer and thereby classified as a carcinogen. Different data showed circadian rhythm and clock genes to play very critical roles in several hallmarks for cancer, apoptosis, control of tumor cell proliferation, DNA repair, and metabolic alterations. In this review, we discussed the role of the circadian clock as a cause and in the management of cancer with several examples of studies that held great promise to use chronotherapy in standard clinical practice in the future. Nonetheless, a profound understanding on the molecular level regarding the factors of the clock that help or prevent cancer is still needed. The development of novel therapeutics targeting clock-mediated cancer-inducing factors is also needed to ensure the survival of cancer patients along with the existing chemotherapeutics.

Keywords: Circadian Clock, Cancer, Clock genes, Chronotherapy.

Introduction

The term “circadian” is derived from the Latin term “circa diem” which means “about a day”. The circadian clock refers to a 24-hour clock inside the human body where the cycle facilitates various cellular function and thus help the body to maintain its homeostasis. This clock senses the day-light cycles and seasonal changes to help the human body keep track of time and optimize our daily life accordingly. This cycle governs the rhythms of sleep/wake cycles, metabolism, feeding/fasting, hormone secretion, and immune function. Disruptions in one or more than one of these rhythms have been found to induce stress factors that can lead to disorders like endocrine disruption, metabolic disorders, or cancer. [1] About 20,000 neurons of the suprachiasmatic nuclei (SCN) region of the hypothalamus receive signals from retinal ganglion cells (mRGC) expressing photopigment melanopsin. The light signals SCN gets from the retina help the SCN neurons to synchronize with the daylight changes in different seasons. [2] At the cellular level, the clock responds to extracellular cues and also regulates the function of numerous genes by post-transcriptional or transcriptional methods. Laboratory and clinical evidence have long suggested the interplay between the circadian clock and cancer. There are numerous mechanisms by which the clock can initiate and

help in the progression of cancer. Some of them are discussed below

- The circadian clock regulates the expression of thousands of genes that are involved in metabolism, DNA repairing, redox regulation, autophagy, cellular secretion, and protein folding, etc. Disruption of circadian rhythms lead to disruption (e.g.Redox imbalance, metabolic reprogramming, chronic inflammation) of these cellular processes too which make the cellular an environment conducive for tumorigenesis.
- The clock also regulates the expression of several secreted factors which have para-endocrine or endocrine functions. Some factors like cytokines, hormones, neurotransmitters signals through downstream signaling pathways or cognate receptors affect the clock function to synchronize it with different tissues. These factors act as biomarkers of circadian function in tissues. Nonetheless, some tumors can produce excess amounts of these circadian clock-relevant hormones which can disrupt the clock.
- There is significant evidence that the circadian clock can interact with proteins that participate in cancer-modulating pathways. Thus, disruption of the clock can prevent or promote cancer.
- Circadian clock proteins and related proteins can sense the cellular environment (e.g. change in the redox state which affects CLOCL/BMAL1 affinity to DNA. The nutrient present in the cell can modulate the level of co-factors and factors influenced post-transitional modification (acetylation, phosphorylation) which can affect the clock proteins too. The change in co-factors, post-translational modification, and redox state brought by the oncogenic programs can modulate the localization, stability, or function of clock proteins.

This review discusses the role of the circadian clock in promoting cancer and also we discuss how the circadian clock and its proteins can be used reversely to counter cancer.

RELATIONSHIP BETWEEN CIRCADIAN RHYTHM DISRUPTION AND CANCER

REGULATION OF THE CLOCK:

The clock mechanism is constituted on an autoregulatory network composed of positive & negative translation-transcription feedback loops. Transcriptionally, the clock is regulated by positive regulators in the loop. The negative regulators of the loop, Cryptochromes (CRY1 & CRY2) and Period(PER1, PER2) like key circadian genes whose expression is regulated by basic helix-loop-helix heterodimeric transcription factors (CLOCK/BMAL1 or CLOCK/NPAS2). CRY and PER form a transcriptional repressor complex which represses the activity of CLOCK/BMAL1 by entering into the nucleus, therefore creating a negative feedback loop that controls the clock. The BMAL1 is also rhythmically controlled by its own stimulating factor RORα while suppressed by Rev-erbα and Rev-erbβ. Various studies confirmed the role of CLOCK/BMAL1 in controlling the clock genes which regulate biochemical, physiological, and molecular processes.[3-5] Posttranslational modulation of CRY & PER makes the change in protein stability, autoregulatory clock feedback loops, and entry of CRY/PER repressors in the nucleus. In a nutshell, we can see the clock is controlled through a diverse group of transcriptional regulatory factors, in the recent studies which are found to be making alterations of clock-regulatory factors that are contributing to the cancer phenotypes.

CLOCK AND BMAL'S FUNCTION IN TUMOR:

Numerous studies indicated that CLOCK and BMAL may have the tumor-suppressive character, as of now the results are conserved among humans and mice. Single nucleotide polymorphisms (SNP) in CLOCK and/or BMAL1 genes have been found associated with increased susceptibility to breast, prostate, ovarian and pancreatic cancers in humans.[6-8] The mice models which expressed dominant-negative Clock mutations showed disruption in the circadian rhythm which resulted in decreased survival rate when compared to the normal ones. BMAL1 has been found to have a significant role in the suppression of prostate, glioma, and lung cancer. In models where

BMAL1 expression was suppressed showed increased metastasis in in-vivo and in-vitro models. Further studies indicated the suppressive action of BMAL1 is regulated by the P13K-AKT signaling pathway.[9] However, exceptions are seen in colorectal cancer where CLOCK and BMAL1 expression was elevated and CLOCK expression seemed to attribute to increased proliferation.[10]

THE FUNCTION OF CRY & PER AS TUMOR SUPPRESSORS:

In addition to Clock and BMAL1 studies showed the role of CRY & PER genes in tumor suppression. Upregulation of Cry1,2,3 with/without SNPs has been found to be associated with increased susceptibility to breast, prostate, colorectal, endometrial, and skin cancer. Several mouse models demonstrated that mice that lack PER1 & PER2 showed an increased risk of tumor development (spontaneous and radiation-induced) as compared to wild mice.[11] Suppression of PER2 showed elevated cell proliferation in human colon cancer through β-catenin and c-Myc which explains the tumor-suppressive role of PER2. PER1 has been found to interact with ataxia-telangiectasia–mutated (ATM) to show its effect on tumor-suppressive genes. However, overexpression of PER1 increased sensitization of human cancer cells to DNA damage-regulated apoptosis.[12] On the other hand, mice lacking CRY1 and/or CRY2 were also found to have an increased risk to develop spontaneous and radiation-induced tumor development.[11] In addition, inhibition of CRY2 expression leads to dysregulation of certain genes which are involved in proliferation, migration, invasion, and apoptosis of tumor cells in breast cancer models.[13] Thus, all these observations consolidate the hypothesis for the involvement of CRY & PER genes in tumor or cancer cell development.

CLOCK DYSFUNCTION AND ITS EFFECT ON THE HALLMARKS OF CANCER

Studies have shown a clear understanding of the role of Clock, BMAL1, CRY & PER family in circadian circulation and molecular basis of tumor-suppressive functions. In the following section, we described the findings which link clock dysregulation to the hallmarks of cancer development.

CANCER CELL SIGNALING:

Sustaining proliferative signaling is considered as one of the significant factors among hallmarks of cancer and the evidence showed an interplay between circadian factors dysregulation and growth factors in cancer. c-Jun N-terminal kinase (JNK) and P38 pathways upstream components exhibit high circadian rhythmicity with the following ones- ASK2, MKK7, MMK3, MMK6, P38γ, P38α, and JNK3. Studies have shown cross-talk in MMK7-mediated JNK activation increased the half-life of PER2 through phosphorylation which alters the circadian timing.[14] GAAD45 family members respond to clock-mediated signaling by directly interact with JNK/P38 components. CRY1 knockdown in-vitro and PER mutated mice showed impaired expression of GAAD45α which increases cellular proliferation.[13] Furthermore, downstream components of the ERK1/2 pathway, MKK2, and ERK2 also show circadian rhythmicity which insinuates the connection of the circadian clock with multiple growth factors signaling pathways. However, more studies are needed to address a relation between the specific growth factor responses in cancer with the above-mentioned observations.

CLOCK'S RELATION WITH DNA DAMAGE RESPONSE (DDR):

Multiple evidence links the circadian clock with DDR where perturbed DDRs contribute to phenotypes of cancer. In murine models, accumulation of DNA damage and neoplasia has been seen as a result of clock disruption. The above observation is likely to be evolutionary conserved, Cryptochromes help in DNA photolyases that catalyze light-dependent DNA repair as seen in drosophila and plants. In mice, ultraviolet B (UVB) irradiation in the epidermis of $Cry1^{-/-}$ & $Cry2^{-/-}$ models applied where Cry2-/- mice showed dampened circadian rhythm in the nucleotide excision repair gene XPA. Time-restricted feeding shifts the phase and amplitude of the clock in the epidermis which ultimately alters the sensitivity

of UVB-induced DNA damage and expression of XPA and impairs the repairing process.[15] Components of molecular clock including PER1, PER2, and TIM play important role in DDR responses. Double strand breaks(DSBs), induced by radiation mediates PER1 to interact with ATM/CHK2. PER1 overexpression activates Myc-mediated cell apoptosis in response to radiation-induced DSBs whereas, PER2 downregulation shows resistance to radiation-induced apoptosis because of delayed CHK2 activation. On the other hand, Per2-/- mice models showed an increased risk for lymphoma.[16,17] TIM also has functions in DDR, it modulates ATR and CHK1 downstream of single-strand DNA breaks and activates CHK2 by ATM modulated downstream of double-strand breaks.[18] From the above pieces of evidence, we can say different circadian components are necessary for response in DDR for single or double-strand DNA breaks.

INFLUENCE OF CLOCK ON CELL DEATH:

Studies have shown direct interplay between the core circadian clock and apoptosis, circadian clock is found to induce or deduce cell apoptosis based on the cell context and clock status as we already saw in cell-cycle regulation. CRY1/2 and PER1 influence the extrinsic tumor necrosis factor-alpha (TNFα) pathway and intrinsic apoptotic pathways to promote cell death.[19] Knockdown of PER1 results in downregulation of antiapoptotic BCL-2 and upregulation of pro-apoptotic BAX, thus exacerbating apoptosis in hepatocellular carcinoma cells. On the other hand, PER2 activates Myc-mediated proapoptotic pathways which induce cell apoptosis by sensitizing cancer cells to radiation-induced apoptosis. On the contrary clock, defective mice models have shown decreased expression of apoptosis-inducing factors.[20] These observations underscore the need of understanding the factors that can control clock-mediated apoptosis and can exacerbate tumorigenesis.

CELL METABOLISM AND THE CIRCADIAN RHYTHM:

The circadian clock needs to be congruous to that of the intricated metabolic pathways in order to maintain physiologic homeostasis in healthy cells. The metabolic clock is independent of transcriptional activities and it is maintained in the redox cycle of thioredoxin/peroxiredoxin/NADPH enzymes, first observed in mammalian red blood cells. This complex shows a 24-hour redox fluctuation metabolizing H_2O_2 in tissues throughout our body.[21] Redox pairs like thiols (glutathione-GSH/GSSG) and coenzymes ($FADH_2/FAD^+$, $NADPH/NADP^+$ & $NADH/NAD^+$) controls the redox state in the body and thus influences electron flux and cellular homeostasis. Evidence from Drosophila, mouse tissue, and human cells showed NADPH can shorten or extend the 24-hour rhythm.[22] Thus, NADPH works as a circadian-regulated and cancer-promoting metabolite. Warburg effect is cancer-associated reprogramming of energy metabolism to predominantly utilization of glycolytic activity despite having aerobic conditions which are characterized by increased NADPH formation and decrease of tricarboxylic acid (TCA) cycle activity with increased synthesis of fatty acids. Light exposure changes the level of melatonin that leads to decreased growth of breast and prostate cancer xenograft due to dysregulation of the Warburg effect.[23] The circadian clock controls chromatin remodeling and metabolic output by the influence of sirtuins (SIRT) which is a family of NAD^+-dependent proteins. SIRT1 directly interacts with the clock and deacetylates PER2, thus altering the clock whereas CLOCK/BMAL regulates the expression of SIRT1.[24]The SIRT-circadian system made an impact through SIRT3 and BMAL on the TCA cycle and fatty acid metabolism. This process is done through SIRT6 governing CLOCL/BMAL recruitment of SREBP1 to promoters of the circadian rhythm.[25] In addition, consistent feeding in mice showed improved metabolic disease even if fed a high-fat diet. For example, clock-mutant mice have shown impaired cholesterol metabolism and more susceptibility to atherosclerosis. Chronic jet-lag to disrupts the rhythm-induced spontaneous hepatocellular

sarcoma in mice models due to dysregulated cholesterol or bile acid and xenobiotic metabolism with the addition of liver metabolic deregulation.[26] The MYC genes activate the CLOCK/BMAL1 directly thus leading to dysregulation of the clock. Recent work showed that high-fat diet influences circadian metabolome and transcriptome because of impaired BMAL1 and peroxisome proliferator-activated receptor-gamma (PPARγ) recruitment.[27] Therefore, it is clear that the circadian clock regulates metabolism through posttranslational modifications and transcriptional remodeling and interferes with nutrient signaling critical to maintaining tumorigenesis.

CANCER MANAGEMENT AND CIRCADIAN RHYTHM

The data available links circadian clock dysfunction to cancer pathways. Chronotherapy is a concept that considers the body's natural rhythms and cycles to treat various illnesses and disorders. The objective of chronomodulated therapeutics is to create a balance between the effectiveness and adverse effects of drugs. Anti-neoplastic agent cisplatin showed significantly different results in breast, prostate, cervical and ovarian cancer when compared the morning dose with the evening one thus indicating the significance of chronotherapy in elevating the efficacy and toxic therapeutic ratio.[28] The role of the clock was also evaluated using clock mutated and wild-type mice. Clock mutant and BMAL1 knockout mice showed increased sensitivity against chemotherapeutics whereas $Cry1^{-/-}$ & $Cry2^{-/-}$ mice showed more resistance to chemotherapy.[29] In addition, genome-wide gene expression study in mice, human lung, and liver tissues indicated that 80% of the FDA-approved drugs tested showed daily rhythm in their targets and respective downstream functions.[30] The antitumor effect and tolerability of a cyclin-dependent kinase inhibitor seliciclib is found to depend on circadian rhythmicity.[31] Acute gastrointestinal mucositis is found to be most severe in patients going through radiotherapy when the therapy is applied in the morning time compared to the evening time, thus implying an interplay between circadian rhythm with the human intestinal mucosa.[32] Patients with nonsmall cell lung cancer (NSCLC), when treated with gamma knife radiosurgery in the earlier part of the day showed better survival rates as compared to the therapy in the later part of the day.[33] However, a dysregulated clock can alter the efficacy of therapeutic agents, so more investigation is needed to understand the mechanisms by which the circadian clock alters cancer therapy. This understanding will help to refine our insight into the subject and implicate the insights to augment the efficacy and lower the toxicity of anti-cancer agents.

Discussion

The connection between the circadian clock and cancer is giving a new hope to cancer treatment and its prevention in the early stage. Several pathways described herein (cell cycle, DDR, and metabolism) are known to influence neoplastic transformation and tumor growth. While perturbation of circadian clock influences cancer, the intervention in lifestyle to maintain a healthy clock, diagnostic markers, chronotherapy along novel therapeutics targeting clock components are showing great promise. Genetic variations in clock genes like Neuronal PAS domain protein 2 [NPAS2] (rs23051560), CLOCK (rs11932595), RORα (rs1482057), BMAL1 (rs2290035, rs969485) expedite the risk of breast and several other cancers while other polymorphisms BMAL1 (rs2278749), RORβ (rs3903529, rs3750420), NPAS2 (rs17024926) reduces the risk.[34] Despite chronotherapy is being studied for decades, there is no standard practice employed yet for cancer treatment. Some studies showed a reduction in proliferation of different cancer cell lines by acute administration of forskolin, dexamethasone, heat shock & melatonin which help to reinstate the circadian clock. However, there is very limited data on the efficacy of these drugs. Along with that further investigation is needed to understand the role of clock genes vs circadian clock function in the tumor as it will help us to understand the type of tumor that would get the most advantage from clock drugs. It is also ambiguous how cancer/tumor cells that have/haven't healthy circadian rhythm affect the activity of existing anti-neoplastic agents? Further investigation is

needed, therefore. In summary, we can say the understanding of the role of the clock and its rhythm to facilitate or impede cancer/tumor is in the nascent stage. A rigorous investigation is still needed in the future for the development of novel drugs targeting clock perturbations and also study is needed to recognize and use the available drugs with the highest efficacy and lesser toxicity values.

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