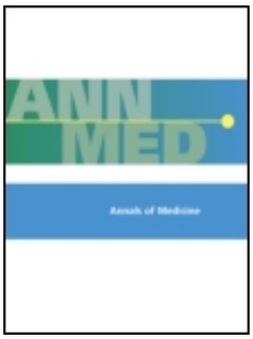

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REVIEW ARTICLE

Circadian clock disruptions and the risk of cancer

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Abstract
Disrupted circadian rhythms may lead to failures in the control of the cell division cycle and the subsequent malignant cell growth. In order to understand the pathogenesis of cancer more in detail, it is crucial to identify those mechanisms of action which contribute to the loss of control of the cell division cycle. This mini-review focuses on the recent findings concerning the links between the human circadian clock and cancer. Clinical implications concern not only feasible methods for the assessment of the circadian time of an individual or for the determination of the best time for administration of a drug of treatment, but also in the future genetic tests for screening and for planning treatment.

Key words: *Carcinogen*, *diurnal*, *epidemiology*, *exposure assessment*, *gene variant*, *occupational*

Introduction

Circadian clocks, the circadian clock genes and their encoded proteins, guide the organism to follow the natural signals of time and help in adaptation to the routine changes in environmental demands. The approximate 24-hour, i.e. circadian, rhythm is clearly present in the human physiological and behavioral processes. Circadian clock genes through their scheduled transcription modify the metabolic cycle and respiration of cells and are thus also important regulators of the cell division cycle. The circadian clock genes encode the proteins that mediate the information to the whole cell and to the network of cells (1). Considering the whole individual, as much as 2% to 10% of all the mammalian genes (the exact proportion varying from tissue to tissue) are regulated by the circadian mechanism (2–4).

From a physiological point of view, the night is an unnatural time to work, and night shift work is very likely to disrupt the circadian rhythms unless no attempt to protect from such disruption is made. In contrast, work at night on a regular basis only makes a difference in that it may not lead to disruption of the circadian rhythms but to a fixed alignment of the rhythms. On the basis of epidemiological and experimental studies, certain cancers are more common among those whose circadian rhythms are constantly disturbed by jet lag, shift work, or increased exposures to light at night (5–15). More studies are still needed, as the human data are still scarce. Regarding e.g. the influence of jet lag on cancer, studies analyzing the risks for cancer are still far too much based on animal models rather than on humans. Thus far, the International Agency for Research on Cancer, being part of the World Health Organization, has recognized shift work that involves circadian disruption as a human carcinogen of group 2A (probably carcinogenic to humans), thereby being

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Key messages

- Circadian clocks guide a number of cancer-related biological pathways.
- Disruption of this timed regulation may predispose individuals to cancer.
- The circadian clock and the cell division cycle are regulated by the same light-induced signaling pathway.
- Long-term circadian misalignment, as it is induced e.g. by work at night, may be permissive to malignant cell growth and tumor development.

equal to e.g. diesel engine exhaust, inorganic lead compounds, or the human papillomavirus type 68. Even so, a substantial proportion of people of working age is engaged in irregular shift work schedules, for instance approximately 25% of the current employees in Finland (16).

Exposure to work at night and to light at night desynchronizes the night-bound hormone production schedules, leading to the misalignment between the sleep phase of the sleep–wake cycle and the circadian rhythms as a whole as well as among the individual circadian rhythms. Therefore, light at night may induce malignant cell growth and tumor development in hormone-dependent cancers in particular (17,18), and this induction is likely through the actions of the proteins encoded by the circadian clock genes PER1 (19) and PER2 (20). Since circadian clock genes and their downstream clock-controlled genes are involved in a variety of cancer-related biological pathways, disrupted functions of these genes and their encoded proteins may enhance cancer development (Table I and Figure 1). In addition, people with certain clock gene variants might be more susceptible to cancers, especially when exposed to a condition involving disruption of the circadian rhythms such as to light exposure at night during shift work.

Circadian rhythm disruption and cancer development

Circadian clocks influence the cell division cycle through a complex regulatory pathway (Figure 1). It is likely that a number of additional pathways contribute to the regulation of circadian rhythms, carcinogenesis, and progression of cancer, as e.g. the NONO (non-POU domain containing, octamer-binding) protein is involved in both transcriptional and post-transcriptional gene regulatory functions and DNA repair (21–23). Thus, it is likely that there are several intersections of the cancer-related and

Table I. Human circadian clock gene variants associated with cancers. References are given in the brackets.

Gene	Gene abbreviation	Cancer (reference)	Mutation	Possible mechanism leading to cancer
Circadian locomoter output cycles kaput	CLOCK	Breast cancer (42,45)	rs7698022, rs11133391, rs11932595, 1048004, and rs3805151	Stimulated cell proliferation, altered hormone signaling pathway regulation
		Prostate cancer (41)	rs11133373	
Cryptochrome1	CRY1	Breast cancer (45)	rs1056560	Altered hormone signaling pathway regulation
		Prostate cancer (41)	rs12315175	
Cryptochrome2	CRY2	Breast cancer (43)	rs11038689, rs7123390, and rs1401417	Hormone stimulation
		Non-Hodgkin lymphoma (34)	rs11038689, rs7123390, and rs1401417	Altered interleukine, MHC, and chemokine gene expression
		Prostate cancer (39,41)	rs2292912, rs1401417	Stimulated cell proliferation, altered hormone signaling pathway regulation
Neuronal PAS domain protein 2	NPAS2	Breast cancer (40,44)	Ala394Thr polymorphism (rs2305160)	Hormone stimulation
		Non-Hodgkin lymphoma (33)	Ala394Thr polymorphism (rs2305160)	Impaired DNA damage response
		Prostate cancer (39,41)	rs1369481, rs895521, and rs17024926	Impaired DNA damage response
Period1	PER1	Prostate cancer (41)	rs885747 and rs2289591	Impaired DNA damage response
Period2	PER2	Prostate cancer (41)	rs7602358	Impaired DNA damage response
Period3	PER3	Breast cancer (38)	Hetero- + homozygous 5-repeat alleles	Stimulated cell proliferation, hormone stimulation
		Prostate cancer (41)	rs1012477	
Aryl hydrocarbon receptor nuclear translocator-like	ARNTL (BMAL1)	Prostate cancer (41)	rs7950226	Hormone stimulation
Casein kinase 1, epsilon	CSNK1E	Prostate cancer (41)	rs1534891	Stimulated cell proliferation

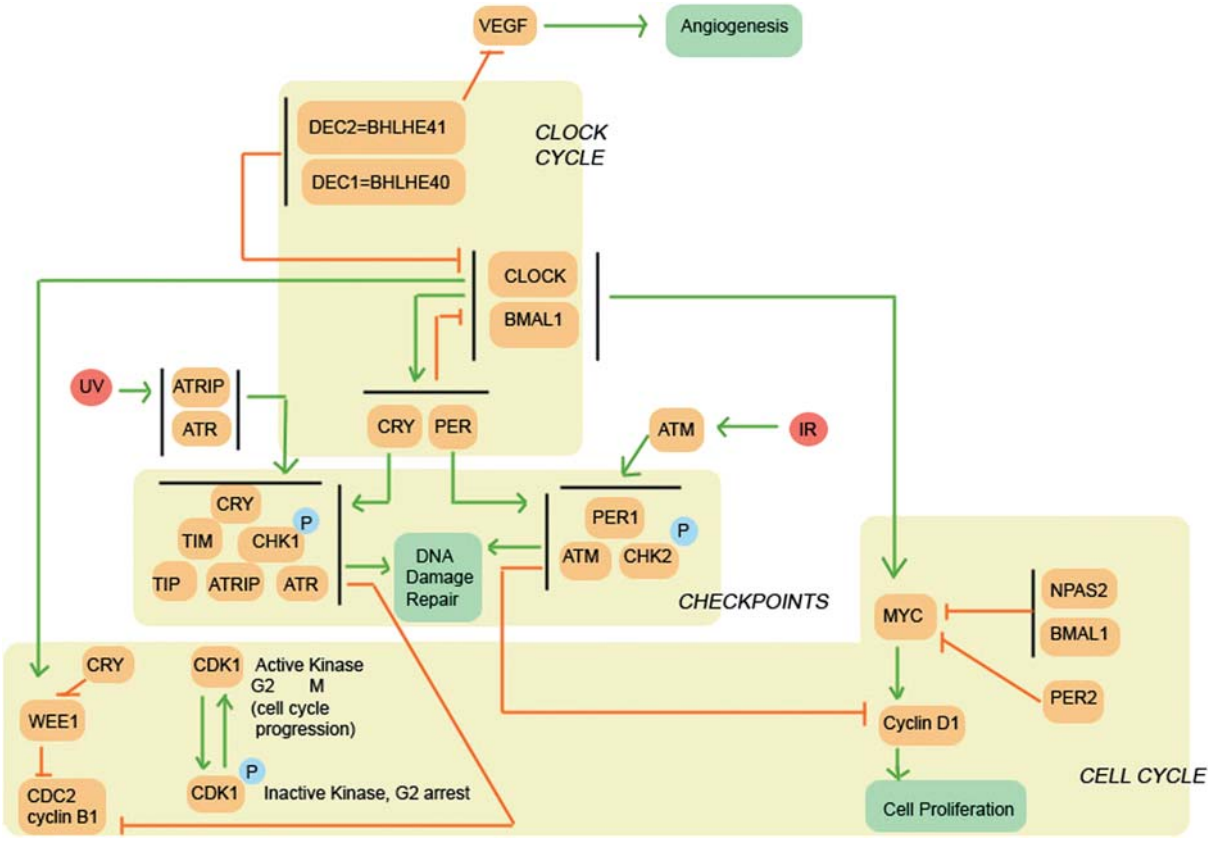

Figure 1. Association between circadian clock and cell cycle. CLOCK:BMAL1 complex regulates directly the WEE1 and MYC signaling pathway, influencing cell proliferation. CRY and PER1 participate in DNA damage repair mechanisms. CRY is directly involved in the ATR:CHK1 DNA damage repair complex by binding with TIM. PER1 on the other hand participates in the ATM:CHK2 DNA damage repair complex. DEC2 regulates VEGF, thus influencing angiogenesis (38,48,49,56,63,64).

circadian pathways. However, it is disruption of the circadian rhythms and the subsequent loss of synchronization in the regulation that is in common here. Therefore, the disruption is the key we think that can predispose individuals to the development of cancer. The mechanism by which the circadian clock is disrupted may make a difference: in particular, there is a common light-induced signaling pathway that regulates both the circadian rhythms and the cell division cycle (24). The molecule of key importance may be different from tissue to tissue, e.g. ARNTL (BMAL1) in the skin (25) and, hypothetically, PER2 or CRY2 in some of the remaining, and their disruption may then lead to a specific mode of cancer.

In recent epidemiological studies, circadian rhythm disruption has been indicated as a risk factor for breast cancer (10,12,13). Long-term night shift work seems to associate with an increased risk for breast cancer (26). However, studies in which the duration of shift work has been quantified demonstrate that robust elevations in risk are seen only after about 20 years of working night shifts, and it is unclear whether there is a risk after shorter durations. Heterogeneity of the exposure metrics and the study outcomes has been problematic in these studies and limited the usefulness of a meta-analysis as a conclusive tool.

Serum or saliva melatonin concentrations can be used as a reliable biomarker of the phase position of the circadian rhythms (27). However, the current data concerning the actions of melatonin as a bioactive protein, the nocturnal synthesis of which is inhibited by exposure to light, in the pathogenesis of cancer are still conflicting (28), albeit that melatonin induces CRY1 expression (29,30) and that melatonin levels, if reduced, are likely to affect the metabolic cascades of the cell, at least those in the liver, through the compromised actions of CRY1 and CRY2 (31). It has been suggested that circadian rhythm disruption influences the regulation of estrogen levels, thereby increasing the risk for developing breast cancer (18). Few epidemiological studies indicate a link between shift work and prostate cancer (6,7). Here, circadian rhythm disruption may also influence the levels of androgens and thereby increase the risk for prostate cancer.

Another line of evidence for the links between the circadian clock and cancer is based on findings which

demonstrate that the long-term circadian misalignment, similar to that which occurs in circadian rhythm sleep disorders, reduces leptin levels throughout the day and night and thereby predisposes to weight gain (32), known to be a risk factor for both breast and prostate cancers. However, further research is needed in order to elucidate whether these hypotheses are correct and, if correct, what the detailed mechanisms of action are.

On the other hand, circadian rhythm disruption that affects the immune response pathways might predispose to non-Hodgkin lymphoma (33,34). Here, the circadian clock gene PER2 in specific may be a key, because mice deficient in the mPer2 gene are prone to malignant lymphoma, having not only a substantial increase in tumor development and a reduced apoptosis in thymocytes after gamma irradiation but also spontaneously malignant lymphoma at younger age (35). So far, only one study has investigated the association of night shift work with non-Hodgkin lymphoma, suggesting an increased risk for non-Hodgkin lymphoma as a result of shift work that involves night work and is therefore likely to cause circadian disruption (9). Moreover, the leptin-guided signals may play a role, since leptin triggers an inflammatory response in tumor tissue by stimulating, e.g. in colorectal cancer, colonocytes to recruit T lymphocytes with a role in antitumor response in the tumor microenvironment (36,37). Currently, it is not known whether leptin has a similar role, if any, in other modes of cancer in humans.

Mechanisms of action

Current evidence suggests that the core circadian clock genes and their variants (Table I) are associated with non-Hodgkin lymphoma, prostate cancer, and breast cancer in humans (38–45). However, the functional role of these gene variants and their clinical relevance are far from clear, as it is not known yet whether the identified gene variants change the transcription, thereby having an effect upstream or downstream in the pathways. Therefore, the gene variants or the expression profiles listed in Table I cannot as yet be applied for disease screening or planning of treatment, respectively, in clinical practice.

A key to understanding the potential mechanisms of action lies in the function and the regulation of the ARNTL (BMAL1) gene (46,47), as it is essential to the circadian rhythm generation in the body. Its protein product ARNTL recruits either the CLOCK or NPAS2 protein to form a heterodimer of transcription factors with more than 100 target genes for each. On the one hand, the CLOCK:ARNTL complex regulates the cell division cycle directly through enhancing Wee1 and c-Myc transcription (48,49). On the other hand, the NPAS2:ARNTL complex suppresses c-Myc transcription (48). The heightened expression levels of ARNTL, due to the reduced actions of PER1, PER2, and CRY2, have been demonstrated to associate with non-small-cell lung cancer (50), epithelial ovarian cancer (51), and colorectal cancer (52), respectively, and their prognosis. Moreover, ARNTL is elementarily involved in the development of B lymphocytes (53), and its disruption has been indicated in a range of hematologic malignancies as well (54).

Reduced PER1 levels have been suggested to impair DNA damage repair and linked to both lung and breast cancer (55,56). PER1 has been shown to be part of the DNA damage repair pathway involving ATM and Chk2 by forming a complex with them that ensures apoptosis after DNA damage (48,49,56). CRYs (CRY1 and CRY2) are part of the ATR-Chk1 DNA damage repair pathway and interact with TIMELESS protein directly (49,56). Recently, TIMELESS has been associated with the ATM-Chk2 DNA damage repair pathway, and mutations in the TIMELESS gene have been found in both breast and colorectal cancer (57). Furthermore, reduced PER2 levels might be involved in the activation of the c-Myc signaling pathway, leading to cell proliferation (38). On the other hand, the overexpression of PER1 (55) and that of PER2 (58) inhibits tumor growth, whereas mutations in the CLOCK gene favor tumor growth by having a downstream effect on CLOCK-binding elements near target DNA damage genes (59).

In addition to the pathways referred to above, disruption of the circadian rhythms might increase the risk for cancer through angiogenesis (60,61). This is a fact because ARNTL controls cancer cell proliferation not only by generating the circadian rhythm, but also by timing DNA replication through thymidylate synthase activity, cell mitosis through WEE1 levels, and growth through vascular endothelial growth factor (VEGF) levels (62). In line with the circadian-related pathogenesis are the findings that impaired sleep is associated with elevated serum VEGF concentrations (63), and that the circadian clock protein BHLHE41 suppresses VEGF expression under hypoxic conditions (64,65).

Conclusions

Since the circadian rhythms and the cell division cycle share common regulatory elements, it is possible, or even likely, that disruption in functions of the circadian clock is a factor predisposing to cancer (66–68). Night work, or any condition similar to it that disrupts circadian rhythms, challenges the

circadian clock to the limit and may thereby cause a failure in the control of the cell division cycle, being permissive to malignant cell growth. In addition, circadian clock gene variants may modulate the physiological responses to such challenges, and *de-novo* mutations in circadian clock genes may contribute to tumor development. Thereby they both have a potential as biomarkers for those cancers known to be influenced by circadian factors or to have a circadian component in the pathogenesis. However, it is not only genetic variants or mutations that count, but environmental stimuli from wrongly scheduled time-givers also influence the development of certain cancers, and as they do so, preventive measures are available and can be taken forward.

Implications of the circadian systems biology in oncology are about to be introduced into clinical practice (69). They include clinically feasible methods for the assessment of the individual's circadian time that are based on the analysis of levels of time-indicating molecules. Such molecules include metabolites derived from a single sample of venous blood and messenger RNAs captured directly from a tissue of interest through biopsy. In the former the assessment can be based on a range of methods, e.g. enzyme-linked immunosorbent assay or mass spectrometry using the approximate 20 time-indicating metabolites (70), whereas in the latter it is based on DNA microarray using the approximate 60 time-indicating genes (71).

Individuals of different circadian genotypes may have marked differences in their responses to toxic anticancer drug metabolites (72). Therefore, methods for the determination of the best time, judging by both efficacy and toxicity, for administration of a drug in the treatment are well justified and welcome. Properties of the tumor such as the cell proliferation rate and the durations of the cell cycle phases may guide not only the drug of choice but also the timing of treatment schedules with the drug (73). As exemplified with irinotecan in the treatment of colon cancer cells, the optimal scheme for any dose is 1) to start the administration between 2 h 10 min and 2 h 30 min *circadian time*, and 2) to administer it for 4–7 hours (74). This scheme times the administration of irinotecan according to the levels of carboxylesterases and permits proteins involved in the elimination of irinotecan to protect healthy cells efficiently. However, despite these advances, there is still a lack of clinical verification and a gap of knowledge concerning the functional significance and the clinical relevance that needs to be explored, in order to have a better understanding of the link between circadian rhythm disruption and cancer disease.

To understand the pathogenesis of cancer in more detail, it is important to identify the details of those mechanisms that contribute to the loss of control of the cell division cycle in particular. All cancers where circadian rhythms are disrupted need to be identified, as some of the circadian-based options available for the treatment may prove to be clinically feasible. However, this step ahead needs to be based on experimental evidence and clinical trials. New potential preventive measures of these circadian-type cancers should then be targeted at large in order to avoid the long-term or recurrent circadian rhythm disruptions. Such actions can be achieved by making living and working circumstances more compatible with the circadian preference of an individual, which is driven by the timing of innate physiology.

Declaration of interest: The authors report no conflicts of interest.

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