INTRODUCTION

Glioma is characterized as the most aggressive brain tumor type with a median survival period of only 14 months and a 5-years survival rate of less than 10% after diagnosis. Current standard treatment strategies include complete or sub-complete surgical resection, alkylating agent administration chemotherapy, and radiation therapy. Alternative treatment can also be applied, including immunotherapy, targeted therapy, and tumor treatment fields (TT fields). Since glioma is characterized by rapid proliferation and aggressive infiltration, a considerable proportion of patients develop local recurrence and central nervous system metastasis.

The circadian rhythm is an essential cyclic oscillation system generated by the endogenous circadian clock. Essentially all mammalian organisms have developed circadian rhythms in order to synchronize social and physiological capabilities with explicit periodicity. The control center of this circadian rhythm is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which regulates the rhythm production of various physiological functions. Accumulating evidence reveals that the circadian rhythm has an impact on glioma pathophysiology. It is still controversial whether the circadian rhythm disruption is a cause or an effect of tumorigenesis. This review discussed the association between cell cycle and circadian clock and provided a prominent molecular theoretical basis for tumor therapy. We illustrated the external factors affecting the circadian clock including thermodynamics, hypoxia, post-translation, and microRNA, while the internal characteristics concerning the circadian clock in glioma involve stemness, metabolism, radiotherapy sensitivity, and chemotherapy sensitivity. We also summarized the molecular pathways and the therapeutic drugs involved in the glioma circadian rhythm. There are still many questions in this field waiting for further investigation. The results of glioma chronotherapy in sensitizing radiation therapy and chemotherapy have shown great therapeutic potential in improving clinical outcomes. These findings will help us further understand the characteristics of glioma pathophysiology.

KEYWORDS

cell cycle, circadian clock, glioma, molecular pathway, therapeutic drug
displayed higher efficacy when administered in tumor-bearing animals at night compared to day/night administration. In mice injected with circadian clock gene Bmal1 knocked-down cells, a higher tumor growth rate was observed. Khan et al. revealed glioma-genesis gene expression changes in the mouse brain after chronic alternating light-dark cycle exposure and suggested a potential connection between circadian clock disruption and glioma genesis risk. Wang F et al. revealed circadian clock disturbance promotes carcinogenesis through circadian clock gene *Per2* deregulation. Glioma also participates in circadian alteration and disruption. Athymic nude mice implanted with LN229 human glioma cells showed an increase in the endogenous period of the circadian clock and a slower resynchronization rate. SCN astrocytes modulate the circadian pacemaker via the regulation of glutamate levels. Meanwhile, increased glutamate levels are characteristic of glioma, suggesting that dysregulation of proper glial function occurring in malignant tissue may impact timekeeping and clock synchronization. In addition, molecules including TNF-α and CCL2 involved in immune response affect the core circadian oscillator. Glioma alters the microenvironment to resist immune attack and cytokines and chemokines can be hijacked and then lead to circadian disruption. Circadian activities associated with cerebrovascular reactivity and brain energy metabolism help to maintain central nerve system homeostasis. Cerebral arteries possess a functional circadian clock and exhibit a diurnal rhythm in vasoreactivity to ATP. Brain metabolites are altered during sleep including acylcarnitines, hydroxylated fatty acids, phenolic compounds, and thiol-containing metabolites. Disruption of these oscillations has been observed in cerebrovascular diseases. However, the circadian activities of glioma are still poorly understood, and circadian rhythm disruption is still controversial whether it is a cause or an effect of glioma genesis. Herein, we discussed the molecular connection between cell cycle and circadian rhythm clock, which are the major cyclic system, and focused on the external factors and internal characteristics associated with the glioma circadian clock. This review also summarized the molecular pathways and therapeutic drugs in glioma treatment by reviewing the circadian clock concerning differential molecular changes to explore the potential value in translational research.

2 | CELL CYCLE AND CIRCADIAN CLOCK

Currently, the chemotherapeutic alkylating agent TMZ and radiation therapy regulate and inhibit cellular proliferation by destructing DNA replication. DNA damage triggers the activation of cell cycle checkpoint pathways, which cause the cell cycle to be suspended, so the DNA repair machinery can detect and repair the damage. The DNA damage response (DDR) maintains genomic integrity while contributing to the resistance to chemotherapy and chemotherapy. The cell cycle checkpoint is an important cellular mechanism that prevents uncontrolled proliferation. The glioma cell cycle circulation has been well characterized, which consists of the rest/growth phase (G0/G1 phase), DNA synthesis phase (S phase), G2 phase, and mitosis phase (M phase). Arresting at G1/S or G2/M phase can effectively inhibit the cell proliferation process. The core cell-cycle regulation mechanism depends on the cyclin-dependent kinase (CDK) activation.

The circadian clock oscillations rely on transcriptional-translational auto-regulatory feedback loops (TTFL), which are regulated by the activity of core molecular components. In mammals, the core clock genes govern circadian rhythm and consist of circadian locomotor output cycles kaput (Clock), brain and muscle ARN-1 like protein 1 (Bmal1), neuronal PAS domain protein 2 (Npas2), period protein family (Per1, Per2, and Per3), and cryptochrome family (Cry1 and Cry2). The clock control genes include differentially expressed in chondrocyte family (Dec1 and Dec2), nuclear receptor subfamily 1, group D member 1(REV-ERBα), retinoic acid receptor-related orphan receptor α (RORA), casein kinase 1 family (CK1ε and CK1δ), and timeless (Tim). These circadian clock genes encode a highly conserved alkaline helix-loop-helix (bHLH) region that binds to DNA sequence “CANNTG” (E-Box), which can be used as a core transcription enhancer. Conserved core components include the bHLH-PAS transcriptional activators, CLOCK/NPAS2, and BMAL1. PERs and CRYs inhibit CLOCK: BMAL1 heterodimer transcriptional activity and in turn their own expression, thus forming the negative feedback loop. An additional loop that is also induced by CLOCK: BMAL1 heterodimerization activates the rhythmic transcription of Rev-erbα and Rev-erbβ. In addition, the CLOCK: BMAL1 heterodimer complex may be involved in activating a second alternative cycle consisting of REV-ERBα and REV-ERBβ which compete at the ROR- binding elements. CK1ε and CK1δ determine the circadian period length, through speed and rhythmicity regulation of PER1 and PER2 phosphorylation. DECs provide feedback and modulate CLOCK activity.

Circadian rhythms persist in the presence or absence of environmental cycles because they are generated by endogenous mechanisms. Their periodic activity is composed of a periodically oscillating network formed by a series of rhythmically expressed proteins, and a variety of circadian clock factors affect the cell cycle by regulating the expression of the cyclin. In the G/S phase, REV-ERBα inhibits p21 to promote cell progression; RORα activates p21 to inhibit cell progression; DEC1 inhibits cyclin D1, and CRY1 acts on Wee1 to inhibit or activate glioma process (Figure 1). Therefore, elucidating the circadian rhythm effect on the cell cycle will provide a prominent molecular theoretical basis for tumor therapy.

3 | EXTERNAL FACTORS AFFECTING GLIOMA CIRCADIAN CLOCK

3.1 | Thermodynamics

Temperature compensation is characterized as the robust output of the circadian rhythm to the temperature fluctuation. Since the system level is temperature-stable while individual components
in the system are usually temperature-sensitive under varying temperatures, the temperature compensation mechanism is peculiar. The Cry1 gene expression fluctuated with the temperature while the other circadian genes showed no significant change. The temperature amplitude showed a tight connection between circadian and metabolic rhythms.

3.2 | Hypoxia

Circadian dysregulation is exacerbated within the hypoxic tumor microenvironment (TME) in glioma. The hypoxia-inducible factor-1α targets were negatively correlated with tumor suppressor Clock gene. Loss of fidelity in timekeeping accelerates tumor development. Timekeeping fidelity loss or gain mechanism may offer a controllable switch for pharmaceutical research. Exploring interactions between the hypoxia and the circadian clock in TME may achieve a therapeutic advantage in hypoxia-modifying compounds combined with first-line treatments.

3.3 | Post-modification

Chromatin modification and post-translational modification (PTM) of protein have a great impact on maintaining the periodic oscillation of the 24 h rhythm. Chromatin modification mainly regulates the transcriptional oscillation of rhythmic genes through histone acetylation, deacetylation, and methylation on the promoters of core clock genes. The Clock gene itself has acetyltransferase activity and can activate the transcription of the core clock gene through the CLOCK:BMAL1 heterodimer; on the contrary, the inhibition of the core clock gene through the PERs/CRYs heterodimer is through regulating histone deacetylation and methylation. Phosphorylation, acetylation, and ubiquitination of protein PTM regulate activation of circadian oscillation. Tyrosine kinases CKIε and CKIδ regulate nucleus/cytoplasm transfer through phosphorylation of the core clock elements. CLOCK acetyltransferase activity can act on the lysine residues of BMAL1 to regulate the BMAL1 acetylation, which in turn influences the CLOCK:BMAL1 heterodimer combination. Protein ubiquitination regulates the core clock proteins’ stability and thus affects circadian rhythms. IRE1α endoribonuclease could lead to PER1 degradation through cleaving the Per1 mRNA. Differential expression of circadian genes in cancer or normal cells may thus provide a molecular theoretical basis for glioma chronotherapy.

3.4 | MicroRNA

Small non-coding RNAs, including MicroRNAs, participate in glioma pathophysiology processes including proliferation, invasion, survival, angiogenesis, and cancer metastasis. There have been reports that miR-124 was downregulated in glioma. MiR-124 decreasing may be responsible for Clock gene expression increasing, indicating its potential therapeutic values in glioma chronotherapy. miR-7239-3p secreted by M2 microglial exosomes is recruited in the TME. MiR-7239-3p in M2 microglial exosomes, not M1 type, inhibits Bmal1 expression, promotes proliferation, and reduces apoptosis of glioma cells. MicroRNAs participate in circadian regulation and act as either suppressors or promoters.
4 | INTERNAL CHARACTERISTICS OF THE GLIOMA CIRCADIAN CLOCK

4.1 | Stemness

Disruption of the circadian clock impairs glioma stem cells (GSCs) stemness in glioblastoma (GBM). Bmal1 or Clock downregulation in GSCs induced cell cycle arrest and apoptosis. Epithelial-mesenchymal transition (EMT) is a core event in promoting tumor cell metastasis, invasiveness, and GSCs populations. The specific phase activation in the Per2 gene is a potential target for treatments that may suppress EMT, minimize GSCs, and limit tumor metastasis. Per2 gene expression was enriched within C6 glioma tumor spheres but not in monolayer cell culture, suggesting that cell interactions or TME enable circadian timing.

4.2 | Metabolism

The molecular circadian clock circadian showed a tight connection with the metabolic/redox oscillator, which presents in organs, tissues, and individual cells. The molecular rhythm disruption may cause metabolic disorders. The synthesis and degradation of glycerophospholipids (GPLs) exhibit an oscillation in metabolisms with a 24h periodicity. Moreover in quiescent cells, the Per1 gene is tightly involved in GPL synthesis regulation. While in proliferating cells, targeting time-dependent high-level redox and low-level GPL state revealed a potential efficient therapeutic pathway in chemotherapy. Constant light, which leads to circadian disruption, promotes anabolic metabolism.

Under circadian disruption, more macrophages were recruited in the TME, genes involved in lipogenesis, and glucose uptake was upregulated.

4.3 | Chemotherapy sensitivity

The chemotherapeutic alkylating agent TMZ and radiation therapy regulate and inhibit cellular proliferation by destructing DNA replication. Chronotherapy affects the TMZ administration sensitivity of murine GBM tumor cells. Optimized TMZ administration time is near the daily peak Bmal1 expression maximized DDR, apoptosis activation, and growth inhibition. Bmal1-deficient cells revealed circadian rhythm disruption in gene expression, TMZ-induced apoptosis, and growth inhibition. Optimizing TMZ administration time in GBM treatment to daily rhythms should be evaluated in prospective clinical trials.

4.4 | Radiation therapy sensitivity

PERs participate in regulating the circadian rhythm in mammalian organisms. High Per1 and Per2 expression were associated with increased sensitivity to irradiation in glioma tissue. Following exposure to irradiation, higher Per1 expression levels lead to serious DNA damage while the expression of important checkpoints in DNA damage, such as CHK2 and P53, increased. Cry2 mRNA and protein levels exhibit 8h periodicity in glioma tissue compared to 24h in normal brain tissue. Higher Cry2 expression in glioma tissues was in association with increased cell proliferation and irradiation resistance. Silencing Clock downregulated c-Myc and Cyclin B1 and led to apoptosis and cell cycle arrest after irradiation.

5 | THE MOLECULAR PATHWAYS INVOLVED IN GLIOMA CIRCADIAN CLOCK

The key molecules of the circadian clock are involved in proliferation, invasion, migration, and tumorigenesis. The pathways involving circadian clock-related molecules are summarized in Table 1.

5.1 | PI3K/AKT pathway

Protein kinase B (PKB/Akt) activation via phosphatidylinositol 3-kinase (PI3K) is highly related to tumorigenesis. In glioblastoma cells, the PI3K pathway regulates Cry expression. Cry is necessary and sufficient to promote the accumulation of oncogene Myc. PI3K/AKT pathway could also be regulated via tyrosine kinase AXL, which is the transcriptional target of REV-ERBβ in glioblastoma cells. The core circadian clock gene Bmal1 knockdown elevated cell invasion and migration through phosphorylated-AKT and matrix metalloproteinase-2 (MMP-2) accumulation. BMAL1 is characterized as a tumor suppressor, which is capable of suppressing cancer cell growth and invasiveness. Recent studies demonstrated that there is a tight molecular connection between circadian rhythms and glioma genesis via PI3K/AKT pathway.

5.2 | TGF-β/Smad

The TGF-β pathway participates in many cellular processes, including cell proliferation, invasion, migration, and extracellular matrix remodeling. TGF-β is also an essential influencing factor of the physiological circadian clock rhythms. TGF-β expression upregulation by adenovirus can induce Bmal1 and Npas2 expression significantly. TGF-β binds and activates the serine-threonine kinase complex membrane receptor to phosphorylate Smad2 and Smad3; after phosphorylation, accumulation of Smad proteins in the nucleus forms complexes with transcription factors Smad4 to regulate transcription. IDH1 R132H mutation affected the TGF-β/Smad signaling pathway. The circadian clock genes Bmal1, Clock, Pers, and Cry expression levels were significantly decreased. Those of the Smad signaling pathway genes Smad2, Smad3, and Smad2-3 were decreased, while phosphorylated (p)-Smad2, p-Smad3, and Smad4 were increased.
# TABLE 1 Research Characteristics of Glioma Circadian Clock Participating Pathways

| Author          | Publishing Time | Tissue/Cell Lines | Interference | Participating Pathways | Main Effects                                                      |
|-----------------|-----------------|-------------------|--------------|------------------------|------------------------------------------------------------------|
| Jarabo P et al. | 2022            | Drosophila glioblastoma model | UAS-cry RNAi fly stocks | PI3K pathway          | PI3K pathway regulates CRY expression in glioblastoma cells, and in turn, CRY is necessary and sufficient to promote Myc accumulation in glioblastoma cells. |
| Gowda P et al.  | 2021            | A172, LN-18       | siRNA-mediated gene silencing | IL-1β-mediated Inflammation | Lactate-IL-1β autoregulatory circuit drives Clock-Bmal1 in glioma, and DHA and IL-1β behave as Clock-Bmal1 targets; Clock-Bmal1 transcriptional network regulates genes associated with glioma progression |
| Gao Y et al.    | 2021            | U87-MG            | LVX-IDH1-mCMV-ZsGreen-PGK-Puro and pLVX-IDH1(MUT)-mCMV-ZsGreen-PGK-K-Puro lentiviruses | TGF-β/Smad | IDH1 R132H mutation may alter the cell cycle and biological rhythm genes in U87-MG cells through the TGF-β/Smad signaling pathway. |
| Ma D et al.     | 2020            | Human astrocyte, U87-MG, U251, glioma stem cells. Intracranial implantation into male Balb/c male nude mice | Lentiviruses packaged in pGMLV-Pe1-Per2 for Per2 overexpression | Wnt/β-catenin | Per2 overexpression could induce glioma stem cell arrest at the G0/G1 phase and suppress glioma proliferation, stemness and invasion ability in vitro and in vivo. Subsequently, the Wnt/β-catenin signaling pathway was identified as the target of PER2 in glioma stem cells. |
| Gwon DH et al.  | 2020            | U87-MG            | Adenovirus-mediated ectopic expression of Bmal1 | cyclin B1-mediated apoptosis | BMAL1 suppresses proliferation, migration, and invasion of U87-MG cells by downregulating cyclin B1, phospho-AKT, and MMP-9. Downregulation of cyclin B1 increased early and late apoptosis due to changes in the levels of BAX, BCL2, and cleaved Caspase-3. |
| Goldsmith CS et al. | 2019    | Human astrocyte; IM3 | VX-745 for p38 MAPK inhibition | p38 MAPK | Inhibition of p38 MAPK activity in IM3 cells at the time of day when the levels are normally low in human astrocytes under control of the circadian clock, significantly reduced IM3 invasiveness. |
| Yu M et al.     | 2018            | LN-18; U118-MG; primary human astrocytes | siRNA-mediated gene silencing | PI3K/AKT axis; actin nucleation and polymerization | AXL mediated partially the regulatory effects of NR1D2 on PI3K/AKT axis and promoted proliferation, migration, and invasion of glioblastoma cells. Besides, Rev-erbβ knockdown remarkably impaired the maturation of focal adhesion and assembly of F-actin, along with downregulated phospho-FAK, and proteins involved in actin nucleation and polymerization (phospho-RAC1/CDC42, WAVE and PFN2). |
| Zhanfeng N et al. | 2016    | U343; subcutaneous implantation into male Balb/c male nude mice | Per2 downregulation modified using a lentiviral transfection of shRNA | MDM2-TP53 | PER2 downregulation inhibits glioma cell apoptosis by activating the MDM2-TP53 pathway |
| Jung CH et al.  | 2013            | U251              | siRNA-mediated gene silencing | PI3K-AKT-MMP-2 | Bmal1 suppresses cancer cell invasion by blocking the PI3K-AKT-MMP-2 signaling pathway. |

Abbreviations: AXL, AXL receptor tyrosine kinase; BAX, Bd2-associated X protein; BCL2, B-cell lymphoma 2; BMAL1, Brain and muscle ARN-t like protein 1; Cdc42, Cell division cycle 42; Clock, Circadian locomotor output cycles kaput; Cry, Cryptochrome; DHA, Docosahexaenoic acid; FAK, Focal adhesion kinase; IL-1β, Interleukin-1 beta; MAPK, Mitogen-activated protein kinases; Myc, Cellular-myelocytomatosis viral oncogene; MDM2, Murine double minute 2; MMP-2, metalloproteinase-2; MMP-9, metalloproteinase-9; p21, Cyclin-dependent kinase inhibitor 1A; PER2, Period 2; PFN2, Profilin 2; PI3K, Phosphatidylinositide 3 kinase; TGF-β, Transforming growth factor-beta; TPS3, Tumor protein P53; WAVE, Wiskott Aldrich syndrome protein; Wnt, Wingless-Type MMTV Integration Site Family.
5.3 | Wnt/β-catenin

The WNT/β-catenin pathway induces the genes transcription involved in cell proliferation, cell invasiveness, nucleotide synthesis, tumor growth, and angiogenesis. Wnt/β-catenin signaling upregulation also induces molecular differential changes in core metabolic enzymes that modify their thermodynamics behavior. This leads to pyruvate dehydrogenase complex (PDK1) and monocarboxylate lactate transporter 1 (MCT1) activation. Consequently, phosphorylation of PDK1 inhibits the pyruvate dehydrogenase complex, which leads to aerobic glycolysis despite the oxygen availability, named the Warburg effect. In glioma cells, the Wnt/β-catenin signaling pathway was identified as the target of Per2 in GSCs. Subsequently, downstream molecular PPARγ is downregulated, resulting in abnormalities in the regulation of circadian rhythms and destruction of circadian clock genes. These results indicated that PER2 plays a critical role in regulating the stemness of GSCs via the WNT/β-catenin signaling pathway.

5.4 | TP53

The MDM2/TP53 pathway is an important pathway for the occurrence and development of tumors. It is well characterized that TP53 is an important tumor suppressor gene. About 50% of tumors have TP53 mutations, resulting in the inactivation of its function. Murine double minute 2 (MDM2) is a key negative regulator of p53 and can mediate the degradation of TP53. MDM2 inhibitors can block TP53 degradation by inhibiting the function of MDM2, possibly restoring the function of TP53 protein. Lowering Per2 expression reduces DNA damage response and cell death following low-dose X-ray irradiation. Per2 was associated with increased activity of TP53 and participating in the DNA destruction during TP53-mediated apoptosis.

5.5 | P38 MAPK

The p38 MAPK expression and activity increase are correlated with poor clinical prognosis, including GBM multiforme; however, the lethal toxicity of p38 MAPK inhibitors limits their therapeutic use. The phosphorylated p38 MAPK protein level was reduced in Clock-deficient cells. The p38 MAPK activity inhibition with specific inhibitor VX-745 led to cell-type-specific periodical changes in the molecular clock, indicating potential therapeutic use of VX-745 in glioma chronotherapy. Under the control of the circadian clock, the p38 MAPK activity inhibition in invasive IM3 cells at the time point when the levels are normally low in human astrocytes significantly reduced IM3 invasiveness.

5.6 | Lactate-IL-1β-Clock Loop

A desynchronized circadian rhythm in tumors is coincident with aberrant inflammation and dysregulated metabolism. The increase in tumor metabolite lactate results in the cytokine interleukin-1β (IL-1β) upregulation leading to inflammatory. IL-1β was correlated with elevated levels of the core circadian regulators Clock and Bmal1. Lactate-IL-1β interaction positively affects the recruitment of CLOCK: BMAL1 to these E-box sites in the nucleus. Lactate-IL-1β-Clock Loop (LIC loop) was found to be correlated with the OS of patients.

6 | THE THERAPEUTIC DRUGS INVOLVED IN GLIOMA CIRCADIAN CLOCK

Current research methods for therapeutic drugs targeting the circadian clock mainly fall into two directions. One class of drugs that are widely used in clinical practice, including TMZ mentioned above, focuses on finding the optimal administration time for treatment. The cancer chronotherapy drug administration thus has been studied on in vivo animal, and potentially represents the combined effects both of time-dependent pharmacokinetics and pharmacodynamics phenomena. Another class of therapeutic drugs regulates the proliferation of tumor cells by interfering with core proteins or substrates in the circadian clock (Figure 2). The two classes of drugs are reviewed in this section.

6.1 | 1A-116

The 1A-116 (ZINC69391) compound was recently exhibited as a novel drug in glioblastoma and other tumors treatment. Both in LN229 and U-87 glioma cell lines, 1A-116 specifically inhibited Rac Family Small GTPase 1 (RAC1) activation to guanine exchange factors such as T-lymphoma invasion and metastasis-inducing protein 1 (Tiam1), by interacting with the Trp56 residue. The effectiveness of 1A-116 could be further optimized by finding the optimized time for the administration. The higher efficacy of 1A-116 was observed at low BMAL1 expression in glioblastoma cells and a differential OS was found when applying 1A-116 at Zeitgeber times 12 (ZT 12) to glioma-bearing nude mice. The time-dependent pharmacological application of 1A-116 is a feasible strategy to improve OS.

6.2 | Melatonin

Melatonin (N-acetyl-5-methoxytryptamine, CAS#: 73-31-4) is a naturally synthesized hormone involved in the biological clock, circadian rhythm, and reproductive physiology. It is produced by the pineal gland and acts on specific receptors and has an important role in overall energy metabolism. Melatonin is a powerful scavenger of reactive oxygen and nitrogen species (ROS/ RNS), and also acts as a stimulator of the antioxidant enzymes leading to a DNA damage decrease. However, high melatonin (mM range) concentrations have been shown to impair the invasion and migration ability of human glioma cell lines and reduce the
viability, while lower concentrations did not produce significant results.\textsuperscript{115,116} Human MT1 and MT2 melatonin receptors share 55\% amino acid sequence similarity, but the two receptors play opposite roles in glioma progression.\textsuperscript{117} MT1 activation and MT2 depression exhibit robust antitumor effects and interfere with the proliferation and metabolism of glioma stem cells.\textsuperscript{118} Melatonin increases calmodulin degradation by direct binding while redistributing calmodulin, thereby arresting the S/M phases and reentry of G0 quiescent cells into the cell cycle.\textsuperscript{119} Melatonin acts antitumor effect via inhibiting the production of cAMP production, resulting in diminished linoleic acid uptake and 15- lipoxigenase oxidation serving as an energy source for tumor growth.\textsuperscript{120}

### 6.3 Curcumin

Curcumin (diferuloylmethane, CAS#: 458–37-7) is a promising phytochemical that can be administered in glioma therapy.\textsuperscript{121} Administration of curcumin can alter molecular circadian timing within cells. The prominent target, BMAL1, is the core gene in molecular oscillators that generates circadian rhythms.\textsuperscript{122} Studies reported that curcumin can affect STAT, PPAR-\gamma, and NF-\kappaB expression within two interacted molecular timing loops.\textsuperscript{121,122} BMAL1 is activated by curcumin via PPAR-\gamma stimulation.\textsuperscript{108} Research has also shown that curcumin activates sirtuin 1, and binds to CLOCK: BMAL1 heterodimer to promote the deacetylation and degradation of PER2.\textsuperscript{69} Although no effect on the circadian mechanism has been reported, 10 \textmuM curcumin treatment did disrupt a single circadian oscillator within the clock unit or coupling between circadian clocks in apoptosis.\textsuperscript{123} During anticancer treatment, curcumin or its analogs should be administered to tumor cells at the optimal stage in maximizing efficacy after determining the circadian phase.

### 6.4 Norepinephrine

Norepinephrine (NA, CAS#: 51–41-2) is primarily located in the brain stem and is involved in behaviors including sleep and awakening.\textsuperscript{124} NA can act on the biological pineal region cells pinealocytes.
Promoting cAMP activates arylalkylamine N-acetyltransferase (AA NAT), which is the melatonin synthesis rate-limiting enzyme. NA administration led to increasing in Per1 mRNA expression via β-adrenergic receptors. Furthermore, this same reaction might be involved in the activities of both protein kinase A (PKA) and the protein tyrosine kinase Src family. The PKA-CREB signaling cascade coupled with β2-adrenoceptors has been shown to play an essential role in the regulation of clock genes including Per1 in cerebellar granule cells and chondrocytes.126

6.5 | REV-ERB agonist

REV-ERBs are essential components participating in the circadian clock. The novel drugs SR9009 and SR9011, agonists of REV-ERBs, are specifically lethal to cancer cells and oncogene-induced senescent cells and do not affect the viability of normal cells or tissues. SR9009 treatment decreased ROS levels and increased the level of lipid droplets, whereas the combined treatment with Bortezomib showed additive or synergistic effects between both drugs in T98G cells. The autophagy regulation and de novo lipogenesis by REV-ERB agonist administration have a great impact on evoking an apoptotic response in malignant cells. Notably, these REV-ERB agonists showed selective anticancer properties, impaired glioblastoma growth in vivo, and improved survival without causing overt toxicity in mice. SR9009 and SR9011 anticancer activity affects several oncogenic drivers, including HRAS, BRAF, and PIK3CA, and persists in the absence of TP53 and under hypoxic conditions which need further illustration.

7 | FUTURE PERSPECTIVE

This review discussed the molecular connection between cell cycle and circadian clock, illustrated the external factors and internal characteristics concerning the circadian clock in glioma, and summarized the molecular pathways and the therapeutic drugs involved in the glioma circadian rhythm. However, the results of chronotherapy for temozolomide and radiation therapy in glioma are currently controversial. Damato AR et al. reported no significant difference in adverse events, quality of life, or OS in prospective randomized TMZ chronotherapy trials. For high-grade glioma patients, radiotherapy treatment time of the day (RT-TTD) did not influence progression-free survival and OS between patients treated in the morning or afternoon. The heterogeneity of each study is worth our attention. Besides tumor grade as a confounding factor should be analyzed separately in the subsequent study. There is still a lack of multi-center, double-blinded random control trials to further elaborate on the influence of the circadian clock in glioma patients.

There are still many questions in this field waiting for further investigation. From the perspective of etiology, whether the changes in circadian rhythm are an essential physiological factor in glioma genesis; From the perspective of treatment, how to accurately identify the patient’s circadian clock during clinical treatment, and whether the treatment regimen is customized based on the circadian clock of the patient; The therapeutic and adverse effects of changing the circadian clock of glioma patients must be considered seriously. Currently, experimental research performed serum shock procedures to synchronize cells in vitro107. In vivo, animals were kept at an inverse 12 h light/12 h dark cycle, facilitating adaptation to the environmental cycle of day and night. Besides, the different TME between in vivo and in vitro are worthy of attention. The circadian clock of laboratory animals may differ significantly from those of humans. Since mice are nocturnal animals, and their active and rest phases are out of phase with humans, there are obvious differences in circadian rhythms in mice and humans.130 In addition, tumor cell-intrinsic circadian rhythms can regulate TMZ cytotoxicity in mice, which showed a strong correlation between drug sensitivity and circadian rhythm, while the effect of TMZ in glioma chronotherapy treatment is still controversial and needs further large-population-based trials for validation. Despite being more complex and expensive than murine models, nonhuman primates share more closely activity patterns with humans, which may provide stronger evidence support for chronotherapy research. The generalization of these conclusions to other species will require additional systematic study. Besides, several non-invasive imaging modalities, including quantitative parametric images of O-(2-[F]fluoroethyl)-L-tyrosine kinetics analysis and MRI approach for noninvasive TME visualization, have been developed for quantitatively assessing the oxygen and energy metabolism within glioma or the microenvironment surrounding glioma. Future studies should include the longitudinal measurement of glioma metabolism, determining how circadian activities may alter the metabolic profile of glioma. Regardless, the results of glioma chronotherapy in sensitizing radiation therapy and chemotherapy are exciting. These findings will help us further understand this pathological process in chronotherapy.

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CONFLICT OF INTEREST
The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Gang Chen https://orcid.org/0000-0002-0758-1907

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