COMBINING IMMUNOTHERAPY AND CIRCADIAN RHYTHMS FOR MORE ACCURATE TREATMENT OF BRAIN TUMORS

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Resume: There is a strong correlation between abnormalities in circadian rhythms and increased susceptibility to cancer and neurological illnesses. Immunotherapy is still not very effective in treating brain tumors, despite its potential in treating other types of cancer. This review examines the relationship between immunotherapy and circadian rhythms in the treatment of brain cancer, with a focus on accuracy through synchronization with the body's internal clock. We examine the ways in which circadian dysregulation impacts anti-cancer immunity and assess the circadian control of immunological responses, including cell localization and functional phenotype. For brain cancer, we also examine and evaluate the efficacy of contemporary immunotherapeutic techniques, such as adoptive cellular treatments, immune checkpoint blockades, and other cutting-edge tactics. In order to maximize the precision of immunotherapy against brain tumors, future options are suggested, including chronotherapy and customized treatment plans.

Keywords: Immunotherapeutic techniques, circadian rhythms, brain cancer, immune system, immunotherapy, immune checkpoints, adoptive cellular therapy, chrono modulated therapy.

Introduction

It is now known that circadian rhythms—from the Latin "circa diem," which means "about a day"—are an external representation of an internal time mechanism that is essential to an organism's ability to maintain homeostatic equilibrium.

A basic molecular clock, comprising an evolutionarily conserved transcriptional-translational feedback loop (TTFL; Fig. 1), is responsible for producing circadian rhythms at the molecular level.5. Positive and negative feedback loops are linked in the molecular clock process. Fundamentally, enhancer box elements (E-boxes) of cryptochrome (CRY1/2), period (PER1/2/3), and tyrosine-protein kinase transmembrane receptors RORα/β/γ and REV-ERBα/β are bound by the transcriptional activators circadian locomotor output cycles kaput (CLOCK; and its paralog, NPAS2) and brain and muscle ARNT-Like 1 (BMAL1), forming heterodimers that stimulate their transcription.5, 6. Following this, PER/CRY heterodimers build up and stop BMAL1/CLOCK activity. Competing for binding

to ROR response element (RORE), a promotor for BMAL1, RORα/β/γ and REV-ERBα/β cause BMAL1 to either be activated or inhibited. The interaction of these feedback loops results in clock-controlled gene expression that fluctuates rhythmically over a period of around 24 hours. The TTFL is responsible for the autonomous circadian rhythms expressed by almost every cell type, including neurons and glial cells.9. Throughout the 24-hour cycle, cell function is driven by oscillations in the expression of the genes that make up the circadian core clock and the genes that they regulate by binding to transcription-enhancing variables.10

The gut clock, for example, controls intestinal motility and food absorption to align maximal monosaccharide uptake with regular eating times.11. Additionally, the kidneys' circadian cycles result in variations in tubular reabsorption and secretion processes, glomerular filtration rate, and renal plasma flow.12 Peripheral clocks must be synchronized everyday to avoid these cellular activities becoming out of harmony across the body.

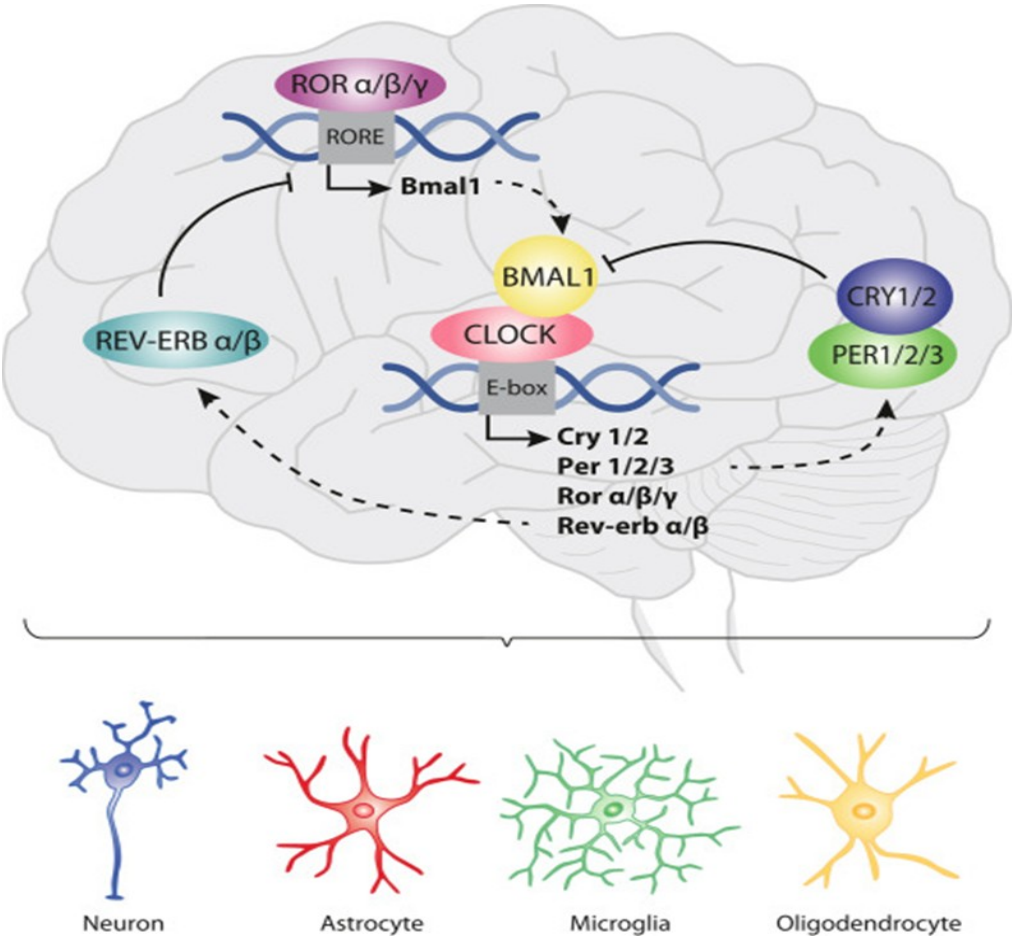

Fig. 1. **Overview of the core clock machinery in the brain.**

The tumor microenvironment's (TME) circadian clock components have a significant role in controlling the stemness of cancer cells, metastasis, and

resistance to treatment.2: This review investigates the role of the circadian rhythm in immunosuppression, the brain TME, and brain tumor growth. Chronotherapy is used to optimize therapy scheduling, and the molecular role of the circadian clock in brain cancer is investigated. The effects of the circadian clock on the immune system and tumor immunology will also be discussed, with an emphasis on how it may improve the effectiveness of immunotherapy. To create successful (immuno)therapies and improve those that already exist, we hypothesize that a deeper knowledge of the intricate biology of brain tumors and TME—with a focus on the significance of the circadian clock—is necessary.

How does the healthy central nervous system's molecular clock work?

Glial cells and almost every other tissue have circadian clock oscillations, which are crucial for the growth and operation of the brain.8. The majority of brain cancers originate from glial cells or their ancestors, therefore knowing how the clock functions in their physiology is important.

The most prevalent glial cell population in the mammalian brain is called astrocytes.5, These cells are essential for the health of the nervous system because they give neurons vital trophic and metabolic support. Perisynaptic astrocyte activities, for example, reduce extra-synaptic buildup and spillover to neighboring synapses by removing neurotransmitters like glutamate from the interstitial space.7 Astrocytes also maintain appropriate synaptic transmission by regulating the ionic balance at the synapse.In vitro cultures of mouse cortical astrocytes have been used in studies to demonstrate that clock genes control the rhythmic variations that astrocytes undergo.8- Astrocytes' daily cycles of ATP release, for instance, are regulated by oscillations of Clock, Per1, Per2, and IP3-dependent calcium signaling.9 Astrogliosis is brought on by low levels of BMAL1, which also functions as a cell-autonomous regulator of astrocyte activation and neurotrophic activity. Microglia are another kind of cell found in the central nervous system (CNS). These immune cells, which resemble macrophages, help the brain develop normally by eliminating dead cells from the developing brain and the adult central nervous system.14 Microglia also play a role in the maintenance and growth of synapses. Microglia have a circadian rhythm that controls their immunological activity, just like the majority of cells.14 Rats, for example, exhibit a circadian rhythm of TNF-α, IL-1β, and IL-6 production that peaks in the middle of the light phase (rest phase). The early development of Alzheimer's disease has been linked to disruption of clock genes in microglia, which can cause chronic neuroinflammation.15.

Finally, the third class of glial cells, oligodendrocytes, are essential for the transmission of signals in the central nervous system. These cells provide a myelin sheath that supports metabolism and speeds up action potential transmission along

the axon. There is currently insufficient proof to conclude that human oligodendrocytes possess a working molecular clock.

It is commonly known that circadian clock disruption is linked to neurological conditions like Parkinson's or Alzheimer's disease.11 Furthermore, disruption of the circadian rhythm, such as that caused by genetic abnormalities or jet lag-induced disturbances of normal physiological balance, has been linked to an increased risk of developing cancer.10 The circadian clock is disrupted in several malignancies.1 Furthermore, there is a correlation between early cancer patient death and the loss of circadian regulation and the ineffectiveness of anticancer therapies.13 Conversely, a healthy circadian rhythm prevents colon cancer and melanoma cells in mice from proliferating and growing into tumors.

Materials and methods

Immunotherapy has completely changed the oncology sector in recent years. These treatments seek to strengthen or stimulate the immune system so that it can target and destroy tumor cells.Twenty Adoptive cellular therapies including chimeric antigen receptor (CAR)-T cell therapy, oncolytic viruses, immune checkpoint inhibitors (ICI), and immunization are a few examples of immunotherapeutic approaches.

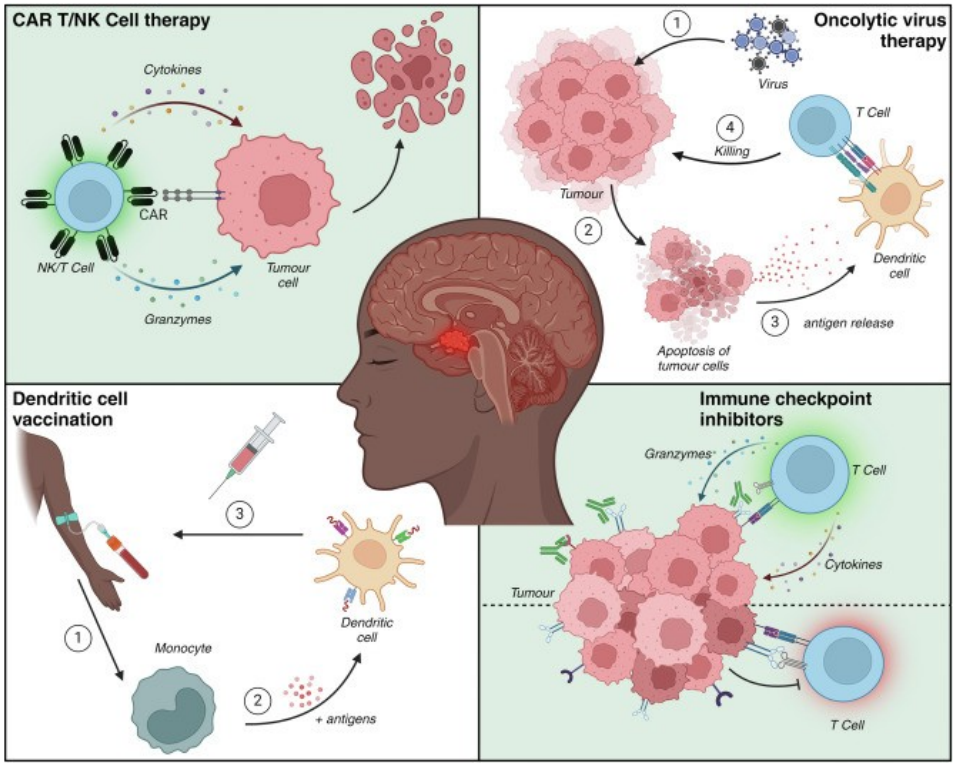

Fig.1. Immunotherapeutic approaches to brain cancer treatment. A number of immunotherapeutic approaches have been developed in recent decades with the goal of stimulating the immune system to produce an anti-tumor response. Via dendritic cells, oncolytic virus therapy and dendritic cell vaccine both stimulate the

immune system's adaptive component. Oncolytic virus therapy depends on activating dendritic cells in vivo, while dendritic cell vaccine therapy uses monocytes to train dendritic cells ex vivo. By using modified receptors, CAR T/NK cell therapy, on the other hand, allows these cells to precisely target and kill the tumor. Immune checkpoint inhibitor therapy eliminates immunosuppression in the TME by inhibiting one or more inhibitory checkpoints, rather than concentrating on immune system training. produced using BioRender. TME: tumor microenvironment; CAR.

Discussion

The effectiveness of immunotherapy may be increased by coordinating treatment with circadian rhythms in terms of chronotherapy. Patients' sleep-wake cycles and clock synchronization (e.g., light/dark cycles, timing of meal intake, influence of electronic gadgets) should be protected for this and the benefit of the patients. In the clinic, it is relatively cheap to investigate the advantages of administering immunotherapy at particular times of the day. Given that tumors with an intact circadian rhythm, like glioblastoma, may exhibit temporal susceptibility to cancer immunity, this would likely be most helpful in these cases.7 Examining the circadian clock's integrity in various brain cancer types may help explain the temporal variance in vulnerability. All cell types that reside in the TME should be aware of this because of their timing. Targeting would be most effective, as we currently understand, when the BBB is most permeable, immune effector cells can easily enter the tumor location, and tumor cells themselves exhibit the least amount of resistance. Additionally, the circadian immunological state of tumor-associated macrophages and microglia has a timely impact on both effector cells and tumor cells. By investigating the brain's circadian rhythms, TME may be able to determine when immunotherapy should be administered.

Nonetheless, many malignancies exhibit disruptions in circadian rhythmicity.4. This lays the groundwork for more accurate molecular clock targeting. Immune evasion is linked to clock disruption; hence, restoring it may mitigate this effect and enhance immunotherapy results.

In conclusion

Many biological functions are carefully regulated by circadian rhythms. Circadian rhythms regulate activity in healthy cells, but in cancer, changes in the expression of the molecular clock frequently promote the survival and growth of cancerous cells, which in turn accelerates the evolution of tumors. The tumor's capacity to create an immunosuppressive TME is further strengthened by these alterations. Brain cancer has been treated with a variety of immunotherapeutic treatments, although their effectiveness is still quite low. The circadian rhythm that regulates

the immune system and TME is a key factor in determining the results of immunotherapy. The treatment of brain cancer may undergo a revolution in therapeutic techniques and greatly increase the effectiveness of immunotherapy if the circadian clock is strategically targeted and harnessed.

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