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Evaluating Circadian Oscillators in Cancer Stem Cells

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Abstract

Cancer is influenced by the ability of cells to maintain circadian rhythms in molecular and metabolic processes. Disturbance of the underlying circadian timing mechanism in circadian clock cells leads to a higher frequency and more rapid progression of cancer. Cancer stem cells with properties of embryonic and somatic stem cells have been implicated as tumor initiators in several types of cancers. Although tumors are reported to have disorganized circadian rhythms, evidence of in vitro circadian rhythms in cancer stem cells of gliomas was recently presented. The possibility and consequences of circadian clocks functioning in cancer stem cells within tumors is examined, and the possible benefits to these cells from circadian timing is discussed in relation to cancer treatments.

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Introduction

Circadian Rhythms and Cancer Cell Survival

The relationship between circadian rhythms and cancer is generally thought to be one of mutual exclusion. Circadian rhythms are approximately 24-hour oscillations in physiology or behavior that are reported to be either poorly defined or lacking in cancer cells [1-3]. Similarly, robust circadian rhythms are thought to suppress carcinogenesis and tumor growth [4-6]. The benefits provided by circadian timing have been discussed and reviewed elsewhere in relation to events external to the organism [7-10]. The ability to anticipate daily occurrence of food sources, favorable temperatures, and mates or avoid predictable hazards such as predators and environmental stressors are just some of the potential benefits offered by the clock that provide adaptive value.

Probably because of adversely timed light exposure and the disrupted circadian timing system that follows [11], individuals working night shifts are reported to have higher incidences of breast cancer [12, 13] and non-Hodgkin's lymphoma [14]. A major cause appears to be light-induced alterations in the daily oscillations of the hormone melatonin [15-19], a possible cancer suppressor [20-22], although not all studies support this mechanism [23]. Altered rhythms in cortisol and other factors that provide timing information throughout the body may also be involved in the effects of light exposure and circadian disturbances during nighttime work [24-26]. Circadian timing disruption might indirectly promote cancer by fostering obesity and the metabolic syndrome [27] or by shortening sleep duration [28-30]. A more proximal cause is shown by the loss of circadian timing in mice or cancer cell lines, through knockout of critical core genes within the timing mechanism, which increases cancer occurrence, progression and invasiveness [6, 31-34]. Circadian clock gene expression is also disrupted and repressed in stomach and colon cancer tissue [35-37], and recent evidence suggests that sequence variations within clock genes can elevate cancer risk [38-41].

Essentially, what has emerged is a homeostasis-based view that a poor clock enables aggressive cancer [42-51]. This short review will examine an additional perspective: that some cancer cells may benefit from circadian rhythms and that tumors may have significant timing abilities. In fact, cancer stem cells (CSCs) may undergo selection for a circadian timing mechanism that could have unique properties in part because of their hypoxic environment [49]. CSCs are distinct among cancer cells in many ways. They divide slowly, thereby evading antimitotic cancer therapies, but can differentiate into rapidly proliferating progenitor cells forming the mass of most tumors. They are also endowed with elevated levels of transmembrane drug transporters (e.g., ABCG2), toxin-degrading enzymes (aldehyde dehydrogenase), and anti-apoptotic transcriptional activators (NFκB) [52-55]. They share with embryogenic and adult stem cells a reliance on the stem cell-maintaining Notch, Wnt/β-catenin, and Hedgehog signaling pathways [56]. The ability of CSCs to survive hypoxia through reliance on glycolysis, as shown in ovarian CSCs [57], suggests that their circadian timing mechanism might have unusual capabilities not used in non-stem cancer cells or non-cancerous cells. Recent discoveries of how metabolic pathways interact with circadian clocks [58] might be advanced by examining CSC circadian oscillators.

Cells can receive circadian timing from other clocks within the body [59] or they can produce their own rhythmic signal through interacting transcriptional and translational molecular loops [60]. Both sources of timing information have their value. For example, regulation

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through endocrine [61] or neural timing signals from central circadian pacemakers, such as the hypothalamic suprachiasmatic nucleus [8], obviates the metabolic costs to cells in maintaining their own timing mechanism. On the other hand, intrinsic timing capabilities endow the cell with the potential to maintain its timing during events that transiently desynchronize the circadian system as a whole. Causes of this timing disruption can be sleep deprivation, illness or, in the modern world, jet lag [62].

The often stated claim that all cells of the body contain a circadian clock falls short when considering available evidence. Many types of cells have not been examined. Furthermore, cells of the testis have not been found to have circadian rhythms, despite much examination [63, 64], although they do express clock genes such as *Per1* and *Per2*. Similarly, embryonic cells are reported to lack a circadian clock, but a rhythm appears upon their differentiation [65]. Some adult stem cells, such as those in the skin, do contain a circadian clock [66, 67]. One possible disadvantage to the organism from having intrinsic cellular timing capabilities distributed in multiple cells of the body is that mutations in some clock cells, as well as their clones, may drive them into a rogue timing state in which their altered circadian rhythms conflict with nearby cells. Such a mutation could lead to an altered period or phase relationship with the rest of the circadian system that impairs timing in cells with which they interact.

Opportunities and Challenges provided by Circadian CSCs

Because of the genetic damage observed in cancer cells, it is possible that their circadian clocks oscillate with an abnormal phase relative to their tissue of origin. Obviously, such a feature could be exploited through daily drug delivery at a particular phase of the cycle to preferentially act on the cancer cells. A more sobering concern is that any therapy designed to improve circadian timing in a cancer patient might also help to strengthen a clock within cancer cells; if circadian timing aids some cancer cells, this approach could ultimately prove damaging. One benefit provided to a cancer cell by its own circadian clock is that it might help in evading circadian oscillations in cell-destroying lymphocytes or melatonin. Although most of the tumor might have a disorganized and ineffective circadian clock, any treatment that enables circadian oscillators identified within CSCs should be considered carefully.

CSCs and somatic stem cells are typically a small population within cell lines or primary cultures and therefore may have only been an insignificant contribution to many studies of circadian rhythms in vitro, particularly ones that failed to detect a circadian rhythm [2]. Consequently, circadian properties of CSCs and other stem cells have remained mostly unexamined. The C6 rat glioma cell line contains CSCs [68-70], and we recently provided evidence that CSCs in attached, monolayer C6 cell cultures lack circadian rhythms, although rhythms were present in the remaining non-stem cancer cells [71], in agreement with previous studies that measured the entire cell population [72]. Surprisingly, tumorsphere cultures containing mostly quiescent CSCs displayed circadian rhythms in *Per2* expression [71]. Because tumorspheres are enriched in CSCs and contain a cell microenvironment resembling that of tumor cells, extrapolation suggests that CSCs within gliomas also contain functional circadian clocks. The same may be true of CSCs within other tumors, and these oscillators may depend on paracrine factors or other cell coupling signals that attached cells do not experience at sufficient concentrations to sustain a rhythm. A parallel process occurs in fibroblast circadian pacemakers that fail to oscillate at low cell density, as shown by single-cell imaging [73].

Obviously, an ideal technology would provide continuous monitoring of individual cells within tumors of live animals, but lacking that the best estimate of tumor rhythms is through ensemble recordings from multiple oscillating tumor cells. If these clocks are not synchronized to the animal's circadian system in a predictable way, then methods similar to those used to shift clock cells in vitro into a common circadian phase should be developed. A common method in use for cell lines, tissue explants and tumorspheres is a two-hour application of elevated (50%) serum, forskolin, dexamethasone, or a temperature pulse followed by return to normal cell culture medium [74-77]. Any circadian clock cells refractive to these stimuli would, of course, not contribute to measured rhythms, unless their oscillator couples its phase to more responsive cellular clocks. It is also conceivable that refractive clock cells might instead couple to each other, producing a second rhythmic component within the measured signal, giving the appearance of an arrhythmic tumor. It should be noted that many agents used to synchronize circadian cell cultures can also induce differentiation of CSCs [71].

The impression that tumors lack organized or functional circadian clocks is challenged by a recent report of how sarcoma and fibrosarcoma tissue explants grown in immunocompromised mice or in culture do express circadian rhythms in clock gene expression, and they are entrained to the host circadian system [78]. Similarly, tumors grown in mice are reported to show circadian rhythms in the clock gene *Bmal1* that are in phase with host circadian rhythms [79].

As in the daily mitotic rhythms of normal tissues, the molecular linkages between the circadian clock and the cell cycle are often cited as instrumental in tumor growth [80-82]. A loss of circadian timing in cancer cells might free mitosis from this constraint, enabling rapid proliferation [83]. Both empirical data and mathematical modeling describe a "phase-locking" between normal cell cycle and circadian oscillations in many organisms [84, 85]. Nevertheless, the relationship is certainly not obligate; the cell cycle can proceed considerably faster than 24 hours in cancer and non-cancer cell lines, including C6, while the circadian rhythm persists [86, 87]. Selectively altering the period of mitotic oscillations leaves the circadian rhythm intact [86]. This uncoupling again supports our contention that circadian clocks are more abundant in tumors than currently perceived, and CSCs could be the most rhythmic of the many cell types present despite their lack of easy observation. Most of the recorded tumor signal can originate in the many other cell types present including numerous non-cancerous stromal cells, particularly when using tissue mRNA assays.

Tumor heterogeneity is apparent in cell cultures and solid tumors. It confounds chemotherapeutic strategies and challenges any easy understanding of cell interactions during cancer progression. Theories based on CSCs as tumor-initiating cells argue that tumor heterogeneity proceeds by way of multiple differentiation events, from CSCs onward, making each tumor a somewhat unique population of difficult drug targets.

Conclusions

Internal processes of the body may selectively favor persistence of CSC clocks that have optimal phase relationships with daily rhythms in nutrient availability, cytokines, hormones, and suppressive or mitogenic components oscillating in the blood. Similarly, various organs of animals oscillate with their own preferred circadian phase relative to the master neural clock in the hypothalamus [88]. Directing clinical or preventative treatments towards the unique properties of CSCs is

therefore a promising approach, and if CSCs prove to have a distinct circadian timing mechanism or phase, then that becomes an important asset for the oncologist. Chronopharmacological approaches for treating cancer could be refined to eliminate CSCs preferentially. As CSCs of various human cancers become better understood they should be screened for their circadian properties and their phase relationships with known physiological rhythms so that their most vulnerable phases can be targeted for treatment.

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