Narrative Review Article

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. This review analyzes current therapeutic approaches for GBM and investigates how circadian rhythm mechanisms affect tumor progression, with the goal of identifying strategies to develop more effective and targeted treatments.

Keywords: Glioblastoma; circadian rhythm; clock genes; BMAL1; CLOCK; temozolomide; chronotherapy; treatment resistance

INTRODUCTION

Glioblastoma (GBM) is 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 (1). These tumors are most commonly known for rapidly spreading, having a poor prognosis, and being highly invasive. While there are many treatments available for GBM, such as intensity-modulated and regular radiation therapy, stereotactic radiosurgery, chemotherapy, etc., the survival rate remains a short 12-18 months, due to it being highly resistant to therapies (2). Because conventional therapies have shown limited success in extending survival, researchers turn to the circadian rhythm as a factor that may influence GBM growth and treatment response.

GBM arises when normal glial cells acquire genetic mutations that disrupt the natural regulatory mechanisms governing their growth. Once these

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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 (3).

The circadian rhythm is the 24-hour internal clock that the body follows, which regulates processes such as hormone release, sleep, digestion, and body temperature (4). In mammals, this rhythm relies on a molecular feedback loop controlled by core genes: BMAL1, CLOCK, PER, and CRY. The CLOCK and BMAL1 proteins activate the PER and CRY genes. As PER and CRY proteins accumulate, they inhibit CLOCK and BMAL1, thereby completing the loop. Additional proteins, such as ROR and REV-ERB, refine this rhythm by modulating BMAL1 production, ensuring the cycle remains precise. This daily rhythm is essential for maintaining critical processes, including cell division, DNA repair, metabolism, and programmed cell death (5). Research shows 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 GBM (6). This review examines current GBM therapies and explores how circadian rhythm mechanisms influence tumor progression to identify strategies to develop more effective and targeted treatments.

CIRCADIAN DISRUPTION IN GLIOBLASTOMA

GBM 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 PER and CRY are downregulated (Figure 1) (7, 8). 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 (9). Tumor microenvironment factors, including hypoxia and inflammation, further aggravate circadian dysfunction (10).

Normally, the circadian clock regulates DNA repair, cell division, and programmed cell death (10). In GBM, BMAL1 and CLOCK are frequently overactive, forming heterodimers that bind to E-box sequences in DNA and activate genes that control the cell cycle (like cyclin D1 and c-MYC, an oncogene that drives cell proliferation) (Figure 1). This overactivation also rewires cellular

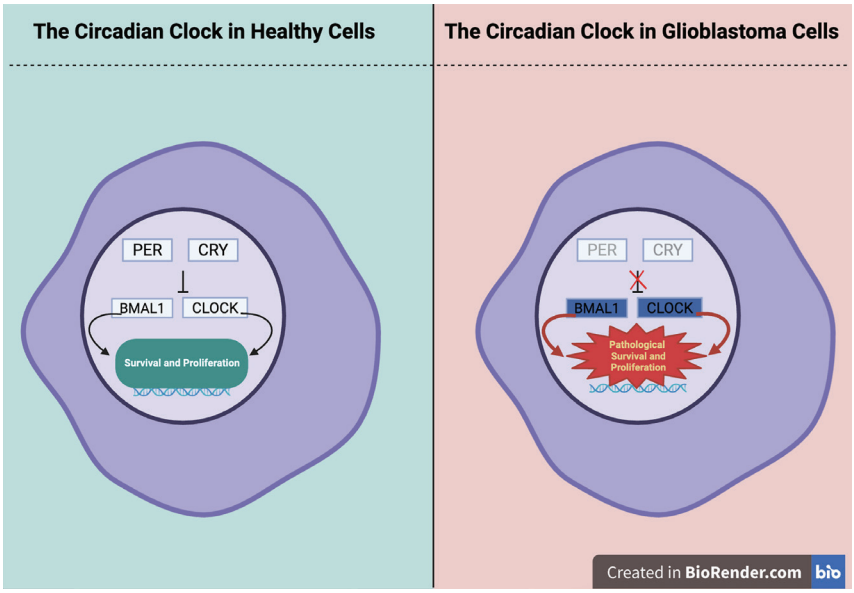

Figure 1. Comparison of circadian clock activity in healthy and glioblastoma cells. In healthy cells, PER and CRY are balanced with BMAL1 and CLOCK, allowing for normal processes of cellular survival and proliferation. In contrast, in GBM cells, PER and CRY are downregulated, while BMAL1 and CLOCK are overexpressed. Hyperactivity in BMAL1 and CLOCK results in pathological survival of highly dysfunctional cells, and excessive proliferation.

metabolism: it upregulates glycolysis, the pentose phosphate pathway, and lipid synthesis, providing energy and building blocks for rapid proliferation (11). At the same time, BMAL1:CLOCK activity promotes anti-apoptotic proteins such as BCL-2 and enhances DNA repair pathways, helping tumor cells survive chemotherapy and radiation (10). When repressor genes such as CRY and REV-ERB are more active, they inhibit BMAL1:CLOCK activity, reduce expression of cell cycle and metabolic genes, slow proliferation, and increase susceptibility to programmed cell death (8).

Experimental evidence supports the importance of circadian regulation in GBM. In vitro studies show that GBM stem cells rely heavily on BMAL1 and CLOCK for survival, with knockdown reducing proliferation and increasing apoptosis, while overexpression accelerates growth (7). In mouse xenograft models, researchers implanted GBM stem cells either with normal BMAL1 and CLOCK expression or experimentally reduced expression of these genes into the brains of immunocompromised mice. Mice receiving BMAL1- or CLOCK-deficient cells developed more slowly growing tumors and survived roughly twice as long as those implanted with unmodified cells (7). Pharmacological activation of the negative arm of the circadian clock using compounds such as KL001 and SHP656 reduced the stem-like properties of GBM cells, meaning their ability to self-renew, drive tumor growth, and resist therapy, and prolonged survival in preclinical models. The negative arm is the feedback mechanism in which cryptochrome proteins (CRY) inhibit BMAL1 and CLOCK activity, effectively acting as a brake on the clock's positive regulators. KL001 and SHP656 stabilize CRY proteins, strengthening this inhibitory feedback, which suppresses BMAL1/CLOCK-driven gene expression and limits tumor cell proliferation, stemness, and growth (7, 9).

THERAPEUTIC IMPLICATIONS OF TARGETING CIRCADIAN RHYTHM

Chronotherapy, which involves timing treatments to match the body's circadian rhythms, shows promise in GBM treatment. Laboratory studies and retrospective clinical data suggest that giving temozolomide at times when BMAL1 activity is highest can improve tumor cell death. Supporting this, a retrospective analysis finds that patients who received TMZ in the morning (when BMAL1 peaks) had a median overall survival of 1.43 years, compared with 1.13 years for those treated in the evening, suggesting better therapeutic efficacy when TMZ is timed to BMAL1 activity (12). Other drugs, such as the proteasome inhibitor bortezomib, are also more effective when delivered according to circadian timing in animal studies (13).

Circadian rhythm markedly affects GBM responsiveness to therapy, particularly through modulation of the DNA repair enzyme MGMT. MGMT (O^6-methylguanine-DNA methyltransferase) counteracts the cytotoxic effects of alkylating agents such as temozolomide (TMZ) by repairing DNA damage. MGMT expression exhibits a circadian rhythm, peaking at specific times of day. Administering TMZ at optimal circadian times enhances its effectiveness by taking advantage of daily fluctuations in MGMT activity. In contrast, treatment during periods of low BMAL1 expression, when MGMT activity is elevated, substantially diminishes TMZ effectiveness. (14). Circadian genes also regulate the tumor suppressor p53 through a feedback loop with PER2; p53 can still become dysfunctional if circadian genes are altered, even without mutation. p53 activates PER2 transcription, and PER2 stabilizes and enhances p53 activity. This loop ensures proper DNA damage detection and triggers p53-dependent pathways, including cell cycle arrest, DNA repair, apoptosis via genes such as BAX, PUMA, and NOXA, and senescence. Disruption of this loop, through p53 mutations or abnormal PER2 expression, weakens the DNA damage response, allowing GBM cells to survive chemotherapy or radiation (15). CRY2 further supports apoptosis by enhancing p53 signaling, and higher CRY2 levels correlate with improved patient survival (16).

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, reduce stem cell growth, promotes apoptosis, and prolongs survival in preclinical models without harming healthy cells (7, 8). Patient-derived xenografts further support these findings, showing that clock-modulating drugs can slow tumor growth and extend survival while maintaining tumor-specific effects (17).

CONCLUSION

Circadian rhythm disruption plays a pivotal role in glioblastoma's aggressiveness, adaptability, and resistance to therapy. Laboratory and clinical findings indicate that tumors characterized by elevated BMAL1

and CLOCK expression with downregulated PER and CRY repressors exhibit faster growth, greater therapeutic resistance, and reduced patient survival by approximately 3–6 months compared with non–circadian-involved tumors (7, 8). These observations underscore how deeply circadian mechanisms influence tumor progression and therapeutic outcomes, suggesting that restoring circadian balance could enhance treatment responsiveness in glioblastoma.

Integrating circadian biology into GBM therapy presents both significant opportunities and complex challenges. Preclinical studies demonstrate that manipulating core clock genes or aligning treatments such as temozolomide (TMZ) with patients' biological rhythms can improve efficacy, minimize toxicity, and extend survival (12, 13). Translating these findings into clinical practice, however, will require personalized approaches, since circadian phases vary widely among individuals. Moreover, ethical and practical considerations, including equitable access, monitoring feasibility, and potential side effects involving sleep, metabolism, and mood, must be carefully addressed.

Future research should focus on clinical trials evaluating chronotherapy in GBM, supported by robust biomarker-based circadian profiling to determine optimal treatment timing. Combining circadian-modulating compounds such as KL001, SR9011, or SHP656 with conventional modalities like radiotherapy and chemotherapy may further enhance outcomes (15, 16). Collaborative interdisciplinary efforts among neuro-oncologists, chronobiologists, and computational modelers will be essential to design effective, personalized, rhythm-aligned interventions.

Overall, although GBM remains among the most aggressive and treatment-resistant malignancies, targeting the circadian system represents a promising frontier. Leveraging temporal biology to refine treatment timing and overcome therapeutic resistance could make GBM care more precise, effective, and patient-centered.

CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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