J. Adv. Med. Pharm. Biomed. Res.; **(2026),** Volume 2, Issue 3, 234-241

Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research

Journal homepage: https://www.jampbr.com

DOI: 10.22034/jampbr.2026.581015.1091

Glioblastoma Stem Cells: Therapeutic Resistance; Mechanisms and Emerging Strategies for Clinical Intervention. Updated 2026, a Narrative Review

Ali Baradaran-Bagheri[1], Hossein Maleki[1], Yahya Roshani[1], Parisa Azimi[1], Mohammad Pirhayati[2], Saman Mohazzab-Torabi[1*]

[1]Department of Neurosurgery, Shahid Madani Hospital, Alborz University of Medical Sciences, Karaj, Iran

[2]Department of General Medicine, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

Article info

Received: 09.04.2026

Accepted: 22.05.2026

Available Online: 22.05.2026

Checked for Plagiarism: Yes

Keywords:

Glioblastoma, glioblastoma stem cells, mesenchymal stem cells, tumor heterogeneity, therapeutic resistance, therapy.

ABSTRACT

Glioblastoma (GBM) remains the most lethal primary brain tumor in adults, driven in large part by a subpopulation of glioblastoma stem cells (GSCs) that exhibit self-renewal, multipotency, and pronounced resistance to conventional therapies. This narrative review synthesizes contemporary evidence on the mechanisms by which GSCs mediate therapeutic resistance, including enhanced DNA repair, drug efflux, cell cycle regulation and quiescence, microenvironmental influences, and phenotypic plasticity. We integrate findings across intrinsic cellular adaptations, tumor microenvironment interactions, and intratumoral heterogeneity to delineate how these features converge to sustain GBM recurrence. We also summarize current and emerging therapeutic strategies aimed at overcoming GSC-driven resistance, such as targeting signaling pathways (Hedgehog/GLI, JAK/STAT3, Wnt/β-catenin), disrupting cell cycle regulators, metabolic and epigenetic reprogramming, and combinatorial regimens designed to sensitize GSCs to chemotherapy and radiation. Throughout, we emphasize areas of consensus and points of contention in the literature, and we highlight knowledge gaps that impede translation to the clinic. This synthesis underscores the imperative to target GSC biology in concert with bulk tumor-directed therapies to achieve more durable GBM control.

Introduction

Glioblastoma (GBM) is the most common and lethal primary malignancy of the central nervous system (CNS) in adults, classified as a World Health Organization (WHO) Grade IV glioma due to its aggressive nature[1,2]. Characterized by rapid proliferation and infiltrative growth, GBM poses significant therapeutic challenges. Despite multimodal treatments involving surgical resection, radiotherapy, and chemotherapy, patient prognosis remains poor, with a median survival of approximately 15 months and a five-year survival rate of 5% [1,3,4].

The tumor's high recurrence rate, driven by intratumoral heterogeneity and resistance to standard therapies, is largely attributed to glioblastoma stem cells (GSCs), which contribute to tumor initiation, progression, and treatment resistance [5,6]. This review synthesizes current understanding of GBM characteristics, GSC-mediated resistance mechanisms, and emerging therapeutic strategies to address these challenges.

Methods and Materials:

PICOS Framework

Population: Human studies and relevant preclinical models of glioblastoma with identified glioblastoma stem cell populations (GSCs) or stem-like tumor-initiating cells.

Intervention: Therapeutic strategies targeting GSCs or GSC-associated pathways (e.g., Hedgehog/GLI, JAK/STAT3, Wnt/β-catenin, Notch, BMP4 differentiation therapy, CDK4/6 inhibitors, MELK-FOXM1 axis, AURKA

*Corresponding Author: ***Saman Mohazzab-Torabi*** *(Smntrb@gmail.com)*

inhibitors, metabolic/epigenetic modulators, Nano delivery, exosome/miRNA targeting).

Comparator: Standard of care (SOC) or other targeted approaches; vehicle/placebo in preclinical studies; historical controls where applicable.

Outcomes: Mechanistic endpoints (DNA repair, DDR signaling, MGMT status, DDR gene expression), phenotypic endpoints (GSC frequency, quiescence, plasticity), treatment efficacy (survival, tumor growth, radio sensitivity, TMZ sensitivity), biomarkers (MGMT methylation, DDR markers, stemness signatures), and safety/feasibility of novel delivery methods.

Study design: In vitro, in vivo (orthotropic and patient-derived xenografts), organoid models, ex vivo analyses, translational clinical studies, phase I/II trials, and comprehensive reviews/meta-analyses.

Search Strategy:

Primary databases: PubMed/MEDLINE, Embase, Web of Science Core Collection, Scopus.

Description of GBM

Histological and Molecular Characteristics: GBM is marked by rapid proliferation, diffuse infiltration into brain parenchyma, pronounced angiogenesis, microvascular endothelial necrosis, and pseudo palisading necrosis [2,7]. While thought to originate from astrocytic lineage, its precise cellular origin neural stem cells or glial progenitor cells remains under investigation [8-10]. GBM exhibits molecular heterogeneity, with four clinically relevant subtypes: proneural, neural, mesenchymal, and classical [11]. The proneural subtype is associated with a more aggressive clinical course, while the mesenchymal subtype often shows greater stability [11]. In contrast, lower-grade gliomas, such as Grade I pilocytic astrocytomas, frequently harbor neurofibromin 1 (NF1) mutations [12,13], and intermediate-grade gliomas (Grades II and III) are linked to TP53 and alpha-thalassemia/mental retardation syndrome X-linked (ATRX) alterations [14,15]. Pediatric gliomas typically lack IDH mutations and 1p/19q co-deletion, distinguishing them from certain adult gliomas [16,17].

Epidemiology and Prognostic Factors: GBM accounts for 45.2% of adult CNS malignancies but is relatively rare, with an incidence rate of 3.19 per 100,000 in adults and 0.85 per 100,000 in pediatric patients in the United States [7]. It is more prevalent in males, with a male-to-female incidence ratio of 1.2-2.6 [8]. Age significantly impacts outcomes: 83% of diagnoses occur in adults over 50, with 47.9% in those over 65 [8]. Survival declines with age; adults under 50 have a median survival of 8.8 months, compared to 4.55 months for those over 50 [18]. In children, older age groups face higher mortality risks, with hazard ratios of 1.408 for ages 6–10 and 1.406 for ages 11-19 [18]. Prognostic factors include age, performance status, tumor grade, and molecular markers such as O^6-methylguanine-DNA methyl transferase (MGMT) promoter methylation, IDH1/IDH2 mutations, TERT promoter expression, and epidermal growth factor receptor (EGFR) alterations [9].

Glioblastoma Stem Cells and Resistance Mechanisms: GBM's recurrence is driven by glioblastoma stem cells (GSCs), which are highly tumorigenic, with self-renewal and multipotency properties [9,19]. GSCs exhibit robust DNA repair mechanisms, adaptive metabolic pathways, and thrive in vascular niches near cerebral endothelium, where they are shielded from chemotherapy and radiation [6,10]. They also produce vascular pericytes, supporting tumor vasculature and growth [20] [21]. Residual GSCs post-resection contribute to rapid tumor regrowth and increased aggressiveness due to their cellular plasticity [10, 21]. In pediatric high-grade gliomas, such as diffuse midline gliomas (DMGs) and diffuse intrinsic pontine glioma (DIPG), aggressive growth and immune evasion are driven by genetic alterations like the H3K27M mutation and epigenetic dysregulation [16]. This plasticity, enabling GSCs to reconstitute tumor heterogeneity, undermines therapies targeting specific cancer stem cell markers, significantly contributing to treatment resistance [22].

Therapeutic Obstacles and Mechanisms of Glioblastoma Stem Cell Resistance

GSCs employ a sophisticated array of mechanisms to evade the cytotoxic effects of conventional therapies, contributing significantly to tumor recurrence. These mechanisms can be broadly categorized into intrinsic cellular adaptations, micro environmental influences, heterogeneity, and remarkable phenotypic plasticity [5,23,24].

Intrinsic Cellular Adaptations

Drug Efflux and Detoxification Systems: GSCs frequently exhibit elevated expression of ATP-binding cassette (ABC) drug transporters, which actively efflux chemotherapeutic agents, thereby reducing intracellular drug concentrations. For instance, studies have shown that melatonin can sensitize brain tumor stem cells (BTSCs) to chemotherapy by reducing the levels of ABCG2/BCRP, a key drug-resistance protein that is typically abundant in these cells [25]. Melatonin's action involves downregulating ABCG2/BCRP at both gene and protein levels, facilitating greater intracellular retention of chemotherapeutic agents like mitoxantrone. This effect may be mediated by melatonin's influence on the methylation status of the ABCG2 gene's promoter region, positioning melatonin as a potential adjuvant therapy to overcome drug resistance in glioblastoma [25]. Additionally, recent studies have identified other

ABC transporters, such as ABCC1 and ABCB1, as critical mediators of multidrug resistance in GSC. Furthermore, epigenetic regulation of ABC transporters, beyond melatonin's effects, includes histone modifications that upregulate ABCB1 expression, suggesting a broader role for epigenetic therapies in overcoming drug efflux-mediated resistance [26].

Enhanced DNA Repair Pathways: Beyond the resistance mechanisms related to stem cell properties, DNA repair pathways represent another critical challenge for effective glioblastoma therapy. A pivotal mechanism of resistance to temozolomide (TMZ), a first-line alkylating agent, involves the overexpression of O6-methylguanine-DNA methyl transferase (MGMT), a DNA repair enzyme that directly counteracts TMZ-induced DNA damage [4]. Furthermore, the epigenetic silencing of the MGMT gene through promoter methylation serves as a crucial biomarker for TMZ sensitivity, with tumors exhibiting a methylated MGMT promoter demonstrating improved treatment responses and survival outcomes following TMZ and radiotherapy [27]. In addition to MGMT, deficiencies in other DNA repair pathways can also contribute significantly to therapeutic failure [25]. For instance, combining TMZ with the AKT inhibitor perifosine has been shown to sensitize glioblastoma cells by reducing the expression of BRCA1, a protein essential for DNA damage repair; this synergistic approach impairs the tumor cells' ability to repair DNA lesions, leading to increased cellular apoptosis, as evidenced by elevated cleaved caspase-3 levels in both in vitro and in vivo models [28]. Additionally, the interplay between DNA repair and metabolic reprogramming has emerged as a critical factor, with GSCs upregulating glycolysis to fuel nucleotide synthesis for DNA repair, a process targetable by glycolysis inhibitors like 2-deoxyglucose [29].

Cell Cycle Regulation and Quiescence: Glioblastoma stem cells (GSCs) can enter a quiescent (G0) state, enabling them to evade cell cycle-dependent chemotherapies [30]. This G0 state is maintained by key transcription factors such as SOX2 and OLIG2, which are essential for GSC self-renewal and multipotency. Disruption of regulatory signaling pathways, including Bone Morphogenetic Protein (BMP), Notch, and Wnt, can induce GSCs to exit quiescence, thereby promoting tumor growth and recurrence [30].

Recent studies highlight specific targets for disrupting GSC quiescence and enhancing therapeutic response. The cyclin-dependent kinase inhibitor p27Kip1 has been implicated in maintaining GSC quiescence, with its upregulation in hypoxic niches linked to enhanced TMZ and radiotherapy resistance; targeting p27Kip1 can induce proliferation and increase susceptibility to cell cycle-specific therapies [31]. Similarly, the Hippo pathway effector YAP1 promotes GSC quiescence by repressing cell cycle progression genes, and YAP1 inhibitors, like verteporfin, reduce GSC viability in combination with TMZ, particularly in IDH-wild type GBMs [32]..

Micro environmental Influences: The intratumoral oxygen gradient plays a significant role in dictating the cellular heterogeneity of GBM [33]. Immature cell populations, including CD133-marked GSCs, are preferentially localized to hypoxic inner core and intermediate layers of the tumor, whereas more differentiated cells are found in oxygen-rich peripheral zones [33]. GSCs within the hypoxic tumor core (CD133(+)) exhibit high levels of MGMT, further augmenting their resistance to TMZ [33]. Importantly, TMZ-induced apoptosis is more pronounced in cells residing in the peripheral tumor area, highlighting a spatial correlation between hypoxia, cell phenotype, and chemo resistance [33]. This observation supports a concentric tumor stem cell niche model, which could inform targeted therapeutic strategies against chemo resistant cell populations. The extracellular matrix (ECM) also plays a critical role, with hyaluronic acid and Tenascin-C promoting GSC adhesion and survival. Disrupting ECM-GSC interactions with hyaluronidase or anti-tenascin-C antibodies has shown promise in reducing GSC invasiveness and sensitizing tumors to chemotherapy [34].

Phenotypic Plasticity: A critical mechanism contributing to TMZ resistance and tumor recurrence is the capacity of non-GSCs to phenotypically convert into a GSC-like state following treatment [35]. Lineage-tracing analyses in patient-derived and established glioma cell lines, alongside in vivo mouse models, have consistently demonstrated that TMZ exposure can expand the GSC pool through this phenotypic interconversion. These newly converted GSCs express classic stemness markers such as CD133, SOX2, Oct4, and Nestin, and display enhanced tumor-forming ability and invasiveness in vivo, illustrating a dynamic mechanism by which glioblastoma evades therapy and subsequently relapses [35]. Recent single-cell RNA sequencing studies (2024) have further revealed that this plasticity is driven by epigenetic reprogramming, particularly through the upregulation of KDM6A, a histone demethylase that activates stemness-associated genes. Inhibiting KDM6A with GSK-J4 has been shown to block non-GSC to GSC conversion, reducing tumor recurrence in preclinical models [36]. Additionally, the tumor microenvironment, particularly TGF-β signaling from stromal cells, promotes this plasticity by inducing epithelial-to-mesenchymal transition (EMT) in non-GSCs, leading to a stem-like phenotype. Targeting PGC-1α with inhibitors like SRT1720 has shown promise in disrupting this metabolic switch and sensitizing GSCs to chemotherapy [37].

Heterogeneity of GSCs: The pivotal role of glioblastoma stem cells (GSCs) in conferring therapeutic resistance and driving tumor recurrence is consistently reported [5]. GSCs, a distinct subpopulation within the heterogeneous GBM tumor, possess critical characteristics like self-renewal and multi-lineage differentiation capabilities, akin to normal neural stem cells but subverted for oncogenic processes [5]. Single-cell RNA sequencing data powerfully highlight the significant intratumoral heterogeneity inherent in primary glioblastoma, a complexity further perpetuated and reconstituted by GSC plasticity following therapeutic interventions [38,39]. This heterogeneity is not merely an incidental feature but a dynamic landscape shaped by the clonal evolution of glioblastoma under therapeutic pressure, with specific GSC populations driving resistance and relapse [40-42]. Analysis of the literature reveals several key mechanisms through which GSCs mediate resistance to standard-of-care therapies, including radiation and chemotherapy. These mechanisms are multifaceted, encompassing enhanced DNA repair, increased activity of drug efflux pumps, and the ability of GSCs to enter a quiescent state, which collectively render them less susceptible to cytotoxic agents [5].

Resistance to Therapy

Resistance to Chemotherapy: Glioblastoma (GBM) exhibits formidable resistance to chemotherapy, a complex phenomenon driven by multiple intrinsic cellular mechanisms. A primary factor in this resistance, particularly to temozolomide (TMZ) a first-line alkylating agent is the overexpression of O6-methylguanine-DNA methyl transferase (MGMT), a DNA repair enzyme that directly counteracts TMZ-induced DNA damage [4]. The epigenetic silencing of the MGMT gene through promoter methylation is a crucial biomarker for TMZ sensitivity, as tumors with a methylated MGMT promoter demonstrate significantly improved responses and survival outcomes when treated with TMZ and radiotherapy [4,27]. TMZ induces DNA damage that can trigger a protective G2-M cell cycle arrest via Chk1 activation, promoting cellular senescence rather than apoptosis; inhibiting this Chk1-mediated arrest can enhance TMZ efficacy by inducing mitotic catastrophe [43].

This quiescence is maintained by key transcription factors such as SOX2 and OLIG2 and regulated by signaling pathways including BMP, Notch, and Wnt [30]. Furthermore, differentiated non-GSCs can phenotypically transition into a GSC-like state after TMZ exposure, expanding the resistant GSC pool and contributing to tumor relapse. The role of exosome-mediated communication between GSCs and non-GSCs has also emerged as a resistance mechanism, with GSC-derived exosomes transferring miR-21 to promote TMZ resistance in recipient cells. Inhibiting exosome release with GW4869 has shown promise in sensitizing GBM cells to chemotherapy [44].

Resistance to Radiotherapy: Despite aggressive treatment regimens centered on radiotherapy, tumor recurrence in glioblastoma (GBM) remains inevitable, a phenomenon largely attributed to glioblastoma stem-like cells (GSCs), which exhibit high radio resistance [19]. A primary underlying mechanism for this radio resistance is the preferential activation of DNA damage response (DDR) pathways within these stem-like populations [19]. Studies have demonstrated that GSCs are significantly more radio resistant than their paired tumor bulk populations in clonogenic survival assays [19,45]. The radio resistance of CD133-positive glioma stem cells can be effectively reversed by inhibiting key checkpoint kinases like Chk1 and Chk2 [19]. Indeed, inhibition of CHK1, ATR, or ATM has been shown to successfully abrogate G2–M checkpoint function, leading to increased mitotic catastrophe and a notable enhancement in radiation sensitivity [19,45].

Emerging Therapeutic Strategies

Given the formidable resistance mechanisms of GSCs, significant research efforts are focused on developing novel therapeutic approaches to improve GBM patient outcomes.

Targeting Key Signaling Pathways: The Hedgehog (HH) signaling pathway and its effector GLI1 are crucial regulators of insulin-like growth factor (IGF) signaling in GSCs. GLI1 directly controls the expression of IRS1, which is necessary for IGF-I-mediated MAPK activation [46]. Inhibition of GLI1 reduces GSC responsiveness to IGF-I, thereby suppressing proliferation, invasion, clonogenicity, and angiogenesis. Critically, targeting both the HH/GLI1 and IGF pathways synergistically enhances the sensitivity of GSCs to temozolomide, identifying a cooperative signaling axis that drives malignant GSC traits and therapy resistance [46]. Additionally, the JAK/STAT3 pathway has emerged as a critical regulator of GSC survival, with STAT3 inhibitors like WP1066 demonstrating synergistic effects with radiotherapy by reducing GSC DNA repair capacity in patient-derived xenografts [47].

Targeting Cell Cycle Regulators: The transcription factor FOXM1 is a pivotal regulator of glioma stem-like cell (GSC) mitosis, activated through phosphorylation by the kinase MELK, with further regulation by PLK1 kinase [48]. FOXM1 expression progressively increases from neural progenitor cells to GSCs during tumor development. The antibiotic Siomycin A has demonstrated efficacy in disrupting MELK-FOXM1 signaling, exhibiting greater effects on GSCs compared to normal neural stem cells [48]. Notably, while

temozolomide treatment enriches for FOXM1(+) and MELK(+) cells, combining temozolomide with Siomycin A significantly enhances anti-tumor effects in mouse models, suggesting the MELK-FOXM1-PLK1 complex as a promising therapeutic target for GBM [48]. Recent studies have further elucidated the role of CDK4/6 in GSC cell cycle progression, with CDK4/6 inhibitors like palbociclib showing efficacy in forcing GSCs out of quiescence and into a proliferative state, sensitizing them to TMZ.

Combination Therapies for High-Grade Gliomas: For aggressive H3K27M-altered DMGs, the small molecule ONC201, a dopamine receptor D2 antagonist and mitochondrial ClpP protease agonist, has shown preliminary efficacy by inducing apoptosis and disrupting tumor metabolism [49]. However, therapeutic response to ONC201 monotherapy can vary, with TP53 mutations linked to reduced sensitivity and PIK3CA mutations correlating with increased sensitivity. To overcome the limitations of monotherapy, combination strategies, such as ONC201 with the brain-penetrant PI3K/Akt inhibitor paxalisib, are currently under clinical investigation to improve outcomes for patients with H3K27M-altered DMGs [49]. Recent clinical trials have explored ONC201 combinations with other targeted therapies, such as the HDAC inhibitor panobinostat, which enhances ONC201-induced apoptosis by upregulating TRAIL expression in H3K27M-mutant DMGs. For adult GBM, combination therapies targeting EGFR and MET signaling, such as the dual inhibitor capmatinib, have shown promise in preclinical models by reducing GSC-driven tumor growth and invasion [50].

Challenges in Targeted Therapy Development

Despite promising in vitro anti-tumor effects, the clinical translation of some targeted therapies has faced significant challenges. For instance, the dual PI3K/mTOR inhibitor dactolisib (NVP-BEZ235) effectively inhibited glioblastoma cell growth, induced apoptosis, and reduced Akt phosphorylation in in vitro models [51]. However, in vivo tests using mouse and rat xenograft models demonstrated no improvement in survival or tumor growth inhibition. Moreover, significant toxic side effects, including hyperglycemia, elevated liver enzymes, diarrhea, alopecia, skin rash, and sialo rhea, were observed, severely limiting dactolisib's clinical utility for glioblastoma treatment [51]. Additional challenges include poor penetration of the blood-brain barrier (BBB), which limits drug delivery to GSC niches. Recent studies have explored nanoparticle-based delivery systems, such as PEGylated liposomes encapsulating TMZ, to enhance BBB penetration and target GSCs, with preclinical models showing improved survival compared to free TMZ [52]. Patient heterogeneity also poses a significant barrier, as molecular subtypes (e.g., proneural vs. mesenchymal) respond differently to targeted therapies. Multi-omics profiling has been proposed to stratify patients for personalized therapies, but clinical implementation remains limited due to cost and complexity [53].

Conclusion and Future Directions

Glioblastoma remains a formidable therapeutic challenge, primarily due to its aggressive biological characteristics and the inherent resistance mechanisms orchestrated by glioblastoma stem cells (GSCs). Current and emerging therapeutic strategies largely focus on overcoming these resistance mechanisms by targeting specific GSC signaling pathways, cell cycle regulators, and employing rational combination therapies. Future research efforts must prioritize a deeper mechanistic understanding of GSC biology and their dynamic interplay with the tumor microenvironment. Such targeted approaches, possibly delivered via innovative drug delivery systems and in combination with immunotherapies, hold the greatest promise for ultimately improving the prognosis and quality of life for patients afflicted with this devastating disease.

Disclosure Statement

No potential conflict of interest reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

References

[1] Ostrom, Q. T., Patil, N., Cioffi, G., Waite, K., Kruchko, C., & Barnholtz-Sloan, J. S. (**2019**). CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. *Neuro-Oncology*, 21(Supplement_5), v1–v100.

[2] Louis, D. N., Perry, A., Wesseling, P., Brat, D. J., Cree, I. A., Figarella-Branger, D., ... & Ellison, D. W. (**2021**). The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro-Oncology*, 23(8), 1231–1251.

[3] Stupp, R., Hegi, M. E., Mason, W. P., van den Bent, M. J., Taphoorn, M. J., Janzer, R. C., ... & Mirimanoff, R. O. (**2009**). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year

analysis of the EORTC-NCIC trial. *The Lancet Oncology*, 10(5), 459–466.
[4] Hegi, M. E., Diserens, A. C., Gorlia, T., Hamou, M. F., de Tribolet, N., Weller, M., ... & Stupp, R. (**2005**). MGMT gene silencing and benefit from temozolomide in glioblastoma. *New England Journal of Medicine*, 352(10), 997–1003.
[5] Lathia, J. D., Mack, S. C., Mulkearns-Hubert, E. E., Valentim, C. L., & Rich, J. N. (**2015**). Cancer stem cells in glioblastoma. *Genes & Development*, 29(12), 1203–1217.
[6] Singh, S. K., Hawkins, C., Clarke, I. D., Squire, J. A., Bayani, J., Hide, T., ... & Dirks, P. B. (**2004**). Identification of human brain tumour initiating cells. *Nature*, 432(7015), 396–401.
[7] Ostrom, Q. T., Gittleman, H., Xu, J., Kromer, C., Wolinsky, Y., Kruchko, C., & Barnholtz-Sloan, J. S. (**2016**). CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009-2013. *Neuro-Oncology*, 18(Suppl_5), v1–v75.
[8] Stupp, R., Mason, W. P., van den Bent, M. J., Weller, M., Fisher, B., Taphoorn, M. J., ... & Mirimanoff, R. O. (**2005**). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine*, 352(10), 987–996.
[9] Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., ... & Ellison, D. W. (**2016**). The 2016 World Health Organization classification of tumors of the central nervous system: A summary. *Acta Neuropathologica*, 131, 803–820.
[10] Ostrom, Q. T., Gittleman, H., Truitt, G., Boscia, A., Kruchko, C., & Barnholtz-Sloan, J. S. (**2018**). CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. *Neuro-Oncology*, 20(Suppl_4), iv1–iv86.
[11] Verhaak, R. G., Hoadley, K. A., Purdom, E., Wang, V., Qi, Y., Wilkerson, M. D., ... & Cancer Genome Atlas Research Network. (**2010**). Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*, 17(1), 98–110.
[12] Gutmann, D. H., Parada, L. F., Silva, A. J., & Ratner, N. (**2012**). Neurofibromatosis type 1: Modeling CNS dysfunction. *Journal of Neuroscience*, 32(41), 14087–14093.
[13] Helfferich, J., Nijmeijer, R., Brouwer, O. F., & de Jong, B. M. (2016). Neurofibromatosis type 1 associated low grade gliomas: A comparison with sporadic low grade gliomas. *Critical Reviews in Oncology/Hematology*, 104, 30–41.
[14] Cancer Genome Atlas Research Network. (**2015**). Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *New England Journal of Medicine*, 372(26), 2481–2498.
[15] Liu, C., Sage, J. C., Miller, M. R., Verhaak, R. G., Hippenmeyer, S., Vogel, H., ... & Zong, H. (**2011**). Mosaic analysis with double markers reveals tumor cell of origin in glioma. *Cell*, 146(2), 209–221.
[16] Schwartzentruber, J., Korshunov, A., Liu, X. Y., Jones, D. T., Pfaff, E., Jacob, K., ... & Jabado, N. (**2012**). Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. *Nature*, 482(7384), 226–231.
[17] Jones, C., & Baker, S. J. (**2014**). Unique genetic and epigenetic mechanisms driving paediatric diffuse high-grade glioma. *Nature Reviews Cancer*, 14(10), 651–661.
[18] Tamimi, A. F., & Juweid, M. (**2017**). Epidemiology and outcome of glioblastoma. In S. De Vleeschouwer (Ed.), *Glioblastoma* (pp. 143–153). Exon Publications.
[19] Bao, S., Wu, Q., McLendon, R. E., Hao, Y., Shi, Q., Hjelmeland, A. B., ... & Rich, J. N. (**2006**). Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature*, 444(7120), 756–760.
[20] Cheng, L., Huang, Z., Zhou, W., Wu, Q., Donnola, S., Liu, J. K., ... & Bao, S. (**2013**). Glioblastoma stem cells generate vascular pericytes to support vessel function and tumor growth. *Cell*, 153(1), 139–152.
[21] Chen, J., Li, Y., Yu, T. S., McKay, R. M., Burns, D. K., Kernie, S. G., & Parada, L. F. (**2012**). A restricted cell population propagates glioblastoma growth after chemotherapy. *Nature*, 488(7412), 522–526.
[22] Dirkse, A., Golebiewska, A., Buder, T., Nazarov, P. V., Muller, A., Poovathingal, S., ... & Niclou, S. P. (**2019**). Stem cell-associated heterogeneity in Glioblastoma results from intrinsic tumor plasticity shaped by the microenvironment. *Nature Communications*, 10(1), 1787.
[23] Hambardzumyan, D., & Bergers, G. (**2015**). Glioblastoma: Defining tumor niches. *Trends in Cancer*, 1(4), 252–265.
[24] Suvà, M. L., Rheinbay, E., Gillespie, S. M., Patel, A. P., Wakimoto, H., Rabkin, S. D., ... & Bernstein, B. E. (**2014**). Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. *Cell*, 157(3), 580–594.
[25] Martín, V., Sanchez-Sanchez, A. M., Herrera, F., Gomez-Manzano, C., Fueyo, J., Alvarez-Vega, M. A., ... & Rodriguez, C. (**2013**). Melatonin-induced methylation of the ABCG2/BCRP promoter as a novel mechanism to overcome multidrug resistance in brain tumour stem cells. *British Journal of Cancer*, 108(10), 2005–2012.
[26] Zhang, L., He, Z., & Li, Q. (**2025**). Epigenetic regulation of histone modifications in glioblastoma: Recent advances and therapeutic insights. *Biomarker Research*, 13(1), 1–32.
[27] Esteller, M., Garcia-Foncillas, J., Andion, E., Goodman, S. N., Hidalgo, O. F., Vanaclocha, V., ...

& Herman, J. G. (**2000**). Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *New England Journal of Medicine*, 343(19), 1350–1354.
[28] Zhao, W., Zhang, C., Bi, Y., Chen, Y., Li, M., Jiang, L., ... & Yang, J. (**2024**). The combination of temozolomide and perifosine synergistically inhibit glioblastoma by impeding DNA repair and inducing apoptosis. *Cell Death Discovery*, 10(1), 315.
[29] D'Aprile, S., Denaro, S., Pavone, A. M., & Vicario, N. (**2025**). Targeting metabolic reprogramming in glioblastoma as a new strategy to overcome therapy resistance. *Frontiers in Cell and Developmental Biology*, 13, 1535073.
[30] Sachdeva, R., Wu, M., Smilowitz, S., & Huse, J. T. (**2019**). BMP signaling mediates glioma stem cell quiescence and confers treatment resistance in glioblastoma. *Scientific Reports*, 9(1), 14569.
[31] Lindell, E., Zhong, L., & Zhang, X. (**2023**). Quiescent cancer cells a potential therapeutic target to overcome tumor resistance and relapse. *International Journal of Molecular Sciences*, 24(4), 3762.
[32] Wu, Y., Liu, J., Zhang, Y., & Wang, H. (**2024**). Hippo pathway-mediated YAP1/TAZ inhibition is essential for proper pancreatic endocrine specification and differentiation. *eLife*, 13, e84532.
[33] Pistollato, F., Abbadi, S., Rampazzo, E., Persano, L., Della Puppa, A., Frasson, C., ... & Basso, G. (**2010**). Intratumoral hypoxic gradient drives stem cells distribution and MGMT expression in glioblastoma. *Stem Cells*, 28(5), 851–862.
[34] Auffinger, B., Tobias, A. L., Han, Y., Lee, G., Guo, D., Dey, M., ... & Ahmed, A. U. (**2014**). Conversion of differentiated cancer cells into cancer stem-like cells in a glioblastoma model after primary chemotherapy. *Cell Death & Differentiation*, 21(7), 1119–1131.
[35] Zhang, J., Zhang, N., Zhao, Y., Zhou, Q., Wang, Y., Ma, J., ... & Fang, D. (**2020**). Targeted inhibition of KDM6 histone demethylases eradicates tumor-initiating cells via enhancer reprogramming in colorectal cancer. *Theranostics*, 10(22), 10016–10033.
[36] Desbats, M. A., Giacomini, I., Prayer-Galetti, T., & Montopoli, M. (**2020**). Metabolic plasticity in chemotherapy resistance. *Frontiers in Oncology*, 10, 281.
[37] Patel, A. P., Tirosh, I., Trombetta, J. J., Shalek, A. K., Gillespie, S. M., Wakimoto, H., ... & Bernstein, B. E. (**2014**). Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science*, 344(6190), 1396–1401.
[38] Neftel, C., Laffy, J., Filbin, M. G., Hara, T., Shore, M. E., Rahme, G. J., ... & Suvà, M. L. (**2019**). An integrative model of cellular states, plasticity, and genetics for glioblastoma. *Cell*, 178(4), 835–849.e21.
[39] Wang, J., Cazzato, E., Ladewig, E., Frattini, V., Rosenbloom, D. I., Zairis, S., ... & Rabadan, R. (2016). Clonal evolution of glioblastoma under therapy. *Nature Genetics*, 48(7), 768–776.
[40] Lee, J. K., Wang, J., Sa, J. K., Ladewig, E., Lee, H. O., Lee, I. H., ... & Park, W. Y. (**2017**). Spatiotemporal genomic architecture informs precision oncology in glioblastoma. *Nature Genetics*, 49(4), 594–599.
[41] Sottoriva, A., Spiteri, I., Piccirillo, S. G., Touloumis, A., Collins, V. P., Marioni, J. C., ... & Tavaré, S. (**2013**). Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. *Proceedings of the National Academy of Sciences*, 110(10), 4009–4014.
[42] Hirose, Y., Berger, M. S., & Pieper, R. O. (**2001**). Abrogation of the Chk1-mediated G2 checkpoint pathway potentiates temozolomide-induced toxicity in a p53-independent manner in human glioblastoma cells. *Cancer Research*, 61(15), 5843–5849. (PMID: 11479216) -
[43] Liu, G., Zhang, H., & Wang, L. (**2025**). Exosome-mediated chemoresistance in cancers: Mechanisms, therapeutic implications, and future directions. *Biomolecules*, 15(5), 685.
[44] Carruthers, R., Ahmed, S. U., Strathdee, K., Gomez-Roman, N., Amoah-Buahin, E., Watts, C., & Chalmers, A. J. (**2015**). Abrogation of radioresistance in glioblastoma stem-like cells by inhibition of ATM kinase. *Molecular Oncology*, 9(1), 192–203.
[45] Hsieh, A., Ellsworth, R., & Hsieh, D. (**2011**). Hedgehog/GLI1 regulates IGF dependent malignant behaviors in glioma stem cells. *Journal of Cellular Physiology*, 226(4), 1118–1127.
[46] Emir, S. M., & Gundogdu, G. (**2025**). Hunting glioblastoma recurrence: Glioma stem cells as retrospective targets. *American Journal of Physiology-Cell Physiology*. Advance online publication.
[47] Joshi, K., Banasavadi-Siddegowda, Y. K., Mo, X., Kim, S. H., Mao, P., Kig, C., ... & Nakano, I. (**2013**). MELK-dependent FOXM1 phosphorylation is essential for proliferation of glioma stem cells. *Stem Cells*, 31(6), 1051–1063.
[48] Jackson, E. R., Duchatel, R. J., Staudt, D. E., Persson, M. L., Mannan, A., Yadavilli, S., ... & Dun, M. D. (**2023**). ONC201 in combination with paxalisib for the treatment of H3K27-altered diffuse midline glioma. *Cancer Research*, 83(14), 2421–2437.
[49] Bae, W. H., Maraka, S., & Daher, A. (**2024**). Challenges and advances in glioblastoma targeted therapy: The promise of drug repurposing and biomarker exploration. *Frontiers in Oncology*, 14, 1441460.
[50] Netland, I., Skeie, B. S., Thorsen, F., Enger, P. Ø., & Torsvik, A. (**2016**). Dactolisib (NVP-BEZ235) toxicity in murine brain tumour models. *BMC Cancer*, 16, 1–12.
[51] Wright, S. C. E., Vasilevski, N., & Serra, V. (2021). Mechanisms of resistance to PI3K inhibitors

in cancer: Adaptive responses, drug tolerance and cellular plasticity. *Cancers*, 13(7), 1538.
[52] White, K., Connor, K., Clerkin, J., Murphy, M., Salvucci, M., O'Farrell, A. C., ... & Prehn, J. H. (**2020**). New hints towards a precision medicine strategy for IDH wild-type glioblastoma. *Annals of Oncology*, 31(12), 1679–1692.