Questions from the Clinic: What is cancer chronotherapy? Do circadian rhythms influence the efficacy of cancer drugs? Can other procedures, like radiotherapy, be timed to optimize their effect?

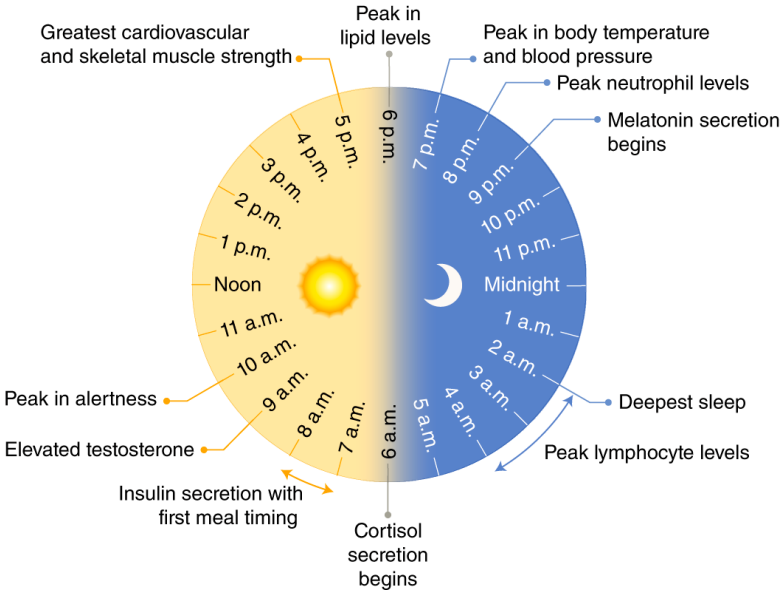

Figure 1: The circadian clock is a biological mechanism in multicellular organisms that governs the initiation and cessation of physiological processes. *Results from scientific studies increasingly suggest the existence of a relationship between disruptions in the circadian clock and cancer metabolism. Image courtesy of Nature Medicine.*

I. Introduction

Over decades of research, scientists have observed that patients with cancer vary considerably in the degree to which they respond to treatment. Although genetic differences can explain this phenomenon to some degree, emerging evidence indicates that other factors influence the efficacy of therapies.[1] In particular, accumulating data across multiple studies show that the majority of today's best-selling drugs work better when taken during specific times of the day.[2] Accounting for the circadian clock (i.e., circadian rhythms) and targeting its underlying mechanisms form the basis of cancer chronotherapy. When paired with radiation, chemotherapy, and immunotherapy, chronotherapy may enhance therapeutic efficacy and simultaneously minimize treatment-related adverse events associated with medical interventions.[3] Despite these benefits, fewer than 1% of investigators running clinical trials incorporate time-of-day considerations into their study protocols.[4] Low clinical awareness and adoption may, in part, stem from mixed results from human trials examining the benefits of chronotherapy in cancer treatment.[5] Resolving these inconsistent findings is critical, as a better appreciation and understanding of biological chronicity may be key in further individualizing cancer medicine and optimizing patient outcomes for years to come.[1]

II. The Biology of Circadian Rhythms

In 2017, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young won the Nobel Prize in Physiology or Medicine for their research on molecular mechanisms governing the circadian clock.[6] Since then, newer findings have implicated the disruption of the circadian clock in the development of many ailments, including cancer.[7] In the brain, the hypothalamus contains a cluster of approximately 20,000 neurons and glial cells that form a "central" clock that modulates secondary clocks in peripheral tissues.[8] These cells comprising the suprachiasmatic nucleus (SCN) respond autonomously to light received by retinal ganglion cells and initiate a signaling cascade that culminates in the expression of *BMAL1*, *CLOCK*, *PER*, and *CRY* – clock genes.[9] In turn, these clock genes modulate the expression of other clock-controlled genes and the synthesis of protein products that fluctuate cyclically during a 24-hour period. More than half of protein-encoding genes show circadian oscillation in distinct patterns across tissues in the body.[8] Perhaps the most well-known, profound rhythm is that of the sleep-wake cycle, in which melatonin

production is promoted in darkness (night) and inhibited in light (day). The central circadian clock in the SCN also tightly modulates the secretion of orexin – a neurotransmitter that promotes wakefulness – during the day portion of the cycle.[10]

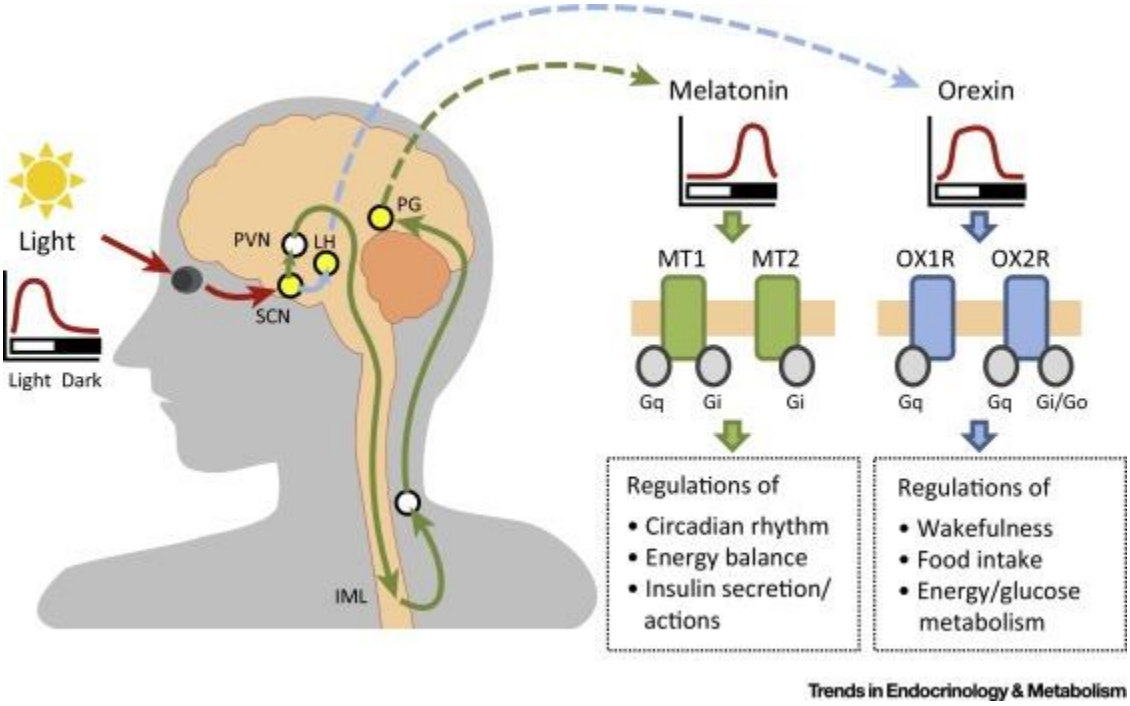

Figure 2: Levels of melatonin and orexin fluctuate cyclically in the central nervous system and promote distinct biological processes during the evening (dark period) and day (light period). IML = intermediolateral nucleus, LH = lateral hypothalamus, PG = postcentral gyrus, PVN = periventricular nucleus, SCN = suprachiasmatic nucleus. Image courtesy of Tsuneki et al. (2016)

Nightshift work, jet lag, artificial light, and other environmental changes can disrupt the circadian clock and drive the development of various cancers.[7] Across different organs, the circadian clock regulates catabolic and anabolic metabolism as well as genes tied to glucose transporters and oxidative phosphorylation. Continuous activation of PI3K/PDK1/AKT, a signaling pathway involved in cell growth and proliferation, promotes the aberrant glycolytic activity that is a hallmark of cancer. Findings from multiple studies have established connections between clock disruption and cancer. In the Nurses' Health Study II (n=114,559), researchers concluded that long-term, rotating night-shift work greatly elevated the risk of breast cancer, particularly among women performed this work as young adults.[11] Separate evidence suggests a link between exposure to artificial light in the evening and melanoma.[8] Chronic jet lag can also induce global changes in gene expression, which in turn alters the levels of several metabolites. These metabolic alterations lead to insulin resistance, non-alcoholic fatty liver disease, and liver steatohepatitis, and ultimately hepatocellular carcinoma.[12]

III. Clinical Trial Data

Today, adoption of chronotherapy remains limited despite the existence of evidence supporting its integration into clinical settings. In a 2016 review, researchers noted that of the 217,258 registered studies ongoing around the world, only 348 included some form of circadian intervention. Of these 348 chronotherapy studies, only 3.4% assessed circadian interventions in the context of cancer.[4] That said, available findings arguably warrant further assessment and confirmation. In one phase III trial

comparing 4-day chronomodulated therapy against standard, 2-day delivery of fluorouracil, leucovorin, and oxaliplatin, investigators noted a disparity in outcomes between men and women with metastatic colorectal cancer. The chronotherapy regimen, dubbed chronoFLO4, decreased the risk of death by 25% in men and increased the risk of death among women by 38% relative to FOLFOX2. This gap in outcomes reveals profound differences in circadian pharmacology and genotypic profiles between the sexes.[13] While disadvantaged in this particular context, women appear to derive greater benefits from chronomodulated radiotherapy used to treat bone metastases.[14]

Scientists have evaluated the effects of radiotherapy during different times of day in numerous randomized, prospective trials, but the best approach remains similarly shrouded in uncertainty. Generally, radiation chronotherapy appears to reduce symptom burden significantly among patients with cancer, with noticeable improvements in tolerability manifesting when administered in the morning.[9] In two studies, median time to the development of grade III/IV mucositis – a radiation-induced side effect – was shorter among patients treated in the afternoon than in patients treated in the morning.[15,16] Results from another randomized study, which evaluated the prevalence of acute gastrointestinal mucositis in cervical cancer, yielded findings contrary to those obtained in the previously mentioned pair of studies, which enrolled patients with head and neck cancers. In this investigation, grade III/IV mucositis manifested more commonly in patients in the morning group than in those treated in the afternoon.[17] Similarly, researchers attempting to find the optimal time to administer radiotherapy in patients with breast cancer have obtained conflicting findings in two studies, with one each in favor of morning and afternoon timing.[18,19]

Currently, on clinicaltrials.gov, there is one active, phase 4 clinical trial evaluating the safety and efficacy of morning and evening endocrine therapy in patients with hormone receptor-positive breast cancer. Scheduled for completion in August 2023, the REaCT-CHRONO trial data is poised to provide insights on many unresolved questions on chronotherapy. If investigators observe that this treatment is better tolerated among patients during a certain time of day, it may spur additional investigations seeking to confirm if similar patterns are present in other cancers.[20] For testicular and ovarian cancers, there exists some evidence to suggest that evening administration of cytostatics leads to better tolerability; response rates between patients in morning and evening cohorts are similar.[21] Peak levels of testosterone and estrogen occur in the morning (7:00-10:00) and reach their daily nadir in the early evening (20:00) before rising again.[22,23]

IV. Logistical Barriers

Conflicting results from existing studies on chronotherapy may result from both methodological differences among studies, as well as an incomplete understanding of circadian rhythms. Across many retrospective reviews, definitions of “morning,” “afternoon,” and “evening” can vary drastically, which limits the degree to which comparisons can be drawn across studies.[24] Additionally, significant interpatient variability also poses a major challenge in the design of trials; the existence of individual “chronotypes” can alter the statistical power of trials comparing chronotherapy to conventional treatments comprising the current standard of care.[1] Inflexible hospital schedules for surgeries and the threat of treatment non-adherence additionally serve as barriers to the adoption of chronotherapeutic strategies in cancer and other medical conditions.[5] Already, only 50% of people with chronic illness follow their treatment recommendations, according to the World Health Organization. By placing more stringent requirements on when drugs must be taken, clinicians may risk having patients deviate from

treatment plans. Drug manufacturers also lack financial incentives to specify a time of day to administer medicines that have already received regulatory approval – such discoveries would require significant upfront investments while offering fewer, clear benefits in return.[2]

V. Conclusions & Future Directions

Chronotherapy for patients with cancer represents another frontier in the current era of personalized, precision medicine. Although findings from existing scientific investigations have yielded inconsistent results, better timing the delivery of therapies may help mitigate the worst treatment-related adverse effects associated with chemotherapy and radiotherapy. As biological understanding of the mechanisms governing circadian rhythms expands, so too does the opportunity to redefine standards of care in patients with various forms of cancer. While logistical barriers, like surgery scheduling and dose administration, may hinder adoption of chronotherapeutic approaches, new technologies may help overcome these barriers in the future. In particular, non-invasive, real-time circadian monitoring and biomarker testing systems could open up new avenues for treatment. Going forward, chronotherapy in cancer deserves further investigation in well-designed, adequately powered clinical trials. If scientists can unlock the mysteries of the circadian clock, clinicians may gain powerful new strategies that can maximize the benefits of existing therapies while minimizing their harmful effects on patients.

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