The Role of the Circadian Clock in Glioblastoma Progression and Treatment

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ABSTRACT

Glioblastoma (GBM) is the most aggressive and treatment-resistant malignant brain tumor in adults. Current therapies, including surgery, radiation, and chemotherapy with temozolomide (TMZ), offer subtle improvements in terms of survival. New and upcoming research highlights the role of the circadian rhythm, the body's internal 24-hour clock, in tumor growth and treatment response. Disruptions in core clock genes such as BMAL1 and CLOCK are common in GBM and have often been linked to increased tumor cell survival and resistance to therapies. Preclinical studies show that targeting the circadian clock, either by inhibiting key clock genes or by timing treatments to align with natural biological rhythms (chronotherapy), can slow tumor progression and improve survival in models. However, clinical trials have shown mixed results, and challenges remain in translating these strategies to practice due to differences in individual circadian timing and various ethical implications about access, safety, and feasibility. Despite these obstacles, the circadian system represents a promising direction for future GBM therapies that may enhance treatment precision and effectiveness.

INTRODUCTION

Glioblastomas are the most frequent and aggressive type of malignant brain tumor in adults, representing about 14.5% of all central nervous system tumors and 48.6% of malignant ones (Szymon Grochans et al.). These tumors are most commonly known for rapidly spreading, having a poor prognosis, and being highly invasive. While there are many treatments available for glioblastomas, such as intensity-modulated and regular radiation therapy, stereotactic radiosurgery, chemotherapy, etc., the survival rate still remains a short 12-18 months, due to it being highly resistant to therapies (Cleveland Clinic). The limited success of other therapies has drawn attention to the role of the circadian rhythm in glioblastoma growth in recent years. The circadian is the 24-hour internal clock that the body follows, which regulates processes such as hormone release, sleep, digestion, and body temperature (Cleveland Clinic). In mammals, the circadian rhythm relies on a molecular feedback loop. Proteins such as CLOCK and BMAL1 drive the expression of other genes, such as PER and CRY, which then, in turn, inhibit CLOCK and BMAL1, creating a roughly 24-hour cycle that regulates cell proliferation, apoptosis, DNA repair, and tumor growth. Research has shown that disruption in these circadian genes can alter tumor growth and activity, emphasizing how circadian rhythm disturbances are closely linked to the aggressiveness and progression of glioblastoma (Lee). This review will examine current glioblastoma therapies and explore how circadian rhythm mechanisms influence tumor progression to identify strategies to develop more effective and targeted treatments.

BACKGROUND

Glioblastoma (GBM) arises when normal glial cells acquire genetic mutations that disrupt the natural regulatory mechanisms governing their growth. Once these controls are compromised, the cells begin to proliferate uncontrollably, resulting in the formation of a dense tumor mass. In contrast to tumors that exhibit well-defined boundaries, GBM infiltrates adjacent brain tissue by traversing white matter and following blood vessels. Due to its ability to intermingle with healthy tissue rather than remaining localized, it is extremely aggressive and

nearly impossible to completely excise through surgical intervention ("Glioblastoma (GBM) - American Brain Tumor Association").

The circadian rhythm, which serves as the body's internal clock, is regulated by a group of core genes: BMAL1, CLOCK, PER, and CRY. These genes collaborate in a feedback loop that approximately repeats every 24 hours. The CLOCK and BMAL1 proteins work together to activate the PER and CRY genes. As the levels of PER and CRY proteins increase, they inhibit the activity of CLOCK and BMAL1, thereby completing the loop. Additional proteins, such as ROR and REV-ERB, refine this rhythm by modulating the production of BMAL1, ensuring the cycle remains precise. This daily rhythm is essential for maintaining critical processes, including cell division, DNA repair, metabolism, and programmed cell death (apoptosis). Disruption of circadian genes can lead to misalignment of these processes, adversely affecting normal cell growth and overall health (Partch et al.).

CURRENT TREATMENTS FOR GLIOBLASTOMA

The current standard treatment for newly diagnosed glioblastoma (GBM) is the Stupp protocol, which combines surgical resection, radiotherapy, and temozolomide chemotherapy. Surgery aims to remove as much tumor as safely possible, though complete removal is rarely achievable due to the tumor's invasive nature. Radiotherapy is given over several weeks, followed by cycles of temozolomide chemotherapy. This regimen works in part by depleting MGMT, a DNA repair enzyme, increasing tumor sensitivity to treatment. Clinical trials have shown that the Stupp protocol significantly improves survival, with a median overall survival of 14.6 months and a two-year survival rate of 26.5%, compared with 12.1 months and 10.4% for radiotherapy alone (Stupp et al.).

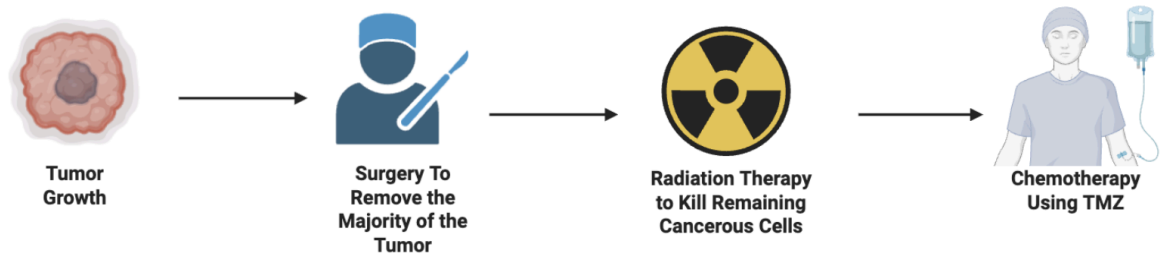

Figure 1 shows the various steps that are generally followed when using the Stupp protocol. These steps are: the glioblastoma grows, surgery is conducted to remove as many cancerous cells as possible, radiation therapy is used to kill any remaining cells affected, and chemotherapy using TMZ.

Tumor-Treating Fields (TTFields) are an innovative therapy for GBM that use low-intensity, alternating electric fields delivered through adhesive pads on the scalp. These fields disrupt cancer cell division, preventing tumor growth and making the cells more vulnerable

to the immune system. When combined with temozolomide chemotherapy, TTFields have been shown to extend survival and slow tumor progression compared with chemotherapy alone (Mun et al.). Their noninvasive, tumor-specific approach makes TTFields a valuable addition to standard treatment strategies.

Bevacizumab (Avastin®) is a targeted therapy for advanced or recurrent glioblastoma, administered intravenously, typically as a single agent. It works by binding to vascular endothelial growth factor (VEGF), which tumors use to grow new blood vessels, limiting the tumor's blood supply and slowing growth. Bevacizumab's long half-life allows for sustained VEGF inhibition, and studies suggest combining it with chemotherapy or other targeted drugs may improve outcomes (Filis Kazazi-Hyseni et al.). Adding bevacizumab to surgery, radiation, and chemotherapy offers a newer approach that slows tumor growth by cutting off its blood supply.

Current immunotherapy approaches for glioblastoma include treatments that try to boost the immune system, such as immune checkpoint inhibitors, therapies targeting tumor-associated immune cells, vaccines, and CAR T or NK cell therapies. These treatments face major challenges because glioblastoma tumors are highly resistant, with a suppressive immune environment and many different types of cancer cells. To overcome this, researchers are testing combination treatments, personalized vaccines, and CAR therapies that target multiple tumor markers, aiming to strengthen the immune response, attack the tumor more effectively, and help patients live longer (Yu and Quail).

CIRCADIAN DISRUPTION IN GLIOBLASTOMA

Glioblastoma cells exhibit significant disruption of the circadian clock, which they exploit to promote growth and therapy resistance. High-grade gliomas often show overexpression of positive clock regulators like CLOCK and BMAL1, while negative regulators such as PER1/2 and CRY1/2 are downregulated (Dong et al.; Sulli et al.). This imbalance breaks the transcriptional feedback loops that normally maintain a 24-hour rhythm, resulting in a loss of correlation in gene oscillation and desynchronization of cellular processes (Relógio and Westermark). Tumor microenvironment factors, including hypoxia and inflammation, further aggravate circadian dysfunction (Nelson and Relógio).

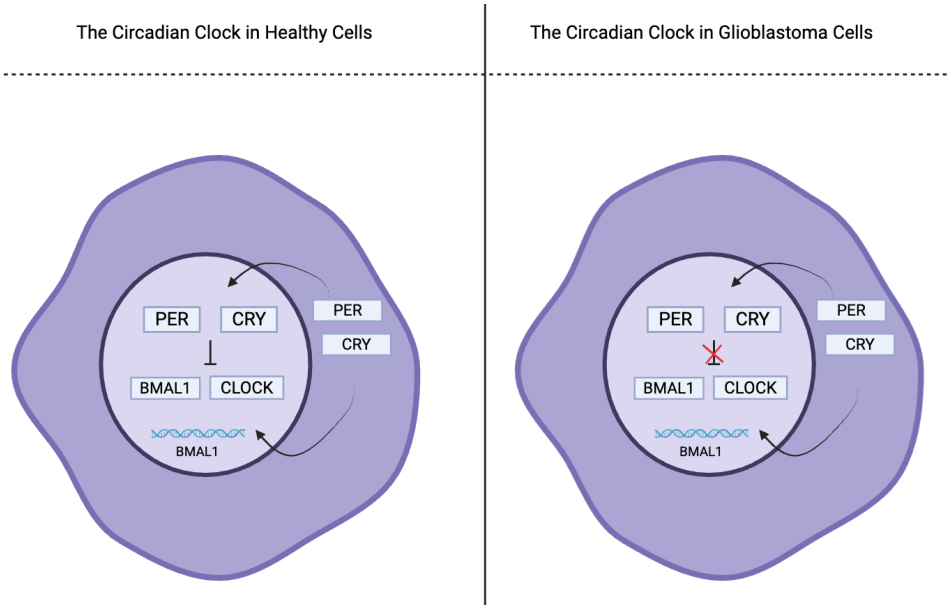

Figure 1 visually shows the contrasts between the circadian clock in healthy cells and in glioblastoma cells. While the healthy cell contains an inhibitor, the glioblastoma cell does not, which is referred to as loss of inhibition.

The circadian system normally regulates key processes like DNA repair, cell division, and programmed cell death (Nelson and Relógio). In glioblastoma, the clock genes BMAL1 and CLOCK often become overactive, driving aggressive tumor growth and rapid cell division. In contrast, when repressor genes such as CRY or REV-ERB are more dominant, tumors tend to grow less quickly (Sulli et al.). By disrupting this balance, GBM gains the ability to grow uncontrollably and resist standard treatments.

Experimental evidence supports the importance of circadian regulation in glioblastoma. In vitro studies show that glioblastoma stem cells rely heavily on BMAL1 and CLOCK for survival, with knockdown reducing proliferation and increasing apoptosis, while overexpression accelerates growth (Dong et al.). In mouse xenograft models, BMAL1 or CLOCK-deficient stem cells failed to form tumors, and treated animals survived twice as long (Dong et al.). Chemical activation of negative clock arms using compounds like KL001 or SHP656 also reduced stemness and prolonged survival (Dong et al.; Relógio and Westermark), demonstrating that GBM growth relies on a hyperactive circadian clock.

Circadian disruption also influences how glioblastoma responds to therapy. The DNA repair enzyme MGMT, which reduces the effectiveness of temozolomide, follows a circadian rhythm. Studies show that giving temozolomide when BMAL1 levels are high leads to more DNA damage and tumor cell death, while treatment during low BMAL1 expression is less effective (Gonzalez-Aponte et al.). Other clock genes, such as PER2 and CRY, help regulate the tumor-suppressor protein p53, and when they are disrupted, GBM cells can avoid apoptosis after DNA damage (Nelson and Relógio). Clinically, patients with high BMAL1 and low PER or CRY expression tend to have worse outcomes (Sulli et al.).

THERAPEUTIC IMPLICATIONS OF TARGETING CIRCADIAN RHYTHM

Chronotherapy, which involves timing treatments to match the body's circadian rhythms, shows promise in glioblastoma treatment. Laboratory studies and retrospective clinical data suggest that giving temozolomide at times when BMAL1 activity is highest can improve tumor cell death, although results from prospective trials have been inconsistent (Petković et al.). Other drugs, such as the proteasome inhibitor bortezomib, have also been more effective when delivered according to circadian timing in animal studies (Wagner et al.).

Direct targeting of core clock genes provides an additional strategy. Inhibiting BMAL1 or CLOCK in GBM cells, or stabilizing repressors like CRY and REV-ERB using compounds such as KL001, SR9011, or SHP656, reduces stem cell growth, promotes apoptosis, and prolongs survival in preclinical models without harming healthy cells (Dong et al.; Sulli et al.). Patient-derived xenografts further support these findings, showing that clock-modulating drugs can slow tumor growth and extend survival while maintaining tumor-specific effects (Wagner et al.).

DISCUSSION

Circadian disruption plays a major role in glioblastoma's aggressiveness, adaptability, and resistance to treatment. Using this knowledge in therapy offers exciting opportunities but also raises scientific and ethical challenges. Personalized chronotherapy could improve outcomes, but because every patient's circadian rhythm is different, treatment schedules would need to be carefully tailored and monitored. Questions of access and equity also remain, along with possible side effects of altering circadian pathways on sleep, metabolism, and mood. Even with these challenges, combining circadian-based strategies with standard treatments holds strong potential to make GBM care more precise and effective.

CONCLUSION

Glioblastoma remains one of the most aggressive and treatment-resistant brain tumors. Circadian rhythm disruption, particularly overactive BMAL1 and CLOCK with downregulated respressors, contributes to tumor growth, stemness, therapy resistance, and poor patient outcomes. Preclinical evidence shows that targeting core clock genes or optimizing treatment timing can reduce proliferation, increase apoptosis, and improve survival in animal models. Translating these findings into clinical practice requires personalization, careful monitoring, and equitable access, but the circadian clock represents a promising avenue for developing more precise and effective therapies for glioblastoma.

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