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Review Article

Circadian Clocks and Malignancy

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Abstract

The circadian molecular clock depicts the ebb and flow of protein production in the cell cycle. It relates to the oscillation of proteins synthesized by circadian genes and circadian controlled genes of the molecular clock, regulated by transcriptional-translational feedback loops (TTFL). In the molecular clock, the oscillation pertains to the movement of proteins between the cytoplasm and nucleus, and the regulation of transcription, translation, phosphorylation, dimerization, and degradation of the proteins. A cellular TTFL is present in each cell, and both the cell cycle and circadian clock have evolutionarily conserved cyclical features from cyanobacteria to higher order mammals. Cell cycle genes controlled by the circadian molecular clock include Wee1, Myc, Cyclin D, thymidylate synthase and p21. These circadian-gated cell division cycles arise from cell cycle and circadian clock crosstalk. The primary feedback loop transcription factors are known as clock genes and BMAL1. These transcription factors activate the the cryptochrome (CYP) genes and period (PER) genes. Dysregulation of the circadian genes and circadian controlled genes can lead to unregulated proliferation and tumorigenesis with genomic and chromosomal instability. Circadian rhythm disruption is associated with risks of many different types of cancer, including prostate, colon, lung, breast, ovarian, endometrial, liver, and hematological malignancies. Knowledge of these processes allows molecular targets to be identified in the search for cancer cure.

ABBREVIATIONS

ARNTL: Aryl Hydrocarbon Receptor Nuclear Translocator-like; AVP: Arginine Vasopressin; BMAL-1: Brain Muscle ARNT-like Protein 1; CLOCK: Circadian Locomotor Output Cycles Kaput; DBP: D-box Binding Protein; CRY: Cryptochrome; E4BP4: E4 Promotor-Binding Protein 4; PER: Period Gene; REV-ERBs: Reverse Strand of ERB Alpha and Beta; RORs: Retinoic Acid-Related Orphan Receptor Alpha Beta Gamma

INTRODUCTION

Not a day passes, not a minute or second without an accouchement,

Not a day passes, not a minute or second without a corpse.

To Think of Time

Walt Whitman

The circadian rhythm helps to harmonize organic balance in all forms of life. It inherently governs a range of physiological and behavioral processes in organisms from fungi and bacteria to the top of the food chain [1]. The process provides an anticipatory mechanism to manage the predictable environmental changes [2]. Circadian synchronization enforces numerous physiological, biochemical and molecular processes [3-6]. Pittendrigh's "escape from light" hypothesis reveals how ancient life forms organized their chemical systems, to ensure that reactions could not proceed unchecked in physiological conditions [7]. By restricting replication events to the darkness, DNA can avoid being exposed to harmful ultraviolet (UV) light [8]. If this protective mechanism fails, DNA dysfunction can result in loss of regulation of DNA repair, an increased oxidative stress response, unchecked proliferation, and carcinogenesis.

The cell cycle is intricately intertwined with the circadian rhythm. The predominant time-keeper of the circadian clock is the suprachiasmatic nucleus (SCN). The SCN, part of the hypothalamus, is ruled by daylight, via the eyes and the pineal gland; however, it is known that the circadian clock also functions independently in every cell on a molecular level, including those cells without a nucleus, and this assists all cells to perform synchronously. The circadian rhythmicity leads to functional confluence, maintenance of the molecular clock and tumor suppression [9].

Epidemiologic evidence

With the knowledge that the circadian clock governs function of tumor suppressor genes and mammalian cell growth and repair, we can identify specific mechanisms of dysfunction [10]. Persistent interruption of the 24-hour cycle, as seen in the aviation industry with jet lag, with extended screen time via computer monitors and smartphones, and in shift workers, leads to increased oxidation and dysfunction of the circadian rhythm, tumor suppression genes, the immune system, and cellular growth and repair [11].

Circadian disruption secondary to shift work was reconfirmed as a Group 2A 'probable' carcinogen by the International Agency for Research on Cancer in 2010. Circadian rhythm disturbance is associated with an increased risk of many different types

of cancer, including prostate, colon, lung, breast, ovarian, endometrial, liver, and hematological malignancies [12-17].

Shift work, which includes night work, is a frequent component of modern work practices. The United States and Europe have a prevalence of 15%-20% and exceeding 30% in mining, manufacturing, healthcare, transport, the hospitality sector, and communications. Emerging evidence is accruing that primary prevention of cancer may include adapting work practices to ameliorate the risks conferred by circadian rhythm dysregulation [18].

The longitudinal duration of shift work for 4 or more nights per month for greater than 1 year confers risk, he as identified in the Nurses' Health Study, which followed 200,000 nurses in the United States, and found that this risk is highest closest to the time of the shift work, with a hazard ratio (HR) of 2.15, subsiding progressively once the shiftwork is stopped [16,17,19,20].

In a cohort of 813 patients who developed breast cancer and a control group of 793 individuals, breast cancer risk became greater in those that frequently slept less in the period during the night when melatonin (N-acetyl-5-methoxytryptamine) levels are highest: odds ratio (OR) 1.14 each night per week. Graveyard shift work conferred an OR 1.6 [13].

In a case-control assessment of Danish nurses, 310 cases of breast cancer highlighted that four controls for each breast cancer case were assigned by incidence density sampling. Nurses that worked rotational night shifts after midnight has an OR of breast cancer of 1.8, compared to nurses that worked exclusively during the day. The OR increased to 2.9 for those nurses that were on permanent or rotating night shifts [13].

Sleep deprivation has been linked with more aggressive hormone-related cancer phenotypes. In a case-control study of early stage estrogen receptor-positive breast cancer, Oncotype DX score correlated with an average number of hours of sleep at night preceding the diagnosis [21]. Less hours of sleep was correlated with higher incidence of recurrence. A meta-analysis of 13 studies involving occupations with night shift work including 7 that evaluated airline cabin crew found an HR of 1.48; for developing breast cancer. The incidence ratio for female flight attendants was 1.44. In this specific instance potential confounders include exposure to cosmic radiation, proxy measures of exposure, and detection bias [21].

The Genica Study, a case-control study that was population-based, showed that women that undertook shift work for one year or greater had an elevated risk for a gene polymorphism in the CLOCK gene OR 3.53 [22]. Identification of CLOCK gene polymorphisms in a case-controlled study of shift workers, with over 2000 participants, found a polymorphism in cancer cases OR of 3.53 [15]. A further meta-analysis of 800,000 women in the British Isle and Northern Island failed to find a higher incidence of breast cancer, although the study was poorly designed, as data collection was also based on a questionnaire and the follow-up period was just 3 years [23].

A Finnish cohort study of 11,370 twins over a 30 year period was able to relate the risk of prostate cancer to those whose working activities occurred more commonly after the standard day-time hours, HR 1.3 [24]. Men who had insomnia have a hazard ratio of close to 2 for developing prostate cancer [25].

A case control study in Montreal from 1979 to 1985 obtained occupational histories and working hours from 3,137 males with new malignancies, and 512 control subjects [26]. Cancer type and respective adjusted odds ratio compared to men that only worked during the day were lung cancer OR 1.76; colon cancer OR 2.03; non-Hodgkin's lymphoma OR 2.31; bladder cancer OR 1.74; rectal cancer OR 2.09; pancreatic cancer OR 2.27; prostate cancer OR 2.77. Equivocal or no evidence was found for stomach, kidney, esophageal sites, and melanoma [26].

While shorter duration of sleep of less than 7 hours per night, as opposed to altered sleep timings, was not found not to have an association with an increased risk in a large meta-analysis, the studies analyzed were based mainly on questionnaires, increasing the risk of recall and information bias. Case-control studies have also been used, and these study designs have risks of selection bias involving a source of cases, using incident or prevalence cases, and appropriate selection of the control. Recall bias is another risk [20].

Supplementary epidemiological considerations are that while there is an afore-described focus on occupational effects of night-shift work and jet-lag, sleep duration and timing of sleep initiation are usually independent. Sleep duration normally depends on individual chronotype with an almost Gaussian distribution with populations of sleep and awake times [27].

Circadian physiology

The circadian clock functions as the central pacemaker of the hypothalamus and also in the peripheral cells. The Supra Chiasmic Nucleus (SCN) synchronizes these peripheral cells through neuronal pathways and also through humoral pathways, such as glucocorticoids and melatonin [28]. The rate of production of melatonin, an indoleamine hormone excreted from the pineal gland, is limited during the daytime, increases as the day progresses and peaks from 2 am to 4 am [13,29].

As the body transitions from light to dark, the SCN sends inputs through the retinal-hypothalamic-pineal pathway. During the light cycle, axons from the retinal-ganglionic cells deliver signals that activate the SCN via the optic nerve. This signal is then distributed to the molecular clock. This is achieved by using chromophore co-factors, specifically flavin adenine di-nucleotide and pterin, which are related structurally to photolyase, a DNA repair enzyme [30].

This neuronal inhibition prevents melatonin from being released by the pineal gland into the circulation [31-33]. As night approaches, the departure of light signals the retinal-ganglion cells to inhibit the SCN, which then sends signals via axons through the intermediolateral nucleus, stimulating the sympathetic nervous system and this induces sleepiness. The pineal gland is mobilized to secrete melatonin into the circulation [28].

While the cell cycle in all cells occurs over 10-30 hours, most mammalian cells aim for a complete revolution in a little over 24 hours [8,34-36]. Mitosis and cell division are known to occur predominantly during the night with the production of cyclic-dependent kinase (CDK)1, with interphase set to occur

during the daytime. CDK1 inactivates the CDK 4/6 pathway [37]. The focus of the G1 phase of the cell cycle is cellular growth and protein synthesis, with DNA transcription and translation occurring during the S phase. The G2 phase is occupied with microtubule production, with little protein synthesis and production of CDK 2, 4 and 6 [38,39] p16 is a tumor suppressor gene involved in deceleration from G1 to S phase. p53 is a nuclear transcription factor which promotes apoptosis [40] p20 and p21 are rhythmically expressed CDK inhibitors. Both are controlled by the clock and regulate the G1-S cell cycle transition facilitating cell cycle arrest [8]. p21 interacts with proliferating cell nuclear antigen which participates in the DNA proliferation complex and DNA replication in S phase [41]. Expression of p20 is independent of p53 whereas p21 can be both dependent and independent of p53 [42]. This differential balance of the two inhibitors results in an S phase set to different times of the day. Myc is a transcription factor that controls 12% - 15% of genes[18]. In vitro experiments established that Myc disrupts the circadian clock by decreasing BMAL1 expression via REV-ERB induction [43]. When central clock components were lost, expression of c-Myc increased [44].

Circadian molecular clock and cell cycle crosstalk

The ebb and flow of protein production in the cell cycle is related to the oscillation of the proteins synthesized by the circadian genes and circadian controlled genes of the molecular clock, which are regulated by transcriptional-translational feedback loops (TTFL) [45]. In the molecular clock, the oscillation pertains to the movement of proteins between the cytoplasm and the nucleus, regulating transcription, translation, phosphorylation, dimerization, and degradation of proteins that are essential for normal cellular functions [46]. Dysregulation of the circadian genes and circadian controlled genes can lead to unregulated proliferation and tumorigenesis with genomic and chromosomal instability [39].

A cellular TTFL is present in each cell, and both the cell cycle and circadian clock have evolutionarily conserved cyclical features from cyanobacteria to higher order mammals. Cell cycle genes controlled by the circadian molecular clock include Wee1, Myc, Cyclin D, thymidylate synthase and p21. These circadian-gated cell division cycles arise from cell cycle and circadian clock crosstalk [18,47-54].

Autonomous oscillations arise as transcription of the PER gene and the CRY gene with which its protein product partners are repressed by their translated protein products [55]. The endogenous circadian clock comprised interconnected TTFL's such as this, as well as determinants of protein phosphorylation, nuclear translocation, degradation of complex components and other post-translational modifications [56]. Mutations in arrhythmic flies first led to localization of the period gene to the X chromosome with arrhythmic flies having missense mutations of period [57]. Other mutations in PER either shorten or lengthen the normal 24-hour circadian period of pupal eclosion [the emergence of the fly from the pupal case]. The abundance of the PER protein in fly neurons has 24-hour rhythmicity with peak PER levels at night [56]. This arises from cycling of transcription of the period gene with maximal levels of period mRNA preceding maximal PER protein levels by several hours, occurring earlier at night [58]. Proteins are translated in the cytoplasm whereas genes are transcribed in the nucleus. PER protein auto inhibits transcription of the period gene. In the flies, this arises when PER binds to another protein called TIM (product of the timeless gene in drosophila), the two proteins can enter the cell nucleus [55]. TIM also blocks the degradation of PER [59]. The cell cycle of expression of PER is abolished in flies which are mutant for timeless, and similarly the cell cycle of timeless is absent in period mutant flies [60] (Figure 1).

The TTFL has been demonstrated in the filamentous fungus Neurospora craasa, in which conservative coupling between these two systems exists via serine/threonine protein kinase-29 [61]. Serine/threonine protein kinase-29 is homologous to mammalian Wee1. In this model system, G1 [CLN-1] and G2 (CLB-1) cyclins oscillate in a circadian fashion. In circadian arrhythmic frqko mutants stk-29 and clb-1 oscillations were abolished. In the fission yeast Schizosaccharomyces pombe, In fission yeast Wee1 overexpression results in greater stoichiometric phosphorylation of Cdc2 threonine residue T14 [62]. Phosphorylation of the tyrosine residue Y15 is also controlled by Wee1. Wee1 has opposing effects to CDK25 phosphatase. Dephosphorylation of CDK2 activates G2-M transition [63]. In budding yeast Saccharomyces cerevisiae phosphorylation of Swe1, a homolog of Wee1, by CDK1 results in Swe1 activation. This is necessary to form stable Swe1-CDK1 complexes thereby maintaining CDK1 in the inhibited state. Conversely, dephosphorylation of CDK1 causes further Swe1 phosphorylation and CDK1 release [63]. In murine hepatocytes, the Wee1 gene is activated by the CLOCK: BMAL1 heterodimer thereby preventing cell cycle progression into mitosis. In murine colon tumor models circadian rhythms of PER1, PER2, D-box binding protein, and reverse strand of ERB (REV-ERB) were less active in cancer cells compared to normal colon with absent rhythmic expression of BMAL1 [51].

Micro RNA's have emerged as important mediators of crosstalk between the circadian molecular clock and the cell cycle. Micro RNA's anneal to messenger RNA to effectively silence the translation of transcribed genes. PER1 expression is diminished in cholangiocarcinoma. It is a target of the small non-coding RNA miR-34a. miR-34a is rhythmically expressed in cholangiocarcinoma [64]. Inhibition of miR-34a decreases tumor growth by affecting cell proliferation, invasion, and migration and therefore it has been inferred that there is therapeutic potential in inhibition of miR-34a or stimulation of PER1 in treating cholangiocarcinoma. Experiments on circadian rhythm knockin mice which evaluated 3'-UTRs found that miR-24 and miR-30 suppress translation of PER2 protein [65].

CONCLUSION

Multiple associations between circadian dysfunction and cancer defects have been identified. This specific knowledge of the timing of the molecular clock has led to identification of targets of molecular pathological processes that cause cancer, by coinciding the timing of chemotherapy administration with production of circadian proteins known to be involved in tumorigenesis. The links between alterations in the circadian rhythm in cancers downstream of common oncogenic alterations are continuously being studied. The 2017 Nobel Prize for Medicine was awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their discoveries on the molecular mechanisms controlling circadian

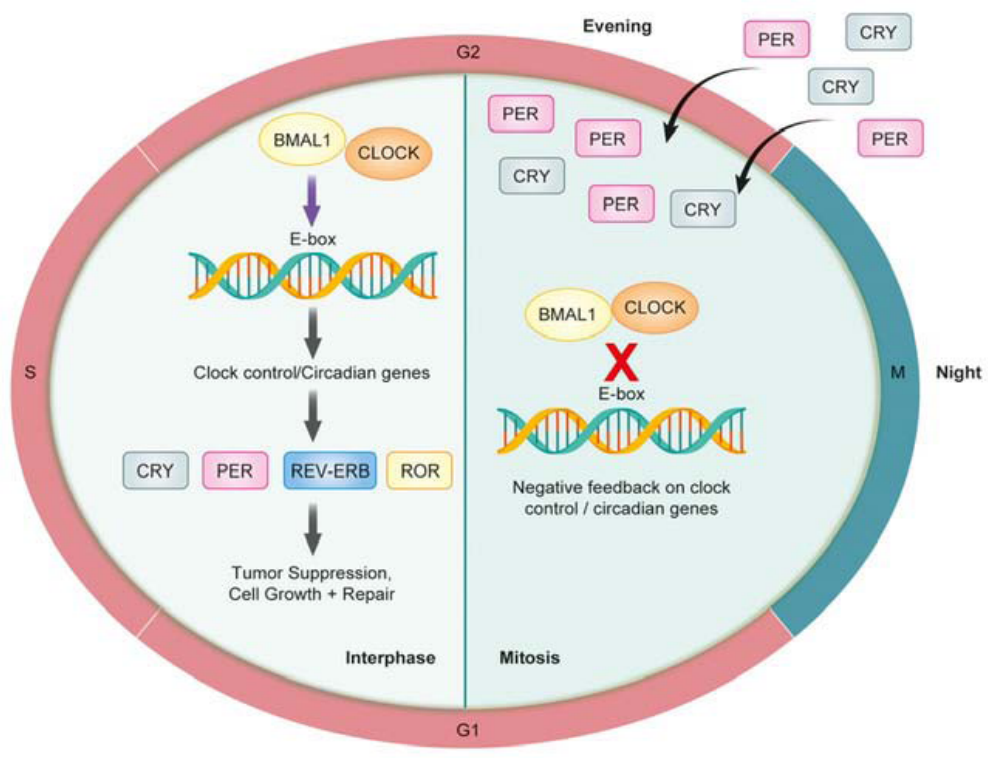

Figure 1 Whilst about 20 circadian genes and circadian controlled genes have been identified, most function as internal cogs that accelerate or decelerate BMAL1 and CLOCK gene function. [Foster, 2014] BMAL1 proteins are expressed in a rhythmical pattern, and CLOCK proteins are produced relatively constantly. During the day, ROR, REV-ERB, PER and CRY protein production results from the unification of CLOCK with BMAL1, producing a heterodimer which binds to the E-box promoter region, marked by period and cryptochrome enhancers. [66] DEC, D-box Binding Protein, E4BP4, and other proteins influence the expression further by competitively binding with E-box, inhibiting the CLOCK:BMAL1 heterodimer from binding with E-box [8,46]. If the CRY and PER proteins are not dimerized, they are degraded, once phosphorylation is triggered by kinases. They are then transferred to the nucleus, from the cytoplasm, and begin to function as part of a negative feedback cycle. This incites inhibition of the CLOCK: BMAL1 heterodimer transcription and coincides with the evening and G2 phase of the cell cycle. The cessation of protein production prepares the cell for mitosis. The rhythmical expression leads to the circadian pattern of the REV-ERB, PER and CRY protein production [8,45].

Abbreviations: BMAL-1 Brain Muscle ARNT-like Protein 1; CLOCK Circadian locomotor output Cycles Kaput; CRY Cryptochrome; PER period gene; REV-ERBs Reverse Strand of ERB Alpha and Beta; RORs Retinoic Acid-Related Orphan Receptor Alpha Beta Gamma

rhythms putting circadian rhythms and cancer in the scientific spotlight. Despite substantial progress, the identification of more in-depth molecular mechanisms remains a challenging task. The reader is referred to www.nobelprize.org for further information.

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