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Human Clock Genes and Cancer

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Abstract

Purpose of Review Modern social life often demands aberrant light exposures (i.e., jet lag, shift work, or nocturnal life style), which results in desynchronization and misalignment of circadian rhythms. Experimental and epidemiological data suggest that circadian disruption, caused by genetic manipulations or forced light/dark conditions, promotes cancerogenesis. Human genetic studies highlight the contribution of individual clock genes to this process, though the exact function is somewhat controversial.

Recent Findings Multiple reports demonstrate an association of genetic variations within clock genes with risk of tumor development. Mutations or deregulated expression of clock genes are frequently detected in different tumors and often show correlation with cancer progression and patient prognosis. Cellular studies report contradictory results that clock genes can inhibit as well as support tumor growth and proliferation in different cells.

Summary Clock genes appear to have multifaceted functions during cancer development and can act both as tumor suppressors or promote cancerogenesis depending on the particular type of tumor. However, the exact conditions and factors which determine such behavior remain elusive and must be investigated in future studies.

Keywords Clock genes · Circadian clock · Cancer · SNP · Mutation

Introduction

In essentially all living organisms, from cyanobacteria to humans, physiological and behavior responses are manifested in 24-h cycles, thereby, improving metabolic fitness and survival under daily changes of food availability, temperature, and light. The circadian system in mammals has a complex hierarchical structure with central clock and peripheral oscillators. The central clock resides in the suprachiasmatic nuclei (SCN) of the brain and perceives light information directly from the retina via optical nerves [1]. In contrast, other organs contain peripheral clocks, which encompass single-cell oscillators found in virtually all cells of the body or cultured cell lines [2]. Entrainment of peripheral oscillators by SCN via humoral and neuronal pathways, or temperature, is crucial to maintain synchrony of central and peripheral body clocks between each other and the external environment [2]. Alternative entraining cues, such as food, can also reset peripheral clocks independent of SCN and shift the balance in the internal synchrony [3].

The molecular apparatus of the circadian system consists of several clock genes interlocked in the cell autonomous network of transcriptional-translational feedback loops (TTLs). Transcription factors CLOCK and BMAL1 heterodimerize to induce expression of negative regulators Periods (*PER1-3*) and Cryptochromes (*CRY1-2*). Translated PERs and CRYs gradually accumulate in the cytoplasm and form macromolecular complexes up to 1 MDa, that later translocate into the nucleus to repress CLOCK and BMAL1 [4]. Consequent degradation of PERs and CRYs allows CLOCK and BMAL1 to launch a new cycle of transcriptional activity, resulting in 24 h oscillations of transcription [5]. Additionally, a family of nuclear receptors REV-ERBs (α and β) and RORs (α, β, and γ) controls rhythmic expression of *BMAL1* gene and other targets through competitive binding to cognate response elements in the promoter region [6]. The molecular clockwork impacts cellular and tissue physiology via the large network of

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clock-controlled genes (CCGs), whose rhythmic expression is regulated by different clock factors on transcriptional and posttranscriptional levels [7, 8].

Tumor-Protective Function of the Circadian Clock

Extensive experimental evidence, obtained on laboratory animals, demonstrates that disruption of circadian rhythms often leads to malfunction of diverse physiological processes [9]. Thus, the question whether circadian disturbances affect human health in similar manner became a subject of intensive investigations. Indeed, multiple epidemiological studies showed that impaired function of the circadian clock promotes development of different disorders, such as metabolic syndrome, cardiovascular disease and cancer [10]. Light exposure at night, shorter sleep duration, and irregular food intake, along with high caloric diets are inevitable attributes of the modern postindustrial society, and cause desynchronization of body clocks. In turn, circadian disruption impacts multiple aspects of human health potentially leading to impaired metabolism and cancer [11, 12]. Indeed, prolonged shift work and chronic jet lag were associated with development of cancer [13–15]. Accumulating evidence in this field prompted the World Health Organization (WHO) to include shift work in the officially recognized list of cancerogenic factors as "probably carcinogenic to humans" [12, 16].

Animal models of circadian disruption, such as chronic jet lag or constant light exposure, clearly demonstrate that the presence of an intact circadian clock system exerts a tumor suppressive function [17–19, 20•]. Furthermore, genetic ablation of clock genes in mice resulted in higher frequency of spontaneous and induced tumors [21, 22••]. Consistently, expression of certain clock genes, such as *Per2*, also suppressed proliferation in murine cancer cells [23]. Together, these findings suggest that synchrony of the circadian system and intact molecular clocks are required to maintain both healthy homeostasis in cell division and to prevent cancer.

Influence of Human Clock Genes on Cancer

Genomic alterations involving clock genes, such as point mutations or copy number variations (CNV), are frequently found in different human cancers (Table 1). As a consequence, tumors often show deregulated expression of clock genes (Table 1). Additionally, human geneticists identified in circadian genes polymorphic regions and small genetic variations, such as single nucleotide polymorphisms (SNPs), which may profoundly affect the function of the gene [25]. In turn, certain polymorphic alleles showed higher frequency of occurrence in different cancer samples, correlating with their malignancy and clinical outcome.

BMAL1

In mice, genetic ablation of single clock gene *Bmal1*, the partner of *Clock*, yielded arrhythmic locomotor activity accompanied by multiple pathological conditions, including accelerated aging and cancer [21, 26, 27, 28•]. Tissue-specific deletion of *Bmal1* in skin resulted in disrupted proliferation of keratinocytes, resembling a pre-cancerous state [29]. In line with these observations, several studies reported reduced expression of *BMAL1* in different types of human malignancies [30–33]. Moreover, certain genetic variants of *BMAL1* gene (rs2278749) negatively correlated with risk of breast cancer [34]. Finally, ectopic expression of *BMAL1* efficiently inhibited proliferation of cancer cells, highlighting the tumor suppressor function of this gene [35, 36].

Concurrently, other groups reported results contrasting with aforementioned previous findings. For instance, expression of *BMAL1* in malignant pleural mesothelioma appeared to be higher than in normal tissues [37••]. Furthermore, *BMAL1* gene was identified as a survival factor for several tumors, since it was required to prevent differentiation of cancer cells and facilitated their mitosis [37••, 38••], suggesting that BMAL1 can also promote tumor growth under certain conditions.

CLOCK

Monoallelic and biallelic mutations of human *CLOCK*, resulting in reduced expression of this gene, were reported in many cases of colorectal cancer [39]. In particular, the truncating mutation *CLOCK T8*, was observed in 47 of 53 cases of colorectal cancer, and led to production of aberrant protein. CLOCK T8 lacked a transactivation domain and acted in a dominant-negative manner, perhaps, similar to $Clock^{\Delta 19}$ mutation in mice [39, 40]. SNP in the 3'UTR of the *CLOCK* gene (rs1801260), which was previously associated with diurnal preference [41], also correlated with development of the colorectal cancer [42]. *CLOCK* SNPs rs1801260 and rs3749474 associated with survival in patients with the colorectal cancer [43]. Interestingly, the latter SNP (rs3749474) and another *CLOCK* SNP (rs3805151) also significantly correlated with risk of breast cancer [44–45], suggesting that *CLOCK* gene polymorphisms may serve as prognostic markers for cancer patients.

It is worthwhile to mention that certain types of breast and colorectal cancers showed higher expression of *CLOCK* gene compared to normal tissues [46, 47, 48••]. Additionally, *CLOCK* gene variants (SNPs rs7698022 and rs11932595) significantly associated with more aggressive ER/PR-negative tumors, which did not respond to hormone therapy and had

Table 1 Frequency of genomic alterations of clock genes in cancer according to Catalogue of Somatic Mutations in Cancer (COSMIC) (cancer.sanger.ac.uk) [24]

Gene	Point mutations	Copy number variation (CNV)		Gene expression	
		Gain	Loss	Overexpressed	Underexpressed
BMAL1	167/31969 (0.5%)	35/8204 (0.4%)	7/8204 (0.09%)	358/9144 (3.9%)	32/9144 (0.35%)
CLOCK	197/32018 (0.6%)	95/11409 (0.8%)	10/11409 (0.09%)	442/9144 (4.8%)	10/9144 (0.1%)
NPAS2	206/31976 (0.64%)	26/8166 (0.32%)	5/8166 (0.06%)	450/9144 (4.92%)	3/9144 (0.03%)
CRY1	149/31979 (0.47%)	19/7086 (0.3%)	4/7086 (0.06%)	465/9144 (5.1%)	45/9144 (0.49%)
CRY2	133/31976 (0.42%)	35/10854 (0.32%)	8/10854 (0.07%)	355/9144 (3.88%)	39/9144 (0.43%)
PER1	295/32963 (0.89%)	16/11069 (0.14%)	31/11069 (0.28%)	331/9144 (3.62%)	7/9144 (0.08%)
PER2	294/32040 (0.92%)	5/8968 (0.06%)	27/8968 (0.3%)	337/9144 (3.69%)	14/9144 (0.15%)
PER3	270/31977 (0.84%)	19/10926 (0.17%)	31/10926 (0.28%)	396/9144 (4.33%)	0/9144 (0%)
REV-ERBα	150/32069 (0.48%)	188/11344 (1.66%)	6/11344 (0.05%)	486/9144 (5.31%)	222/9144 (2.43%)
REV-ERBβ	133/32158 (0.41%)	19/8078 (0.24%)	14/8078 (0.17%)	430/9144 (4.7%)	31/9144 (0.34%)
RORα	152/32133 (0.47%)	20/10096 (0.2%)	16/10096 (0.16%)	338/9144 (3.7%)	9/9144 (0.1%)
RORβ	8/32069 (0.02%)	20/10575 (0.19%)	13/10575 (0.12%)	325/9144 (3.6%)	0/9144 (0%)
RORγ	211/34156 (0.62%)	308/14638 (2.1%)	4/14638 (0.03%)	781/9144 (8.54%)	14/9144 (0.15%)
TIMELESS	303/32040 (0.95%)	38/9060 (0.42%)	1/9060 (0.01%)	656/9144 (7.17%)	45/9144 (0.49%)

poorer prognosis [46]. Moreover, similar to BMAL1, CLOCK appeared to be required for proliferation of certain tumors [38••, 49], arguing against its role as a tumor suppressor gene.

NPAS2

NPAS2 is considered as a functional homolog of CLOCK with partially overlapping role in the TTLs mechanism [50]. Polymorphisms in the promoter and coding regions (rs2305160, Ala394Thr) of *NPAS2* gene were significantly associated with increased risk of certain tumors, such as breast cancer, non-Hodgkin's lymphomas, hepatocellular carcinomas, and melanomas [51–54]. Colorectal cancer showed lower expression of *NPAS2* compared to healthy tissues, negatively correlating with tumor size, stage and metastasis. Subsequent depletion of *NPAS2* with siRNA resulted in increased proliferation, migration and invasiveness of tumor cells [55].

In contrast, *NPAS2* expression in hepatocellular carcinoma cells was upregulated, compared to peri-tumoral tissues, and positively correlated with both tumor progression and poorer prognosis. Furthermore, knockdown of *NPAS2* in these cells yielded decreased tumor growth and proliferation, whereas *NPAS2* overexpression produced an opposite effect [56], asserting that NPAS2 is necessary for development of certain tumors.

PERs

PERs were the first clock genes linked to the cancer development in humans and mice [57–59]. The initial evidence hinting to the tumor suppressor function of mammalian *PERs* originated from experiments on $Per2^{m/m}$ mice, which developed tumors after γ-irradiation [57]. Indeed, *PER2* gene, transfected in sarcoma cells, suppressed proliferation and tumor growth in a dose-dependent manner [60]. Moreover, antiproliferative properties were also attributed to *PER1*, which suppressed cell growth in several tumor cell lines, and showed reduced expression in lung cancer [61]. Consistently, other cancers also exhibited decreased activity of *PER* genes [59, 62–66]. Moreover, lower levels of *PERs* often correlated with higher malignancy and poorer survival [30, 63]. Remarkably, a conserved residue in human *PER2*, Serine 662, mutated to Glycine in case of Familial advanced sleep-phase syndrome (FASPS) [67], played a prominent role in tumorigenesis. Transfection of *PER2 S662G* and *S662D* variants markedly increased oncogenic transformation and decreased apoptosis in $Per2^{-/-}$ mouse embryonic fibroblasts (MEFs) [68].

A variable number tandem repeat (VNTR) sequence within *PER3* gene (rs57875989), containing 4 or 5 copies of a 54-bp sequence (18 amino acids), was previously linked with diurnal preference (*PER3* 4/4 evening and 5/5 morning phenotype) and sleep homeostasis [69]. The same VNTR region showed significant association with higher risk of breast cancer for *PER3* 5/5 carriers [58]. Moreover, individuals carrying five alleles in *PER3* were also more susceptible to formation of adenomas [70]. Besides this observation, several other polymorphic regions in *PER3* gene were shown to modify risk of cancer. For instance, SNP (rs228729) significantly correlated with risk of lung cancer [64], whereas SNP (rs2640908) associated with overall survival in patients with hepatocellular carcinoma [71].

Nevertheless, expression of *PERs* is not generally reduced during cancerogenesis. Significantly higher levels of *PER2* mRNA and protein were detected in samples from gastric cancer [72]. Similarly, expression of *PER1* and *PER2* positively correlated with tumor size in colorectal carcinomas [73]. Therefore, although *PERs* exhibit mostly antioncogenic properties, it might not be the case in some specific tumor types.

CRYs

The link between cancer and *CRY* genes is particularly interesting, since mammalian *CRYs* have high sequence homology to photolyases, enzymes involved in repair of the light-induced DNA damage [74]. Indeed, lower expression levels of *CRY1* and *CRY2* were reported in different cancers [75]. Polymorphisms in *CRY1* (rs1056560) and *CRY2* (rs1401417) genes also significantly modified risk of breast cancer [45]. SNP (rs1056560) in 3′UTR region of *CRY1* gene correlated with overall survival in gastric cancer and modulated patients' response to platinum-based adjuvant chemotherapy [76]. Several genetic variants of *CRY2* showed significant association with susceptibility to non-Hodgkin's lymphomas [77].

Interestingly, loss of Cry proteins in murine models significantly reduced the risk of cancer [78]. In addition, higher expression of *CRY1* correlated with poor prognosis in patients with colorectal cancer [79], suggesting tumor promoting functions for CRY1.

REV-ERBs and RORs

Activation of both REV-ERBα and β by a synthetic agonist (SR9011) suppressed the viability of breast cancer cells, hinting at the tumor suppressor potential of these transcriptional regulators [80]. Nevertheless, certain breast cancer tumors showed amplification of the genomic region containing *REV-ERBα* gene [81, 82]. Proliferation of highly aggressive ERBB2-positive breast cancer cells was dependent on REV-ERBα [83]. Moreover, pharmacological inhibition of REV-ERBs in cancer cells led to enhanced cytotoxicity and improved sensitivity to anticancer drugs [84].

A family of RORs include three members (RORα, RORβ, and RORγ), which antagonize REV-ERBs and activate transcription of target genes [85]. The function of RORs, however, spans beyond the regulation of circadian rhythms, since RORs are also implicated in differentiation and maturation of various cell types [86]. Mounting evidence suggests that RORs may play a tumor suppressor role in cancer related pathways [87]. Indeed, ligand-induced activation or transfection of exogenous *RORα* inhibited proliferation and tumor growth in different cancer lines [88–90]. Mice with targeted deletion of *Rorγ* were highly susceptible to development of aggressive highly metastatic T-cell lymphomas [91]. Finally, different tumors and cancer cell lines showed reduced expression levels of *RORs*, often correlating with higher malignancy and poor prognosis [92–97].

Accordingly, multiple genetic variations within *RORs* genes were associated with risk of cancer, such as SNPs in *RORα* (rs7164773, rs10519097, rs1482057, and rs12914272 for breast cancer) and *RORβ* (rs3903529, rs3750420, and rs7867494 for breast cancer) [34, 44, 98].

Notably, a particular isoform of RORα, RORα2, promoted cell motility and migration in breast cancer cells and showed elevated protein abundance in breast cancer tumors [99]. Additionally, expression of *RORβ* was found to be increased in the highly metastatic leiomyosarcoma of uterus [100]. In turn, prostate cancer showed higher expression of *RORγ*, correlating with malignancy and metastasis. Subsequent siRNA-depletion of *RORγ* or treatment with its chemical antagonists impaired viability of prostate cancer cells and hampered tumor growth [101••].

TIMELESS

Although, TIMELESS is a mammalian homolog of the bona fide component of the Drosophila clock, it does not have clearly assigned function within mammalian TTLs [102]. Nevertheless, TIMELESS was suggested to mediate DNA damage induced resetting of the circadian clock and facilitate coupling of the circadian oscillator with the cell cycle [103, 104]. Furthermore, TIMELESS had a critical role in DNA damage-mediated activation of both check-point kinases CHK1 and CHK2, thus, influencing proliferation and sensitivity to anti-cancer drugs in tumor cells [103, 105–107]. Consistent with this, deregulated expression of *TIMELESS* was documented in several tumors, such as lung and breast cancers, negatively correlating with patient survival [106, 107]. Genetic variants of *TIMELESS* gene (rs2291738 and rs7302060) were also significantly associated with development of breast cancer [108].

Conclusions

Experimental studies, in combination with epidemiological and genetic data, favor the concept that human circadian clock and, in particular, clock genes play an important role during tumorigenesis. According to the prevailing hypothesis, clock genes manifest predominantly antioncogenic properties and inhibit uncontrolled proliferation via homeostatic regulation of cell division. Altered expression or mutations of clock genes per se are rather unlikely to be a primary driver of cancer, though these aspects may definitely contribute to growth and progression of tumors via disrupted

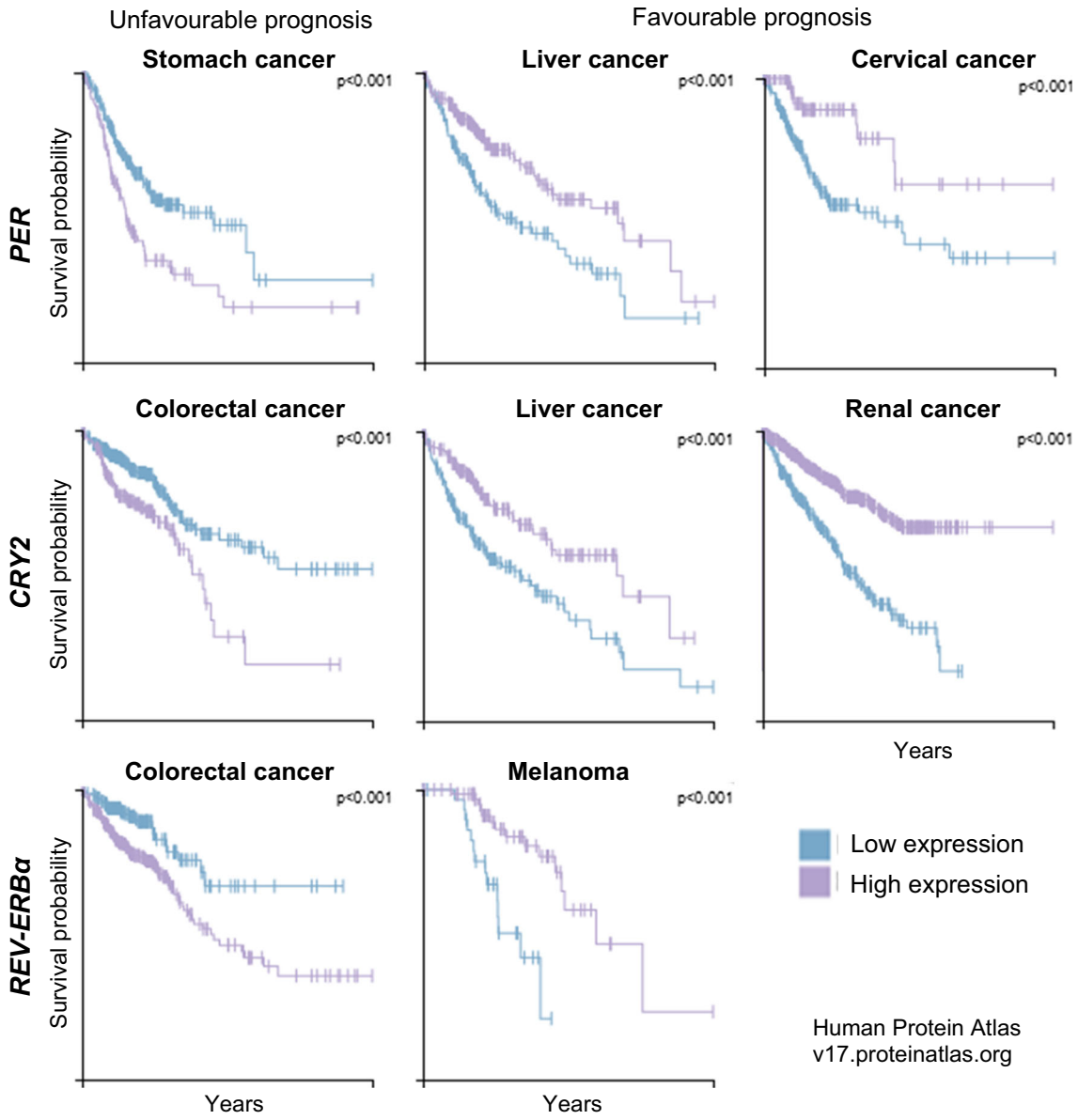

Fig. 1 Prognostic value of clock gene expression in different cancers. Kaplan–Meier survival graphs of patient cohorts, grouped upon expression levels of *PER1*, *CRY2*, and *REV-ERBα*. Images and data available from v17.proteinatlas.org

temporal control of physiology at the local and systemic levels. On the other hand, clock genes may also support tumor growth under certain conditions, since many cancers express high levels of clock genes and require them for survival. Perhaps, these effects depend on the type of cancer and the tissue of tumor origin. Indeed, low or high expression levels of several clock genes in tumors from different tissues may have opposite prognostic values (Fig. 1). For instance, high expression of *PER1* in stomach cancer had a negative prognosis on survival of patients, whereas in the case of liver and cervical cancers—higher expression of *PER1* was linked to a more favorable prognosis [109–111]. Similar phenomena can be also observed for *CRY2* and *REV-ERBα* (Fig. 1), suggesting that individual mutational signatures occurring in different cancers may define the overall influence of clock genes on tumor physiology. Thus, future research, focused on the exact molecular mechanisms determining such tumor-specific behavior, will help us to improve our comprehension of mutually driven interactions between the circadian clock and cancer.

Compliance with Ethical Standards

Conflict of Interest Anton Shostak declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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