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# Chronotherapy and the molecular clock: Clinical implications in oncology ☆

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ABSTRACT

The circadian timing system drives daily rhythmic changes in drug metabolism and controls rhythmic events in cell cycle, DNA repair, apoptosis, and angiogenesis in both normal tissue and cancer. Rodent and human studies have shown that the toxicity and anticancer activity of common cancer drugs can be significantly modified by the time of administration. Altered sleep/activity rhythms are common in cancer patients and can be disrupted even more when anticancer drugs are administered at their most toxic time. Disruption of the sleep/activity rhythm accelerates cancer growth. The complex circadian time-dependent connection between host, cancer and therapy is further impacted by other factors including gender, inter-individual differences and clock gene polymorphism and/or down regulation. It is important to take circadian timing into account at all stages of new drug development in an effort to optimize the therapeutic index for new cancer drugs. Better measures of the individual differences in circadian biology of host and cancer are required to further optimize the potential benefit of chronotherapy for each individual patient.


**Contents**



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## 1. Introduction

### 1.1. The circadian timing system

The circadian timing system is a hierarchical network that temporally coordinates biological and physiological processes along the 24-h day [1–11]. Endogenous, self-sustained, 24-h rhythmic oscillations within the hypothalamic pacemaker, the paired suprachiasmatic nuclei, are entrained to the 24-h changes in external environment through input signals from sensory organs and from other brain areas [1–10]. In turn, the hypothalamic pacemaker generates behavioral rhythms and synchronizes ubiquitous clocks in peripheral organs through neuronal, physiological and endocrine output signals, resulting in measurable and therapeutically exploitable circadian variations [1–8,10,12–14]. Thus, rhythms in hormonal secretions including cortisol, catecholamines and melatonin, autonomic nervous system activity, core-body temperature, physical and cognitive performance (Fig. 1) form a dynamic physiological network which resets and coordinates the peripheral molecular clocks. These rhythms can be monitored and serve as biomarkers of the circadian timing system [1–8,12–15].

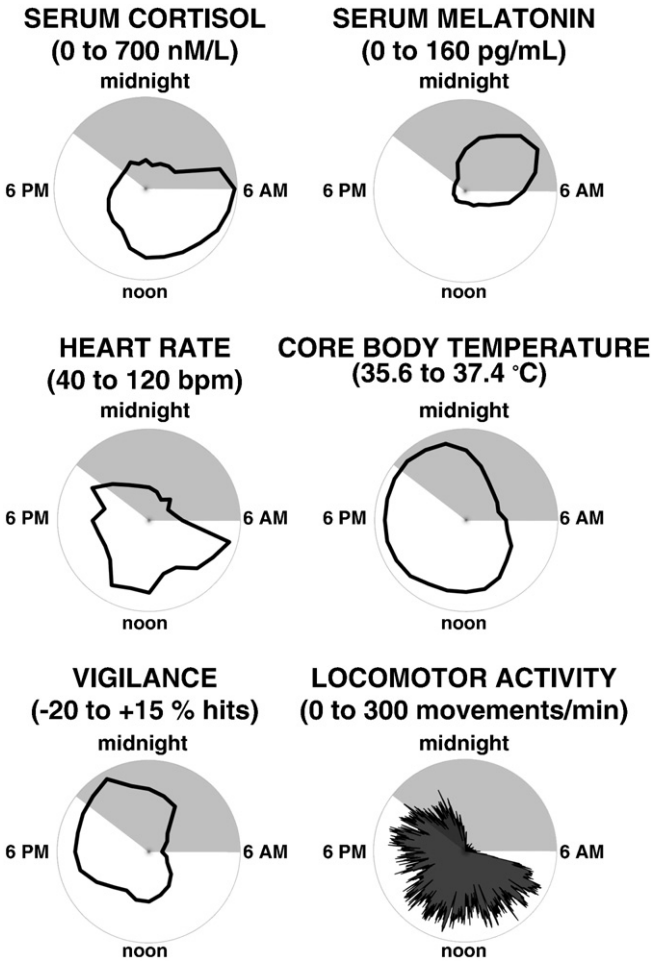


**Fig. 1.** Examples of six markers of circadian physiology in humans. The white part of the circle represents daylight (from 06h00 till 22h00), the grey part represents the night (from 22h00 till 06h00). For each rhythm, the scale indicated goes from the centre of the circle (lowest value) to the periphery or the circle (highest value). Serum cortisol (upper left panel), with low values in the night, peak in the early morning, and decreasing values through the day; serum melatonin (upper right panel), with high values at night and extremely low values through the day; heart rate (middle left panel), with higher values during active daytime, and lower values during nighttime rest; core-body temperature (middle right panel), whose decrease coincides with nighttime sleep; vigilance (bottom left panel), expressed as percentage of correct reaction to a stimulus, with lowest values at subjective night and better performance during daytime; locomotor activity (bottom right panel), with large difference between the daytime active span and the restful nighttime span.

Each mammalian cell is equipped with a self-sustained molecular clock, resulting from interconnected and auto-regulatory transcriptional, post-transcriptional and post-translational loops involving a genetic network of at least 15 gene products [1,13,16–25]. Alongside these identified core clock genes, at least 10 other proteins, including several kinases and the proteasomal machinery, are implicated in the control of clock protein stability and degradation, thus regulating the abundance, activity and subcellular localization of the core clock proteins [1,13,16–25]. This molecular clock generates self-sustained ~24-h cyclic oscillations in individual cells, which can be entrained by internal cues, such as endocrine and temperature rhythms [1,10,13,16–25]. One of the main outputs of the ticking molecular clock within each cell is the coordinated transcription of ~10% of the genome with a circadian rhythmic pattern [1,10,16,25–35]. The circadian transcriptome is tissue-specific, and constitutes the molecular basis of circadian rhythms in the whole organism. Clock genes expression at the mRNA and/or protein levels has been reported in 17 tissues of healthy human subjects and/or cancer patients [1,36–67] (Table 1).

This orchestration is controlled by specific activation of the transcription of clock-controlled genes by core clock proteins [30,31,68] (Fig. 2). Moreover, several of the clock-controlled genes have themselves properties of transcriptional factors, thus amplifying the oscillatory signals generated by the molecular clock, acting through other specific promoters [30,31,68] (Fig. 2). Clock-controlled genes are not only limited to protein-encoding sequences, since further fine-tuning of regulation and tissue specificity of the circadian transcriptome and its associated circadian proteome is provided by cyclic variations in microRNA (miRNA) expression and regulation of translation [69–81]. Another level of coordinated circadian transcriptional regulation relies on the chromatin remodeling by core clock proteins through histone modifications, producing dynamic changes in chromatin transitions [33,82–84].

### 1.2. Relevance of circadian perturbation in cancer

Large epidemiologic studies have shown a significant association between circadian disruption induced by shift-work and higher risk of cancer. In the first Nurses' Health Study cohort, involving 121,700 female nurses younger than 55 years at study entry, extended periods of rotating night work were significantly associated with a 36% increased risk of breast cancer, colorectal cancer (35%), and endometrial cancer (43%), independent of other known risk factors for each of these cancers [85–88]. A subsequent Nurses' Health Study cohort, involving 116,678 female nurses younger than 42 years at study entry, further confirmed the risk increase in breast cancer, with an even more important increase in relative risk (79%) [88]. In men, rotating shift-work was found to be significantly and independently associated with increased risk of prostate cancer, in two independent cohorts in Japan and Canada [89,90]. These human epidemiologic studies, and evidence from rodent studies for the carcinogenicity of light during the biological night, led a 24-members Working Group for the World Health Organization International Agency for Research on Cancer to conclude that shift-work, that leads to circadian disruption, was probably carcinogenic for humans (level of evidence 2A) [91].

Experimental data linking the molecular clock and the cell division cycle (reviewed in [92–97]) have raised the possibility that clock genes may play an important role in human cancer development and progression. Large population-based studies have documented a relatively high degree of polymorphism in human clock genes [98–103], and several of the germline clock genes variants have been shown to affect the phenotype of the subject [1,13]. In recent case–control studies, clock gene polymorphisms have been associated with a significant modification of the risk of non-Hodgkin lymphoma,