Drug resistance in glioblastoma: Challenges, mechanisms and therapeutic strategies (Review)

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Abstract. Glioblastoma multiforme (GBM), the most aggressive and prevalent type of brain cancer, presents a formidable therapeutic challenge due to its high degree of drug resistance. Despite advances in chemotherapy, targeted therapy and immunotherapy, patient outcomes remain dismal, with a 5-year survival rate of only 7%. Resistance mechanisms are multifactorial, including the restrictive nature of the blood-brain barrier (BBB), tumor heterogeneity and adaptive responses within the tumor microenvironment (TME). The BBB limits drug delivery, while efflux transporters further reduce therapeutic efficacy. Additionally, the vast molecular genetic and cellular heterogeneity of a glioblastoma enables the survival of resistant subpopulations, such as glioblastoma stem cells, that evade treatment. Chemotherapy resistance in GBM, particularly to temozolomide, is driven by factors such as O^6-methylguanine-DNA methyltransferase upregulation, defective mismatch repair, hypoxia-induced gene expression and activation of several signaling pathways, such as the NF-κB, Hippo and Wnt pathways. Targeted therapies have shown limited success due to activation of compensatory pathways and tumor plasticity, while immunotherapeutic approaches are hindered by an immunosuppressive TME. Recently identified resistance mechanisms, including exosomal transfer of noncoding RNAs and metabolic reprogramming, further complicate treatment. Future directions should emphasize overcoming these challenges through combination therapies, enhanced drug delivery systems and precision medicine approaches. Emerging strategies include targeting persister cells, leveraging metabolic vulnerabilities and integrating AI-driven drug discovery approaches and nanotechnology. Robust patient stratification and biomarker-driven interventions are critical for tailoring therapies and improving outcomes. The present review highlights the urgent need for innovative, multidisciplinary approaches to address the complexity of GBM resistance and advance therapeutic strategies for this lethal disease.

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Abbreviations: GBM, glioblastoma multiforme; BBB, blood-brain barrier; TME, tumor microenvironment; TMZ, temozolomide; TJ, tight junction; P-gp, P-glycoprotein; BCRP, breast-cancer-resistance protein; MGMT, O6-methylguanine-DNA methyltransferase; MMR, mismatch repair; TMB, tumor mutational burden; MSI-H, microsatellite instability-high; PFS, progression-free survival; OS, overall survival; GSC, glioma stem-like cell; RTK, receptor tyrosine kinase; EMT, epithelial-mesenchymal transition; VP, Verteporfin; HGG, high-grade glioma; ncRNA, non-coding RNA; miRNA/miR, microRNA; lncRNA, long non-coding RNA; circRNAs, circular RNAs; ceRNA, competing endogenous RNA; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; PDGF, platelet-derived growth factor; Shh, sonic hedgehog pathway; PDGFR, PDGF receptor; BEV, bevacizumab; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; VEGF, vascular endothelial growth factor; IDH, isocitrate dehydrogenase; MEK/MAPK, mitogen-activated protein kinase; PARP, poly ADP-ribose polymerase

Key words: glioma, glioblastoma, drug resistance, chemoresistance, targeted therapy, immunotherapy

Contents

1. Introduction

Cancer, characterized by the uncontrolled proliferation and spread of abnormal cells, remains one of the world's most pervasive and deadly diseases. While advancements in therapy have improved outcomes for certain patients, several patients exhibit recurrent or refractory disease, primarily due to drug resistance. This phenomenon, where cancer cells evolve to evade the effects of chemotherapy, targeted therapy or immunotherapy, remains a major barrier to long-term treatment success.

Among the several types of cancer, brain tumors are particularly lethal. Annually, over 300,000 new cases of brain cancer are diagnosed globally, leading to >250,000 deaths. In the United States alone, an estimated 25,400 new brain tumor cases and ~19,000 deaths were predicted in 2024 (1). Brain tumors are also the leading cause of cancer-related deaths in children and adolescents under the age of 19 (2). The 5-year relative survival rate for brain and other nervous system cancers in the U.S. stands at ~34%, highlighting the urgent need for improved detection and more effective therapies (1).

Despite the ongoing development of therapeutics, brain cancer remains among the most difficult malignancies to treat. This is largely due to the aggressive biology of the disease and the unique challenges posed by the brain's protective environment. The blood-brain barrier (BBB), while essential for maintaining neural homeostasis, limits the penetration of most chemotherapeutic and biologic agents, posing a major hurdle for effective drug delivery.

Treatment strategies for brain tumors include chemotherapy, targeted therapy and immunotherapy. Temozolomide (TMZ), an oral alkylating agent, remains the cornerstone of chemotherapeutic regimens, supplemented by agents such as carmustine, lomustine, vincristine, procarbazine and etoposide. Targeted agents like vorasidenib [isocitrate dehydrogenase (IDH)1/2 inhibitor] and bevacizumab [BEV, a vascular endothelial growth factor (VEGF) inhibitor] have shown utility in specific subtypes. Immunotherapeutics, including anti-PD-1 antibodies pembrolizumab and nivolumab, are under active investigation in clinical trials, particularly for GBM.

GBM, the most common and aggressive malignant brain tumor, accounts for ~50% of all primary malignant brain tumors. It exhibits a particularly poor prognosis due to its rapid progression and formidable resistance to existing therapies. The 5-year survival rate for GBM remains at a dismal 7% (3,4), reflecting the urgent need for novel therapeutic strategies.

The aim of the present review is to provide a comprehensive and integrative analysis of the molecular and cellular mechanisms driving therapeutic resistance in GBM, with a focus on emerging and underappreciated pathways such as exosomal non-coding RNAs (ncRNAs), metabolic reprogramming and dysregulated signaling networks [such as the Wnt/β-catenin, Hippo, PI3K/Akt and MAPK]. Importantly, beyond being merely a descriptive overview, the therapeutic implications of these mechanisms, including how they might be exploited for combination regimens, drug delivery innovations and precision medicine approaches, are also discussed. By bridging mechanistic insights with actionable strategies, the present review seeks to support the development of more effective, resistance-overcoming treatments for GBM, ultimately improving clinical outcomes in this intractable disease.

2. BBB

BBB is a dynamic interface that regulates molecular transport between systemic circulation and brain parenchyma. While essential for neuroprotection, its structural and functional complexity poses significant challenges for treating brain tumors. The structural organization of the BBB plays a crucial role in its function as a selective and protective interface between the systemic circulation and the brain. Its key structural components contribute to its function through the following ways:

Endothelial cells and tight junctions (TJs). Brain microvascular endothelial cells form the primary barrier with TJs composed of claudins, occludins and zonula occludens proteins. These TJs create a high trans-endothelial electrical resistance (>1,800 $\Omega \cdot cm^2$), restricting paracellular passage of polar molecules and toxins (5). Bicellular (claudin-5) and tricellular (angulin-1) junctions further regulate permeability.

Supporting cellular components. Pericytes stabilize endothelial junctions via platelet-derived growth factor receptor (PDGFR)-β signaling, and their loss leads to barrier leakage, especially in gliomas (6). Astrocytes cover >99% of the endothelial surface, and along with pericytes, maintain BBB integrity. Microglia modulate the BBB but can also disrupt it by secreting inflammatory cytokines.

Basement membrane. The 50-100 nm extracellular matrix, rich in collagen IV and laminins, provides structural support and regulates leukocyte trafficking, ensuring vascular stability and selective permeability. These structural elements collectively restrict solute exchange, regulate selective transport and maintain homeostasis, which are essential for neuroprotection. However, these same features significantly contribute to drug resistance in GBM through several mechanisms (7).

Heterogeneous BBB disruption. In brain tumors, the BBB has leaky regions but retains an intact BBB in non-enhancing tumor areas, creating sanctuaries for cancer cells (8). In high-grade glioma (HGG) tumors, surgical and imaging data show that tumor cells extend beyond contrast-enhancing MRI regions, with PET tracers confirming metabolic activity in these areas, indicating BBB integrity. Drug penetration studies reveal poor delivery of several therapies to non-enhancing tumor regions due to active efflux transporters. Additionally, imaging-pathology mismatches highlight that abnormalities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences, which are sensitive to edema and infiltrative tumor regions, represent infiltrative tumors without sufficient BBB disruption for effective drug delivery. Clinically, most GBM recurrences originate near contrast-enhancing regions, but infiltrative cells in non-enhancing areas contribute to progression. Therefore, there is a need for therapies that can effectively target tumor cells beyond contrast-enhancing regions, addressing both enhancing and non-enhancing compartments for improved treatment outcomes.

Efflux transporters. Overexpression of ATP-dependent efflux transporters, such as P-glycoprotein (P-gp) and breast-cancer-resistance protein (BCRP), in tumor endothelial cells reduces intracellular drug concentrations. For example, $HER2^+$ breast cancer brain metastases exhibit upregulated expression of BCRP, limiting trastuzumab efficacy (9).

Signaling pathways. The Wnt and sonic hedgehog (Shh) pathways contribute to BBB integrity and, when dysregulated in GBM, also affect drug penetration (10). Wnt signaling promotes

BBB integrity by maintaining the expression of key vascular stability proteins and suppressing factors that increase permeability. β-catenin activation, a key component of Wnt signaling, helps regulate claudin-5 and Glut1, which are essential for BBB function. Experimental knockout of β-catenin, as well as LRP5 and LRP6, leads to increased expression of PLVAP, a protein associated with vascular fenestrations, resulting in abnormal BBB leakiness. Furthermore, paracrine Wnt inhibitors such as WIF1 and DKK1, secreted in Wnt medulloblastomas, disrupt BBB integrity, but their experimental inhibition restores normal vascular function. These findings highlight that active Wnt signaling is crucial for maintaining a tightly regulated and selective BBB by preventing the formation of fenestrations and excessive permeability.

The Shh pathway plays a critical role in maintaining BBB integrity through both structural and immunological mechanisms (11). Astrocytes secrete Shh, which binds to Patched-1 and Smoothened receptors on endothelial cells. This binding enhances the expression of tight and adherens junction proteins, strengthening the BBB and reducing permeability. Additionally, Shh suppresses proinflammatory responses by inhibiting chemokine secretion, preventing leukocyte adhesion and modulating T cell activity. Disruption of Shh signaling can lead to BBB breakdown and heightened inflammation. Therefore, Shh is essential for both the development and therapeutic maintenance of BBB function.

Several strategies to enhance drug delivery by overcoming the BBB have been proposed and some have been evaluated in clinical trials with various degrees of success (12). Direct drug administration via intra-tumoral, intranasal or intrathecal routes allows localized delivery (such as carmustine and trastuzumab) but faces challenges, including neurotoxicity and inconsistent efficacy (13,14). Chemical modifications, such as increasing lipophilicity or encapsulating drugs in nanoparticles (for example, liposomal doxorubicin), improve BBB penetration and targeted delivery (15). Inhibition of P-gp and BCRP efflux transporters enhanced brain penetration of doxorubicin and vemurafenib *in vitro* and *in vivo* (16,17).

Physical disruption techniques, including focused ultrasound, laser-induced thermal therapy and osmotic disruption (mannitol), temporarily open the BBB to facilitate drug entry (18). Ongoing clinical trials are evaluating ultrasound-mediated BBB disruption systems, such as Exablate and SonoCloud-9, which use focused or implantable ultrasound with microbubbles to transiently and noninvasively open the BBB, enhancing the delivery of carboplatin to GBM tumor sites (NCT04417088; NCT03744026).

Tumor-tropic neural stem cells engineered to deliver anticancer agents show promise in clinical trials (19). Ongoing studies are evaluating BBB-penetrating analogs of approved drugs, such as Berubicin (a doxorubicin analog) (NCT04762069) and Buparlisib (a PI3K inhibitor) (NCT01349660), for their potential to improve outcomes in recurrent or refractory GBM.

While these strategies demonstrate potential in preclinical and early clinical studies, challenges like side effects, invasiveness and variable efficacy hinder widespread adoption, with future research focusing on refining combination therapies and BBB modulation techniques.

3. Resistance to chemotherapy

Since 2005, the Stupp protocol has been the standard of treatment for GBM. It consists of radiation combined with TMZ following surgery (20). While this protocol has improved 2-year survival rates from 10.4 to 26.5% compared with radiation alone, >90% of patients with GBM still develop resistance and experience relapse (21). Uncovering the molecular drivers of chemotherapy resistance in GBM is therefore critical for advancing more effective therapeutic strategies. The following sections outline key resistance mechanisms and their clinical implications.

Upregulation of O^6-methylguanine (O^6MeG)-DNA methyltransferase. TMZ functions by inducing O^6MeG adducts that cause DNA breaks, cell cycle arrest and apoptosis, leading to cell death (22,23). TMZ resistance in treatment-naïve patients with GBM is mediated predominantly by the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT), which removes the methyl adducts formed by TMZ, thereby preventing DNA damage and rescuing cancer cells from death (24). In GBM, the MGMT promoter is often methylated, silencing its expression and rendering tumors more sensitive to TMZ. However, TMZ treatment can apply selective pressure, potentially leading to demethylation of the MGMT promoter, increased MGMT expression and subsequent repair of TMZ-induced lesions, resulting in acquired resistance (25). MGMT promoter methylation status remains one of the most robust and clinically relevant predictive biomarkers of the response to TMZ. Several clinical trials have explored the prognostic and therapeutic relevance of MGMT methylation status in both newly diagnosed and recurrent GBM. The CENTRIC (NCT00689221) and Alliance A071102 (NCT02152982) trials investigated the addition of cilengitide and veliparib, respectively, to standard chemoradiotherapy in MGMT-methylated GBM. Both trials failed to demonstrate survival benefits, highlighting the challenges of improving outcomes beyond TMZ in this subgroup (26,27).

Conversely, trials targeting MGMT-unmethylated GBM have focused on TMZ-sparing strategies. A Phase II trial of VAL-083 with radiotherapy showed early promise by bypassing MGMT-mediated resistance (NCT03050736). Similarly, a study comparing etoposide and cisplatin to TMZ (NCT05694416) aims to identify more effective chemotherapeutic options. Immunotherapy combinations, such as nivolumab and ipilimumab with radiation (NCT04396860), are also under evaluation in this difficult-to-treat population.

The GENOM 009 study (NCT01102595) reaffirmed the prognostic value of tissue-based MGMT methylation but found limited utility in serum-based assays (28). These trials collectively underscore the critical role of MGMT status in GBM therapy and the ongoing pursuit of personalized treatment approaches, particularly for patients with unmethylated tumors.

Defective DNA mismatch repair (MMR). TMZ causes O^6MeG mismatches with thymine, which are normally recognized by the MMR system. Functional MMR triggers apoptosis in response to such damage. Deficiencies in the MMR system, including mutations in genes such as MSH6, MLH1 and

PMS2, impair DNA repair, contributing to resistance (29-31). MMR-deficient GBMs may appear responsive initially but often recur with hypermutation phenotypes and TMZ resistance (32). Hypermutation phenotype MMR-deficient GBMs with a high tumor mutational burden (TMB) are excellent candidates for immunotherapy (33). Immunotherapy has shown remarkable success in MMR-deficient tumors across various cancer types, including colorectal cancer, leading to FDA approval of the PD-1 checkpoint inhibitor pembrolizumab for any microsatellite instability-high/MMR-deficient solid tumors, a landmark tumor-agnostic approval. However, early trials, including KEYNOTE-028 (NCT02054806) and a Phase II window-of-opportunity study (NCT02337686), found pembrolizumab to be safe but with limited clinical benefit in recurrent GBM, showing modest 6-month progression-free survival (PFS) rates (~40-44%) and a median OS of 14-20 months. Additionally, pembrolizumab was studied in a multi-cancer, Phase II trial (NCT02886585) focused on patients with brain metastases, including those with GBM. In this setting, the intracranial benefit rate was 42.1%, and certain patients with GBM exhibit survival exceeding two years (34). These findings suggest that a subset of patients with GBM may derive durable benefits from PD-1 blockade, although predictive biomarkers remain undefined, and support further studies to identify biomarkers and mechanisms of resistance.

Glioma stem-like cells (GSCs). GSCs are a quiescent subpopulation within the tumor that exhibits stem-like properties, including self-renewal and the ability to repopulate the tumor after treatment. Nestin, a marker of neural stem cells, is also expressed in GSCs and can serve as a biomarker to identify this resistant population. In preclinical models, Nestin$^+$ GSCs were shown to persist after TMZ therapy and regenerate proliferative tumor cells (35). Remarkably, selective ablation of these Nestin$^+$ cells using genetic approaches significantly impaired tumor growth. These findings underscore the therapeutic potential of targeting GSCs to improve GBM treatment outcomes.

Survivin is emerging as a functionally relevant and potential marker of GSCs, particularly in the context of therapeutic targeting. Survivin (*BIRC5*) is highly expressed in GSCs compared with non-stem GBM cells. Its inhibition selectively reduces the viability and self-renewal capacity of GSCs (36). Furthermore, downregulation of Survivin sensitizes these cells to chemotherapeutic agents, highlighting its critical role in GSC maintenance and therapy resistance.

Building on these preclinical findings, clinical strategies targeting Survivin have begun to show promise. The SurVaxM vaccine trial, a Phase II clinical study, evaluated a vaccine for the Survivin protein in combination with TMZ and granulocyte-macrophage colony-stimulating factor in patients with newly diagnosed glioblastoma. Initial results have been encouraging, with 96% of participants progression-free at 6 months and 93% alive at 12 months, demonstrating substantial improvement over historical benchmarks (37).

Efflux transporters and TMZ resistance in GBM. Efflux transporters play a pivotal role in mediating resistance to TMZ in GBM by actively reducing intracellular drug concentrations, thereby diminishing its therapeutic efficacy. Munoz *et al* (38) demonstrated that TMZ is a substrate for P-gp. In GBM cells with upregulated MDR1 mRNA levels (which encodes P-gp), there is increased efflux of TMZ, lowering its intracellular concentration and reducing its cytotoxicity. P-gp inhibitors restored TMZ sensitivity, confirming its role in resistance. Another study found that hypomethylation of the ABCB1 and ABCG2 promoters led to overexpression of these transporters, facilitating drug efflux and decreasing TMZ efficacy in GBM cells. Epigenetic regulation was a key driver of this phenotype (39). Elevated levels of ABCA1, a protein traditionally associated with lipid transport, are linked to poor clinical outcomes. Silencing ABCA1 expression increases the sensitivity of glioma cells to TMZ, indicating its involvement in drug efflux and resistance mechanisms (40). Mechanistically, ABCA1 contributes to TMZ resistance by altering the TME, specifically by promoting M2 macrophage infiltration, a phenotype associated with immune suppression and tumor progression. The p53/E2F7 axis was shown to transcriptionally upregulate ABCA8 and ABCB4, both contributing to reduced intracellular accumulation of TMZ and enhanced resistance in GBM (41). Silencing E2F7 resensitized cells to TMZ.

Additional support for TMZ being a substrate of efflux transporters such as P-gp and BCRP comes from studies showing that genetic deletion or pharmacological inhibition of these proteins, using agents like elacridar (GF120918), significantly enhanced brain penetration by 1.5-fold, and antitumor efficacy of TMZ in mice with orthotopic or intracranial GBM tumors. Similarly, Reversan, another efflux transporter inhibitor, also markedly enhanced TMZ activity in patient-derived primary and recurrent GBM models (42). These observations suggest that inhibiting efflux transporters to enhance intracellular TMZ levels may re-sensitize GBM cells to TMZ. However, despite promising preclinical data, this approach has not yet translated to clinical success, likely due to the complexity of resistance mechanisms and safety concerns at effective doses. Nonetheless, it remains an active area of research with potential for identifying a clinically viable efflux transporter inhibitor.

Hypoxia. Hypoxia, a defining feature of aggressive gliomas such as GBM, arises when rapidly growing tumors outpace their blood supply (43). This oxygen-deficient microenvironment stabilizes hypoxia-inducible transcription factors HIF-1α and HIF-2α, which orchestrate a broad transcriptional program that enhances tumor cell survival, therapeutic resistance and disease progression. Key downstream targets of these factors include MGMT, which contributes to TMZ resistance by reducing intracellular TMZ levels (44).

HIF-2α promotes the expression of GSC signature genes, supporting the maintenance and expansion of this inherently TMZ-resistant subpopulation (45). Moreover, hypoxia induces SHOX2 expression, a gene associated with TMZ resistance, particularly in MGMT-unmethylated gliomas and TMZ-resistant cell lines (46).

Hypoxia also modulates the apoptotic machinery to support resistance. For example, HIF-1α upregulates miR-26a under hypoxic conditions, which in turn suppresses pro-apoptotic

proteins Bad and Bax, thereby inhibiting mitochondrial apoptosis and contributing to TMZ resistance (47).

Collectively, these interconnected hypoxia-driven mechanisms underscore the pivotal role of hypoxia in driving therapeutic resistance in GBM. In response, several clinical trials have been launched to explore therapeutic strategies that either inhibit or leverage hypoxia in GBM. These approaches include hypoxia-activated prodrugs, oxygen therapeutics and inhibitors targeting HIF proteins, to enhance tumor sensitivity to conventional treatments or disrupt hypoxia-mediated survival pathways.

One notable trial, NCT01403610, evaluated evofosfamide (TH-302), a hypoxia-activated prodrug, in combination with BEV in patients with recurrent GBM who had failed prior BEV treatment (48). PFS at 4 months was 31%, which was a statistically significant improvement over the historical rate of 3%, although the clinical significance of this may be limited. Another trial, NCT03216499, investigated PT2385, a selective HIF-2α inhibitor, in patients with first recurrent GBM (49). While no radiographic responses were observed, patients with higher systemic drug exposure showed improved PFS, suggesting potential pharmacodynamic relevance.

Addressing tumor oxygenation directly, NCT02189109 explored NVX-108, an oxygen therapeutic designed to improve tumor oxygen levels and enhance the effects of radiotherapy and chemotherapy in newly diagnosed GBM (50). Preliminary results demonstrated effective tumor reoxygenation without affecting normal brain tissue, with indications of improved survival outcomes. These findings support further exploration of oxygenation strategies in GBM therapy.

Several early-phase trials focused on inhibiting *HIF-1α*, a central regulator of hypoxic adaptation. These include EZN-2208 (NCT01251926), EZN-2698 (NCT01120288), PX-478 (NCT00522652), OKN-007 (NCT01672463) and Icaritin (NCT02496949). These agents employ a range of mechanisms, from downregulating HIF-1α mRNA to promoting its degradation, and were primarily studied for safety and pharmacodynamic effects, with limited efficacy data reported (51).

In conclusion, while targeting hypoxia in GBM presents a compelling therapeutic avenue, clinical trials to date have yielded mixed results, with most agents demonstrating safety but limited efficacy in monotherapy settings. However, these studies highlight the potential for hypoxia-directed therapies to complement existing treatments. Ongoing research focusing on patient stratification, drug combinations, and biomarkers of hypoxic response will be key to unlocking the full therapeutic potential of these strategies in GBM.

Dysregulated intracellular signaling pathways. While DNA repair mechanisms, such as MGMT upregulation and defective MMR, are well-established contributors to TMZ resistance, dysregulated intracellular signaling pathways, especially the PI3K/Akt and MAPK pathways, play an equally critical role in mediating resistance in GBM.

PI3K/Akt/mTOR pathway. The PI3K/Akt/mTOR signaling pathway plays a central role in GBM resistance to TMZ. It is frequently dysregulated in GBM, in up to 88% of tumors, primarily due to upstream receptor tyrosine kinase (RTK) alterations such as epidermal growth factor receptor (EGFR) amplification, activating mutations of PI3CA (p110) or PIK3R1 (P85), or loss of PTEN expression (52).

One mechanism through which PI3K/Akt/mTOR confers TMZ resistance is metabolic reprogramming, known as the Warburg effect. Akt upregulates PDK1, which inhibits pyruvate dehydrogenase, suppressing oxidative phosphorylation and promoting glycolysis (53). This metabolic shift supports tumor cell survival under hypoxic conditions and contributes to resistance. Dichloroacetate, a PDK1 inhibitor, can reverse this effect, particularly in EGFRvIII-positive GBMs, restoring TMZ sensitivity (54).

Another key resistance mechanism involves the response to hypoxia and the promotion of angiogenesis. Akt stabilizes HIF-1α, which enhances the transcription of VEGF and other hypoxia-response genes, driving angiogenesis and increasing tumor survival in hypoxic microenvironments (55). HIF-1 also induces the expression of CXCL12 and its receptor CXCR4, promoting tumor cell proliferation and invasiveness (56).

Additionally, NF-κB is activated via Akt-mediated degradation of its inhibitor, IkB. This activation leads to increased transcription of pro-survival genes and has been strongly linked to both poor prognosis and TMZ resistance (57).

The PI3K/Akt pathway further promotes resistance by inhibiting apoptosis. It modulates the upregulation of anti-apoptotic proteins such as Bcl-2 and Mcl-1, which inhibit apoptotic processes and contribute to chemoresistance. For example, studies have shown that the inhibition of PI3K and Bcl-2 can sensitize glioblastoma cells to apoptosis by downregulating Mcl-1 and phospho-BAD, highlighting the role of these proteins in therapy resistance (58). Moreover, the PI3K/Akt pathway influences the overexpression of other anti-apoptotic factors such as MDM2, a negative regulator of the tumor suppressor p53, thereby further inhibiting apoptotic pathways (59,60). Akt also increases the expression of survivin, an inhibitor of apoptosis, which blocks TMZ-induced cell death. Inhibition of survivin has been shown to increase TMZ sensitivity in GBM cells (61).

Furthermore, the activation of the PI3K/Akt/mTOR pathway in general, and mTOR in particular, positively regulates autophagy in response to TMZ-induced DNA damage, leading to tumor cell survival under therapeutic stress (62). Moreover, the CaMKKβ/AMPKα/mTOR signaling axis has been linked to the upregulation of TRPC5, a protein that triggers autophagy and contributes to TMZ resistance. Targeting mTOR-mediated TRPC5 expression is thus emerging as another potential strategy to sensitize GBM cells to TMZ and overcome therapeutic resistance (63).

In summary, the PI3K/Akt pathway orchestrates multiple survival strategies in GBM, altering metabolism, suppressing apoptosis, enhancing angiogenesis and modulating transcription factors, all of which collectively foster resistance to TMZ. In recent years, multiple clinical trials have evaluated pharmacological inhibitors targeting this pathway as a strategy to overcome TMZ resistance, with mixed results.

One of the more advanced clinical efforts involved GDC-0084 (Paxalisib), a dual PI3K/mTOR inhibitor evaluated in a Phase IIa trial (NCT03522298) in patients with newly diagnosed GBM with unmethylated MGMT promoter status, an indicator of poor TMZ response. Administered post-chemoradiation, GDC-0084 showed manageable toxicity

and modest clinical activity, though its definitive efficacy remains to be confirmed in larger, controlled studies (64).

Combination approaches have also been tested. A Phase I study of temsirolimus (a mTOR inhibitor) with perifosine (an AKT inhibitor) in recurrent malignant gliomas reported acceptable safety but limited efficacy (NCT01051557), with disease stabilization rather than regression being the most common outcome. Similarly, the dual PI3K/mTOR inhibitor voxtalisib (XL765) was combined with TMZ (± radiotherapy) in early-phase studies (NCT00704080) (65). Although biologically active, these agents were generally associated with tolerable side effects but only modest improvements in progression-free survival.

Other compounds, such as NVP-BEZ235, sapanisertib (TAK-228) and CC-115 have shown encouraging preclinical efficacy, particularly in inducing apoptosis and sensitizing GBM cells to TMZ (66). However, their clinical development in GBM has been limited by toxicity, lack of clear efficacy signals, or logistical challenges in crossing the BBB (NCT02133183).

In summary, while targeting the PI3K/AKT/mTOR pathway remains a rational and biologically validated strategy to circumvent TMZ resistance in GBM, clinical translation has thus far yielded limited success. Future approaches may require improved patient stratification, rational drug combinations and more effective brain-penetrant inhibitors to fully exploit this pathway therapeutically.

MAPK pathway. The MAPK signaling pathway plays a central role in mediating resistance to TMZ in GBM, operating through multiple mechanisms. Among these, the JNK isoform MAPK8 is upregulated in TMZ-resistant GBM cells (67). This activation suppresses apoptosis, thereby allowing tumor cells to evade drug-induced death. Inhibition of MAPK8 restores TMZ sensitivity and increases apoptotic activity, positioning it as a promising therapeutic target to overcome resistance.

The ERK arm of the MAPK pathway is activated by TMZ-induced reactive oxygen species (ROS). Upon activation, it induces autophagy, which serves as a cytoprotective mechanism that helps glioma cells survive the cytotoxic effects of TMZ (68). However, this pathway can be disrupted by resveratrol, which inhibits ROS production and ERK activation, leading to decreased autophagy and increased apoptosis.

Another critical arm of the MAPK cascade is the p38 MAPK pathway, which enhances TMZ resistance through the upregulation of Nrf2, a key regulator of antioxidant responses (69). By promoting detoxification and neutralization of ROS, Nrf2 enables glioma cells to survive the oxidative stress induced by TMZ. Targeting the p38-Nrf2 axis offers a potential approach to weaken this protective mechanism and resensitize tumors to treatment.

Beyond its individual components, the MAPK pathway functions as a convergent hub, integrating upstream signals from RTKs [(such as EGFR and mesenchymal-epithelial transition (MET)] to drive proliferation, suppress apoptosis and stabilize resistant phenotypes. This convergence underscores the resilience of MAPK signaling in maintaining cell survival under therapeutic pressure. Furthermore, MAPK is tightly interconnected with other resistance networks, including DNA repair pathways, autophagy and metabolic reprogramming, and supports the persistence of GSCs, a subpopulation that is crucially involved in failure of therapy and in recurrence.

In addition to these intrinsic mechanisms, adaptive resistance to TMZ also involves the MAPK pathway, particularly through feedback activation of ERK and p38 (70). p38 MAPK activation is associated with a mesenchymal-like phenotypic shift in GBM cells, characterized by enhanced migratory capacity, immune evasion and resistance to apoptosis. This mesenchymal transition is a hallmark of aggressive, therapy-resistant tumors. By promoting both stress adaptation and phenotypic plasticity, the p38 MAPK pathway emerges as a key enabler of TMZ resistance and tumor progression, suggesting that targeting this pathway could help counteract adaptive resistance mechanisms in GBM.

Taken together, these findings illustrate that the MAPK pathway contributes at multiple levels, including apoptosis evasion, redox balance, stem cell maintenance and adaptive plasticity, making it a compelling target for combinatorial strategies aimed at overcoming TMZ resistance in glioma and GBM.

Several clinical trials have explored MAPK pathway inhibitors as a strategy to overcome GBM resistance to TMZ, with varying degrees of success. One of the early efforts was a Phase II trial of TLN-4601 (NCT00730262), a Ras-MAPK pathway inhibitor, tested as monotherapy in recurrent GBM. Unfortunately, the trial reported no PFS at 6 months and a median overall survival (OS) of just 130 days, indicating limited efficacy.

Sorafenib, a multi-kinase inhibitor targeting RAF, was evaluated in multiple trials. In NCT00597493, sorafenib was combined with TMZ in patients with recurrent GBM, yielding a median PFS of 6.4 weeks and an OS of 41.5 weeks (71). Another trial, NCT00544817, tested sorafenib with the standard Stupp protocol in an adjuvant setting, showing a PFS of 6 months and an OS of 12 months (72). These studies suggested only modest benefits.

More recent studies have focused on targeting specific mutations in the MAPK pathway. The combination of dabrafenib and trametinib, BRAF and MAPK inhibitors respectively, is under investigation in NCT03919071, a Phase II study involving patients with BRAF V600E-mutated HGGs, including GBM. Similarly, NCT03973918 is assessing the efficacy of binimetinib and encorafenib, another MEK and BRAF inhibitor pair, in BRAF V600-mutated gliomas. Both trials are ongoing and aim to exploit genetic vulnerabilities in the MAPK pathway.

LY2228820, a p38 MAPK inhibitor, was studied in NCT02364206, a Phase II trial combined with the Stupp protocol. The trial has been completed, but the results remain unpublished. This agent represents an alternative mechanism of MAPK inhibition, targeting stress-related kinases involved in TMZ resistance.

Finally, pazopanib, a broad-spectrum multikinase inhibitor, is being tested in combination with TMZ in the ongoing Pazoglio trial (NCT02331498). This Phase I/II study is currently enrolling and aims to determine whether pazopanib can enhance the effectiveness of standard TMZ therapy in patients with newly diagnosed GBM.

Collectively, these studies highlight both the challenges and evolving strategies in targeting the MAPK pathway to

combat TMZ resistance in GBM, with an increasing emphasis on genetically defined patient subgroups.

Wnt/β-catenin signaling. Dysregulated Wnt signaling, particularly through the canonical (β-catenin-dependent) pathway, plays a central role in GBM resistance to TMZ and other chemotherapies (73).

One of the key mechanisms involves the promotion of GSC characteristics and maintenance of stemness (74). Wnt ligands such as Wnt3a are highly expressed in GBM and drive this stem-like phenotype, which is closely linked to therapeutic resistance. Activation of the canonical pathway is marked by nuclear accumulation of β-catenin, often facilitated by proteins like FoxO3a, and this nuclear translocation is associated with increased resistance to TMZ (75).

Wnt/β-catenin signaling also promotes epithelial-mesenchymal transition (EMT), enhancing tumor cell motility, invasiveness and plasticity, all of which contribute to chemoresistance (76). Endothelial cells within the TME can transdifferentiate into mesenchymal-like cells via a c-Met-mediated axis that activates β-catenin, leading to the expression of multidrug resistance-associated proteins and further promoting TMZ resistance. This microenvironment-driven cell plasticity adds another layer of complexity to therapy resistance in GBM.

Another important mechanism is the positive regulation of MGMT by Wnt signaling. (77). The pharmacological inhibition of Wnt signaling using agents such as salinomycin, celecoxib and Wnt-C59 has been shown to reduce MGMT expression and restore TMZ sensitivity in resistant GBM cells. Furthermore, TMZ itself can activate Wnt/β-catenin signaling through a PI3K/Akt/GSK-3β-dependent cascade that operates independently of the ATM/Chk2 DNA damage response pathway, suggesting that Wnt pathway activation is a downstream effect of TMZ exposure, potentially fueling resistance (78).

In addition, FERMT3 (also known as kindlin-3), an integrin-activating adaptor protein, has been implicated in GBM chemoresistance through its role in promoting integrin-mediated activation of Wnt/β-catenin signaling (79). Knockdown of FERMT3 results in decreased β1-integrin activity, reducing Wnt pathway activation and sensitizing GBM cells to TMZ.

MicroRNAs (miRNAs or miRs) also play a critical role in modulating Wnt/β-catenin signaling and influencing chemoresistance in GBM. For example, downregulation of miR-126-3p and miR-129-5p in TMZ-resistant GBM cells leads to constitutive Wnt activity and enhanced tumor proliferation and resistance, while their overexpression inhibits Wnt signaling and restores chemosensitivity (80,81). By contrast, miR-21 is upregulated in resistant GBM, promoting Wnt pathway activation and tumor survival (82).

A regulatory circuit involving miR-125b/miR-20b sustains Wnt activity in proneural GSCs by suppressing its negative regulators, further contributing to tumor growth (83). Additionally, IGF-1 has been shown to upregulate miR-513a-5p via PI3K signaling, which suppresses NEDD4L, an inhibitor of Wnt/β-catenin signaling, thereby enhancing GBM progression and TMZ resistance (84). These findings underscore the complex, multilayered regulation of Wnt signaling by ncRNAs and highlight additional potential therapeutic targets for overcoming chemoresistance in GBM.

Collectively, these findings highlight the multifaceted role of aberrant Wnt/β-catenin signaling in sustaining GSCs, promoting EMT and invasive behavior, modulating MGMT and other drug metabolism genes, and enabling microenvironmental plasticity, all of which converge to promote TMZ resistance in GBM. Targeting this pathway, therefore, offers a promising strategy to overcome therapeutic resistance.

Currently, there are no clinical trials specifically investigating the inhibition of the Wnt/β-catenin pathway in patients with GBM. However, several Wnt pathway inhibitors, originally developed and tested for other types of cancer, have shown promise in preclinical models of GBM. These include LGK974 (WNT974), which has been shown to significantly reduce GBM cell proliferation and stemness markers *in vitro* (85); XAV939, a tankyrase inhibitor that enhances GBM cell radiosensitivity by promoting β-catenin degradation (86); SEN461, which reduces glioma cell viability and tumor volume in xenografts (87) and E7386, which is in Phase Ib/II trials for other solid tumors and appears to eliminate drug-resistant cancer stem cells in preclinical GBM models (88).

Despite these encouraging results, translating Wnt pathway inhibition into effective GBM therapies poses significant challenges. BBB limits the ability of several systemic drugs, including Wnt inhibitors, to reach therapeutic concentrations in the brain. Additionally, the toxicity of Wnt pathway inhibition, due to its essential role in tissue homeostasis, can lead to undesirable side effects such as bone fragility. Another important consideration is the role of Wnt/β-catenin signaling in adult neurogenesis, raising concerns that pathway inhibition might impact cognitive function or neuronal repair.

In conclusion, while no clinical trials have yet targeted the Wnt/β-catenin pathway specifically in GBM, the pathway remains an attractive target based on compelling preclinical evidence. Continued efforts to develop brain-penetrant inhibitors with favorable safety profiles are essential. Addressing the challenges of BBB permeability and limiting systemic toxicity is critical for the eventual success of Wnt-targeted therapies in the treatment of GBM.

Hippo pathway. Dysregulation of the Hippo pathway leads to overexpression of its key effectors, YAP and TAZ. These proteins activate downstream target genes that promote cell survival, proliferation, glioma growth and malignancy. Elevated levels of TAZ and YAP are associated with poor outcomes in gliomas (89). TAZ (both protein and mRNA) is highly expressed in GBM and correlates with reduced survival. Similarly, high YAP expression is observed across glioma grades and predicts shorter survival (90). Importantly, TAZ knockdown impairs tumor formation in mouse models, underscoring its functional role in glioma pathogenesis.

The Hippo pathway also contributes to multidrug resistance in GBM through dysregulated YAP/TAZ activity. Overexpression of TAZ reduces TMZ cytotoxicity by upregulating the anti-apoptotic protein MCL-1, thereby making glioma cells resistant to apoptosis (91). In addition, the YAP-TAZ-TEAD complex promotes TMZ resistance by inducing Hippo target genes such as CTGF and Cyr61 through TGF-β1-mediated Smad/ERK signaling (92). CD109, another regulatory protein, further contributes to chemoresistance by activating IL-6/STAT3 signaling and enhancing GSC stemness. CD109 also stimulates the Hippo pathway; its loss leads

to reduced nuclear YAP, decreased STAT3 activity, diminished GSC stemness and impaired tumorigenicity, highlighting its role in both chemo- and radio-resistance (93). Finally, the Hippo pathway interacts with other signaling networks such as mTOR, Wnt/β-catenin and Notch, further reinforcing therapy resistance in GBM (92).

As of April 2025, there are no clinical trials specifically investigating Hippo pathway inhibitors for overcoming GBM resistance to TMZ. However, considering the role of the Hippo pathway in glioma tumor progression, chemoresistance and immunosuppression in GBM, the targeting of the YAP/TAZ transcriptional axis could be a potential therapeutic strategy.

Previous research has led to the identification of small-molecule inhibitors aimed at disrupting YAP/TAZ-TEAD interactions. Verteporfin, initially used in photodynamic therapy, has demonstrated the ability to inhibit YAP/TAZ-TEAD binding, induce apoptosis and suppress oncogenic gene expression in EGFR-amplified/mutant GBM models (94). Clinical data from a Phase 0 trial showed effective intra-tumoral delivery of liposomal Verteporfin and reduced YAP/TAZ nuclear localization (NCT04590664) (95).

Other inhibitors under development and primarily tested in other cancer models include GNE-7883, an allosteric pan-TEAD inhibitor and ETS-003, a potent compound that blocks YAP/TAZ-TEAD binding and downstream gene expression (96,97). IAG933, currently in Phase I clinical trials, shows broad inhibition across TEAD paralogs and is being assessed for antitumor activity in solid tumors, including GBM (NCT04857372) (98).

Collectively, these agents represent a new class of potential therapies designed to overcome YAP/TAZ-mediated resistance mechanisms and enhance the effectiveness of standard treatments such as TMZ. Ongoing research and clinical validation will determine their translational potential in glioma therapy.

Exosomal ncRNAs and TMZ resistance in glioblastoma. Exosomal ncRNAs [ncRNAs, including miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs)], are increasingly being recognized as central mediators of chemoresistance in GBM (99). Encapsulated within exosomes and secreted into the TME, these ncRNAs enable intercellular communication and orchestrate a range of molecular processes that influence tumor progression, therapy resistance and recurrence.

miRNAs as regulators of resistance and sensitivity. miRNAs are small regulatory RNAs that control gene expression post-transcriptionally and play crucial roles in apoptosis, drug efflux, DNA repair and oncogenic signaling pathways. Dysregulation of miRNAs in GBM contributes substantially to TMZ resistance.

miR-21, one of the most prominent oncomiRs in GBM, is upregulated in response to TMZ. It promotes resistance by targeting tumor suppressors such as *PTEN*, *PDCD4* and *RECK*, thereby enhancing cell survival and impairing apoptosis (100).

miR-328 is frequently downregulated in TMZ-resistant cells and it targets ABCG2, a drug efflux transporter. Its suppression leads to increased efflux of TMZ, reducing intracellular drug accumulation and therapeutic efficacy (99).

miR-29c modulates TMZ sensitivity by targeting DNA methyltransferases DNMT3A and DNMT3B, indirectly downregulating *MGMT*, a DNA repair enzyme that confers TMZ resistance. In GBM, miR-29c is often downregulated, contributing to elevated MGMT levels and reduced TMZ efficacy (101).

Interestingly, certain miRNAs enhance chemosensitivity to agents beyond TMZ. Members of the miR-302-3p/372-3p/373-3p/520-3p family increase susceptibility to tyrosine kinase inhibitors (TKIs) such as sunitinib and axitinib by downregulating the PI3K/AKT and MAPK signaling pathways (102).

lncRNAs as multifaceted mediators of resistance. lncRNAs contribute to drug resistance through a range of mechanisms, including transcriptional regulation, chromatin remodeling, miRNA sponging and modulation of signaling cascades. H19, SBF2-AS1, MALAT1 and ADAMTS9-AS2 are overexpressed in GBM and associated with TMZ resistance. These lncRNAs promote EMT, enhance DNA repair and inhibit apoptotic signaling (99).

Specifically, *H19* activates Wnt/β-catenin signaling to maintain stemness and promote EMT (103) and SBF2-AS1 sponges miR-151a-3p, leading to upregulation of XRCC4, a DNA repair factor (104). *MALAT1* promotes TMZ resistance in glioma through multiple mechanisms. Li *et al* (105) demonstrated that transfection of MALAT1 upregulates EMT and multidrug resistance genes, such as ZEB1 and MDR1, respectively, both *in vitro* and *in vivo*, collectively reducing glioma cell sensitivity to TMZ. In addition, other studies have shown that MALAT1 promotes chemoresistance and cell proliferation by suppressing miR-203, which targets thymidylate synthase, and by sponging miR-101, thereby blocking its inhibition of autophagy in glioma cells (106). ADAMTS9-AS2 promotes TMZ resistance by upregulating the FUS/MDM2 ubiquitination axis, specifically by enhancing FUS expression, which increases MDM2-mediated ubiquitination processes and leads to decreased apoptosis and increased survival of GBM cells under TMZ treatment (107).

By contrast, tumor-suppressive lncRNAs, such as CASC2, can augment the sensitivity of malignant cells to TMZ by enhancing its ability to suppress cell proliferation through the regulation of miR-181a, which, in turn, upregulates PTEN expression and downregulates phosphorylated AKT levels (108).

circRNAs as stable sponges shaping resistance. circRNAs are covalently closed RNA loops with high stability that function predominantly by sponging miRNAs or modulating protein interactions. They are emerging as key regulators of drug resistance in GBM.

circNFIX is overexpressed in glioma and promotes tumor growth and resistance to TMZ by sponging miR-34a-5p, which normally suppresses NOTCH1, thereby activating the Notch signaling pathway. Downregulation of circNFIX or overexpression of miR-34a-5p reduced glioma cell proliferation, migration and survival both *in vitro* and *in vivo*, highlighting the role of circ-NFIX in glioma progression (109). Additionally, exosomal circ-NFIX can transfer TMZ resistance from resistant glioma cells to sensitive glioma cells by

promoting migration and invasion while inhibiting apoptosis, and suppression of circ-NFIX restores TMZ sensitivity by upregulating miR-132 (110).

circHIPK3 is upregulated in TMZ-resistant glioma and promotes tumor progression, metastasis and drug resistance by acting as a competing endogenous RNA (ceRNA) for miRNAs. For example, circHIPK3 sponges miR-421 to upregulate the oncogene ZIC5, whose expression drives glioma cell proliferation, migration and drug resistance; circHIPK3 knockdown reduces ZIC5 levels, inhibits tumor growth and enhances TMZ sensitivity (111). In a parallel pathway, circHIPK3 sponges miR-524-5p to increase KIF2A expression, thereby activating the oncogenic PI3K/AKT pathway and contributing to proliferation, metastasis and resistance to TMZ (112).

circ_0043949 is overexpressed in TMZ-resistant GBM cells and exosomes, where it contributes to chemoresistance by functioning as a ceRNA. It sponges multiple miRNAs, including miR-876-3p, miR-7161-3p and miR-6783-3p, thereby upregulating targets like integrin α1 (ITGA1) and suppressing miR-140-mediated inhibition of EMT (113). These actions collectively enhance the proliferation, invasion and survival of GBM cells, and exosomal circ_0043949 can transfer resistance traits to other cells, as shown in xenograft models.

Among the additional circRNAs upregulated in recurrent GBM tissues and TMZ-resistant cell lines are circASAP1 and circ_0000936. circASAP1 confers resistance by sponging miR-502-5p, which leads to NRAS upregulation and activation of the NRAS/MEK1/ERK1/2 signaling pathway (114). Of note, its depletion restores TMZ sensitivity in resistant xenograft models. Likewise, circ_0000936 promotes resistance by suppressing miR-1294, and its downregulation sensitizes glioma cells to TMZ (115). These findings underscore both circRNAs as potential therapeutic targets for overcoming TMZ resistance in GBM.

Exosomal ncRNAs play pivotal roles in mediating chemoresistance in GBM by regulating apoptosis, drug efflux, DNA repair and key signaling pathways. Their dual function as biomarkers and active effectors makes them compelling targets for therapeutic intervention. Strategies aimed at inhibiting oncogenic ncRNAs or restoring tumor-suppressive ones, either directly or by blocking their exosomal transfer, offer promising avenues to overcome TMZ resistance and improve patient outcomes.

Currently, no clinical trials specifically target exosomal ncRNAs to counteract TMZ resistance in GBM. However, preclinical studies, including those aforementioned, have identified several exosomal ncRNAs involved in resistance mechanisms, highlighting potential targets for future therapies. One notable study employed CRISPR-Cas9 screening to identify resistance-associated genes in the mesenchymal subtype of GBM. It then used an exosome-based system to co-deliver siRNAs targeting genes such as *RASGRP1* and *VPS28*, the small-molecule inhibitor EPIC-0412 and TMZ (116). This combination significantly reduced tumor burden *in vivo*, though further validation is needed for clinical translation. Future clinical efforts should focus on developing exosome-based delivery systems for targeted therapy, using circulating exosomal ncRNAs as biomarkers to predict TMZ resistance, and combining exosomal ncRNA-targeted strategies with standard treatments to overcome resistance

3. Resistance to radiotherapy

Radiotherapy for GBM has seen significant technological advancements, evolving from 2D whole-brain radiotherapy to 3D conformal radiotherapy, intensity-modulated radiation therapy and volumetric arc therapy (117,118). These modern techniques offer improved targeting and reduced damage to healthy tissues. Stereotactic and hypofractionated approaches have also been introduced, offering more precise delivery and shorter treatment durations, respectively (119). Despite these improvements, clinical outcomes remain poor due to intrinsic and acquired resistance to radiation in patients with GBM, especially in recurrent cases. Overall, technological progress in radiotherapy has not translated into substantial survival benefits for patients with GBM.

The Stupp protocol, which consists of maximal safe surgical resection followed by concurrent radiation therapy and TMZ chemotherapy, and subsequently adjuvant TMZ, represents a multimodal treatment approach. This complexity makes it challenging to isolate the specific contribution of radiation resistance in clinical settings. Nonetheless, radiotherapy resistance in GBM is broadly attributed to three key factors: Hypoxic niches, dysregulated DNA damage response (DDR) and GSCs, each of which has been extensively discussed in earlier sections.

A recent study using patient-derived xenograft (PDX) models of GBM have further substantiated these resistance mechanisms. A notable finding is the existence of radiation-tolerant persister (RTP) cells, a subpopulation that survives radiotherapy through enhanced DNA repair capabilities and sustained GSC-like properties (120). These RTP cells exhibit elevated activity in both homologous recombination (HR) and non-homologous end joining pathways, rendering them highly resilient to radiation-induced DNA breaks. Mechanistically, constitutive activation of NF-κB signaling in RTP cells leads to increased expression of the transcription factor YY1, which suppresses miR-103a. This suppression, in turn, upregulates FGF2 and XRCC3, promoting DNA repair and maintenance of stemness. Of note, restoring miR-103a levels using transferrin-functionalized nanoparticles has been shown to significantly enhance radiosensitivity in PDX models, offering a promising therapeutic strategy to overcome radio-resistance and prevent recurrence.

Fang *et al* (121) have demonstrated that DNA-dependent protein kinase (DNA-PK) plays a critical role in maintaining GSC properties by stabilizing the transcription factor SOX2, a key regulator of stemness and therapeutic resistance in GBM. Specifically, DNA-PK phosphorylates SOX2 at serine 251, preventing its ubiquitination and subsequent degradation, thereby sustaining its function. Pharmacological inhibition of DNA-PK using NU7441 destabilizes SOX2, promotes GSC differentiation, enhances radiosensitivity and leads to tumor regression and improved survival in glioblastoma-bearing mice. These findings position DNA-PK as a compelling therapeutic target for overcoming radio-resistance in GBM.

In parallel, other studies have shown that repeated radiation exposure induces metabolic and transcriptional adaptations, including mitochondrial biogenesis and enhanced oxidative stress tolerance. Quiescent $CD133^+$ GSCs may be reactivated

following radiation, upregulating key self-renewal genes such as BMI1 and SOX2, which contribute to tumor repopulation (122). Additionally, radiation promotes IGF1 secretion, which induces N-cadherin-mediated cell-cell adhesion, enhancing GSC survival by suppressing differentiation and protecting against apoptosis via Clusterin secretion. A previous study showed that this IGF1-N-cadherin axis drives the development of a radioresistant GSC phenotype marked by reduced proliferation, increased stemness and membrane-localized β-catenin accumulation, which suppresses Wnt signaling and differentiation (123). Crucially, this adaptive resistance can be reversed by CRISPR-mediated knockout of N-cadherin or pharmacologic IGF1R inhibition with picropodophyllin, underscoring its therapeutic relevance.

A particularly comprehensive investigation created radiation-selected (RTS) PDX models by serially irradiating treatment-naïve GBMs (124). These RTS models closely mimic clinical recurrence and revealed significant alterations in gene expression and kinase activity. Interestingly, specific lncRNAs were identified as regulators of DNA repair and other resistance-associated pathways. Kinomic profiling of RTS tumors uncovered elevated activity of several kinases, including JAK, fibroblast growth factor receptor and Ephrin kinases. Fortunately, small-molecule inhibitors targeting these kinases were able to re-sensitize RTS tumors to radiation in preclinical settings (124).

Collectively, these findings illustrate that GBM resistance to radiation is a multifactorial and adaptive process, involving intricate crosstalk between DNA repair, stemness, metabolism, signaling and tumor microenvironmental cues. Targeting these mechanisms, especially those unique to resistant subpopulations, may offer novel therapeutic opportunities to enhance the efficacy of radiation therapy in GBM.

In this context, radiosensitizers have emerged as a promising strategy to improve the effectiveness of radiotherapy without increasing radiation doses, thus reducing collateral damage to healthy tissues. Radiosensitizers function by interfering with cellular mechanisms that normally protect tumor cells from radiation-induced damage. These mechanisms include inhibition of DNA repair enzymes [such as poly ADP-ribose polymerase (PARP), ATM and ATR] (125), disruption of redox homeostasis via thiol depletion or pro-oxidant activity, suppression of stemness pathways and mimicking the electrophilic activity of oxygen to overcome hypoxia-associated resistance. Several chemotherapeutic agents and targeted inhibitors have demonstrated radio-sensitizing effects in preclinical GBM models and early clinical studies including: i) Gemcitabine, which disrupts DNA replication by incorporating into the DNA strand (126); Talazoparib and veliparib (PARP inhibitors) that impair single-strand break repair (127); iii) Gefitinib (an EGFR inhibitor) that enhances radiation-induced cytotoxicity (128); iv) histone deacetylase inhibitors (quisinostat, valproate and vorinostat) to affect chromatin remodeling and DNA repair (129,130); v) Chloroquine (an autophagy inhibitor), to enhance radiation-induced apoptosis (131); vi) Adavosertib (a WEE1 inhibitor) that disrupts cell cycle checkpoints (125); and vii) Papaverine (a mitochondrial complex I inhibitor) to improve tumor oxygenation and radiosensitivity in hypoxic tumors (132).

Despite promising preclinical data, translation to clinical success has been limited. Several radiosensitizers have progressed to Phase I/II clinical trials, including ascorbate, sulfasalazine, trans-sodium crocetinate, NVX-108 and others; however, most have failed to show significant improvements in progression-free or OS in patients with GBM (133).

Among radiosensitizer classes, oxygen mimetics and metabolic modulators hold special promise for alleviating tumor hypoxia, a known driver of radio-resistance. Compounds containing nitro groups, hydrogen peroxide and mitochondrial inhibitors, such as papaverine have shown potential in preclinical models but face challenges in effective tumor delivery due to poor vascularization (132).

Thus, while radiosensitizers remain a viable therapeutic adjunct, there is an urgent need to identify biomarkers predicting radiosensitizer response, improve drug delivery to hypoxic tumor regions, develop combinatorial strategies targeting both DNA repair and tumor metabolism, and validate novel agents in robust GBM models, including PDX and radiation-selected systems.

By addressing these challenges, radiosensitizers may fulfill their therapeutic potential as key enhancers of radiotherapy outcomes in glioblastoma.

4. Resistance to targeted therapy

Glioblastomas are classified based on genetic features rather than just histology. GBMs are categorized into three subgroups based on differential gene expression: Proneural, classical and mesenchymal, each of which is driven by distinct molecular alterations (134). There has been increasing interest in developing targeted drugs to address genomic abnormalities specific to subtypes, such as EGFR amplification in the classical subtype, NF-κB hyperactivation in the mesenchymal subtype and PDGFR mutation in the proneural subtype.

Glioma cell lines and primary GBM tissues exhibit upregulated expression of PDGF and PDGFRs, particularly in the proneural subtype, characterized by a high rate (35%) of focal PDGFRA amplification. PDGFRβ expression is specific to GBM endothelial cells, being absent in normal brain vessels, highlighting its potential for GBM-specific targeted therapy (135).

Several anti-PDGFR agents, including olaratumab (an anti-PDGFRα antibody with significant tumor growth inhibition activity in xenograft models, but minimal clinical efficacy), CP-673,451 (a small molecule targeting PDGFRα and PDGFRβ to induce terminal differentiation of GBM cells) (136), crenolanib (CP-868,596, exhibiting brain penetration and *in vivo* PDGFR phosphorylation inhibition) (137), and avapritinib and ripretinib (targeting PDGFRα mutations, with avapritinib showing improved CNS penetrance) (138), have demonstrated promise in preclinical GBM models, but their clinical efficacy remains uncertain, with varying degrees of success and limitations observed in patient trials.

BEV, a monoclonal antibody targeting VEGF isoforms, has been extensively studied in regard to GBM. After promising results from Phase II trials, the FDA approved BEV in 2009 for recurrent GBM. In the BRAIN trial, BEV achieved a 6-month PFS rate of 42% as a single agent and 50% when combined with irinotecan, though OS was similar between groups.

Despite exceeding benchmarks, trials for BEV in combination therapies for primary GBM have shown disappointing results, partly due to pseudo-responses that mimic tumor shrinkage on imaging without true clinical benefit (139,140).

EGFR amplification is prevalent in 57% of primary GBM cases, predominantly in the classical subtype and may involve extracellular mutations, constitutively active EGFRvIII or extrachromosomal DNA, which exacerbates intra-tumoral heterogeneity and complicates drug targeting (141,142).

Although anti-EGFR therapies (such as dacomitinib, gefitinib and osimertinib) have been explored, their clinical efficacy is limited by tumor heterogeneity, resistance mechanisms and poor BBB penetrance (143). Resistance arises from compensatory signaling activation (such as PI3K and MET), and mutations like C797S and G724S that hinder drug binding (144). Emerging approaches, such as antibody-drug conjugates (for example, ABT-414), show promise but face challenges, including loss of EGFR amplification in resistant clones and inefficient BBB penetration (145).

Combination therapies targeting both EGFR and downstream effectors (for example, DDR1 and KRAS-driven MAPK activation) have demonstrated synergistic effects in overcoming resistance. However, improved specificity of EGFR inhibitors for GBM-associated mutations and combinatorial strategies are crucial for advancing GBM treatment.

Efforts to inhibit the PI3K/AKT/mTOR pathway using drugs such as GDC-0068 and GDC-0084 have shown potential, but resistance often arises (146-148). Studies focusing on the BRAF V600E mutation in a small fraction of gliomas have demonstrated that second- and third-generation BRAF inhibitors, combined with MEK inhibitors, may provide some benefit. However, the limited presence of BRAF mutations in gliomas reduces the overall impact of these findings.

In addition to the aforementioned small kinase inhibitors, other inhibitors targeting MET, FGFR, vascular endothelial growth factor receptor, MEK and PKCβ have been evaluated in clinical trials for GBM (21,149). However, these agents demonstrated limited efficacy, likely due to the acquisition of resistance.

Resistance mechanisms to kinase inhibitors in GBM can be broadly categorized into four groups: Mutations, coactivation of multiple RTKs, adaptation and alternative routes (bypass).

Mutations. Patients with GBM often possess mutations in the extracellular domain of kinases, unlike other types of cancer. EGFR mutations in GBM primarily occur in the extracellular domain, and this difference in mutation location may contribute to primary resistance (150).

Coactivation of multiple RTKs. GBMs often have multiple activated RTKs within a tumor, such as EGFR, ERBB3, PDGFR and MET (151), granting them resistance to single-agent inhibition.

Adaptation. Tumors can adapt to treatments over time. As discussed previously, GBM cells can suppress EGFRvIII protein expression in response to erlotinib treatment (152).

Alternative routes (bypass). Tumors can activate alternative signaling pathways to bypass the inhibited kinase. Examples include NF-κB pathway activation in response to combined EGFR and MET inhibition (153) and IGF-1R activation mediates resistance to EGFR inhibitors through activation of PI3K and AKT signaling (154).

IDH mutations are highly prevalent in >80% of WHO grade II/III gliomas, frequently occur in secondary glioblastomas (73% of cases), and are rare in primary glioblastomas (3.7%) (155). IDH-mutant GBM cells show synthetic lethality with PARP inhibitors due to impaired HR repair pathways. Several PARP inhibitors are under clinical investigation for GBM treatment.

Olaparib can cross the BBB but did not meet response-based thresholds in patients with IDH-mutant glioma (156). Niraparib was shown to exhibit improved tumor exposure and sustainability than olaparib, with ongoing studies evaluating its combination with radiotherapy. By contrast, IDH1/2-wildtype gliomas show limited tumor-suppressing effects with PARP inhibitors due to functional BRCA1/2 recruitment to the HR repair pathway.

IDH inhibitors such as ivosidenib and vorasidenib have been developed to block the production of the oncometabolite D-2-hydroxyglutarate (D-2-HG). D-2-HG drives gliomagenesis via epigenetic alterations, including hypermethylation that silences tumor suppressor genes and maintains stemness. While these IDH1/IDH2 inhibitors show promise in early clinical trials (157), resistance mechanisms remain an active area of investigation.

In conclusion, targeted therapies have shown success in other types of cancer, but not in GBM. New studies and clinical trials should address and solve this problem using preclinical models, improving BBB penetration and assessing combination therapies.

6. Resistance to immunotherapy

Immune checkpoint inhibitors have shown success in other types of cancer but have failed to show efficacy in GBM.

Nivolumab (anti-PD-1 antibody) plus radiotherapy failed to improve OS compared with the standard treatment of radiotherapy plus TMZ (158). Neoadjuvant PD-1 blockade with pembrolizumab, though it induced T cell-cell and cDC1 activation, failed to counteract the immunosuppressive tumor-associated macrophages (TAMs) in recurrent GBM (159). Both intrinsic and acquired resistance mechanisms contribute to the absence of efficacy of immunotherapy in GBM, as described below.

Immunosuppressive TME. GBM creates an environment that supports immune evasion through TAMs, GSCs and myeloid-derived suppressor cells (160,161). These suppress cytotoxic T cells and promote immune evasion by upregulating immunosuppressive proteins like CHI3L1 (162). Furthermore, the loss of S1P1 receptor on T-cell surface promotes T-cell dysfunction due to the sequestering of T-cells within the bone marrow (163).

Tumor heterogeneity. Tumor heterogeneity, discussed in the previous sections, contributes to immunotherapy resistance in GBM at both the molecular and cellular levels, allowing a range of subclonal populations with distinct genetic mutations and developmental states to coexist and evolve within the same tumor (43,164). This diversity enables therapy-resistant clones to survive treatment, adapt and repopulate the tumor, often with new genetic alterations, ultimately driving tumor

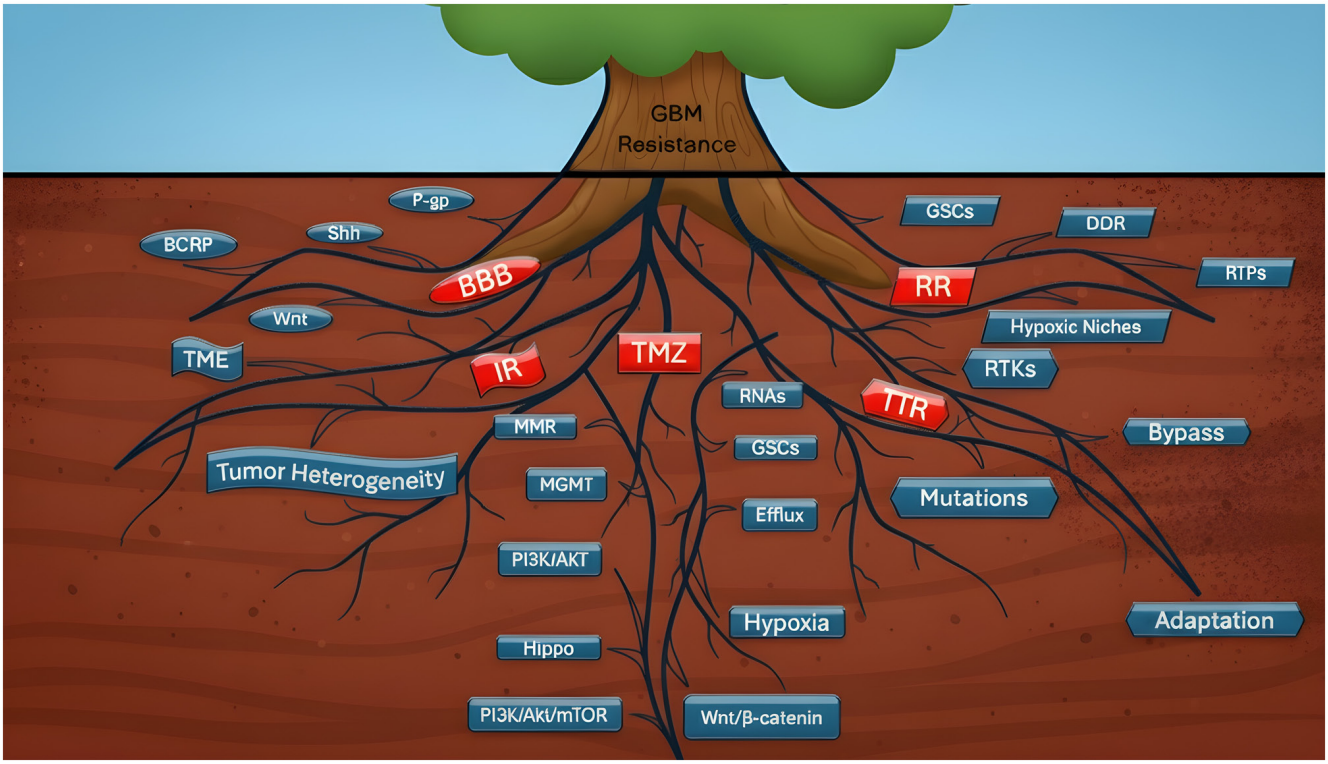

Figure 1. Root causes of therapeutic resistance in GBM. Schematic representation of the interconnected mechanisms that sustain GBM resistance, depicted as a tree where the visible trunk represents clinical resistance and the hidden root system illustrates its molecular and cellular drivers. Major resistance categories are highlighted in red as BBB, IR, TMZ resistance, RR and TTR. BBB serves as a physical barrier co-opted by the tumor to reduce drug penetration. Overexpression of efflux transporters such as P-gp and BCRP in tumor endothelial cells decreases intracellular drug concentrations, while dysregulation of Wnt and Shh pathways further limits permeability. IR is reinforced by the highly immunosuppressive TME, which includes TAMs, GSCs and MDSCs that suppress cytotoxic T-cell activity. Molecular heterogeneity further sustains therapy-resistant clones. TMZ resistance is driven by MGMT upregulation, DNA MMR defects and activation of PI3K/Akt, Hippo and Wnt/β-catenin pathways. Additional contributors include efflux transporters, GSCs, a hypoxic TME and exosomal RNAs. TTR reflects the failure of precision approaches despite subtype-specific alterations (EGFR in classical, PDGFR in proneural, NF-κB in mesenchymal GBM). Resistance mechanisms include kinase domain mutations, RTK coactivation (EGFR, ERBB3, PDGFR, MEK), adaptive suppression of EGFRvIII and bypass signaling via NF-κB or IGF1R-PI3K/AKT activation. RR arises from hypoxia, enhanced DDR and GSC-mediated repair capacity. RTP cells survive through homologous recombination and non-homologous end joining. Together, these mechanisms form a deeply interconnected 'root system' that allows GBM to withstand chemotherapy, radiotherapy, targeted therapy and immunotherapy. This conceptual framework emphasizes that resistance arises not from a single pathway but from a dynamic, adaptive network, underscoring the need for rational combination regimens, precision therapies, and innovative delivery strategies to overcome therapeutic failure in GBM. GBM, glioblastoma multiforme; BBB, blood-brain barrier; IR, immunotherapy resistance; TMZ, temozolomide; RR, radiotherapy resistance; TTR, targeted therapy resistance; TME, tumor microenvironment; TAM, tumor-associated macrophage; GSC, glioma stem-like cell; MDSC, myeloid-derived suppressor cell; MGMT, O^6-methylguanine-DNA methyltransferase; EGFR, epidermal growth factor; MMR, mismatch repair; PDGFR, platelet-derived growth factor; RTL, receptor tyrosine kinase; DDR, DNA damage response; RTP, radiation-tolerant persister; P-gp, P-glycoprotein; BCRP, breast-cancer-resistance protein; Shh, sonic hedgehog; MEK, mitogen-activated protein kinase.

recurrence and rendering monotherapies and some combination therapies ineffective.

To improve outcomes, immune-based therapies should be combined with approaches targeting the immunosuppressive mechanisms of glioblastoma. For example, co-targeting chemokine receptors such as CXCR4, often overexpressed in GBMs, alongside immune-checkpoint inhibitors has shown potential in preclinical studies (165). Rational combinations of therapies addressing tumor-immune compositional changes and leveraging immune-stimulatory mechanisms may maximize therapeutic success.

7. Conclusion and future directions

Despite decades of research, GBM remains among the most refractory of cancers. The current treatment paradigm is consistently undermined by a constellation of resistance mechanisms, ranging from poor drug penetration across the BBB and intra-tumoral heterogeneity to robust compensatory signaling and immune evasion.

Key mechanisms of drug resistance in GBM include limited drug penetration due to the BBB and its variable permeability, as well as active drug efflux by ATP-binding cassette transporters. The extensive heterogeneity of GBM, including molecular, genetic, cellular and spatial heterogeneity, gives rise to therapy-resistant subpopulations, notably GSCs. The TME, characterized by hypoxic niches and immunosuppressive myeloid cells, further facilitates resistance to both targeted and immune therapies. In addition, resistance is driven by intrinsic factors such as DNA repair activity (for example, MGMT expression or MMR defects), mutations in critical signaling pathways (such as p53, Rb or RTK/Ras/PI3K) and metabolic rewiring. GBM cells also exhibit antioxidant upregulation and dysregulated alternative splicing, all of which contribute to a formidable capacity to evade therapy (Fig. 1).

The present review emphasizes that overcoming such multifaceted resistance requires more than additive or sequential strategies; it demands mechanistically informed, rational combinations that account for the adaptive plasticity of GBM. For example, combining PI3K/mTOR inhibitors with agents targeting downstream anti-apoptotic proteins (such as Bcl-2 or Mcl-1) may disrupt resistance circuits more effectively than monotherapy. Similarly, dual inhibition of the MAPK and autophagy could thwart adaptive survival mechanisms.

.Rather than relying on generic combination therapies, future strategies should emphasize biologically justified, context-specific approaches tailored to the molecular and cellular landscape of each patient's tumor. Progress will also depend on bridging the translational gap between preclinical models and clinical endpoints, particularly in evaluating therapies targeting rare subpopulations or modulating the TME.

In summary, advancing GBM therapy demands a paradigm shift, from reactive management of resistance to proactive, mechanistically anchored intervention, with a relentless focus on therapeutic precision and clinical feasibility.

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Competing interests

The authors declare that they have no competing interests.

References

1. National Cancer Institute: Cancer Stat Facts: Brain and Other Nervous System Cancer. https://seer.cancer.gov/statfacts/html/brain.html.
2. National Center for Health Statistics: Declines in cancer death rates among youth: United States, 2001-2021. NCHS Data Brief No. 484, November 2023. https://www.cdc.gov/nchs/products/databriefs/db484.htm.
3. Schaff LR and Mellinghoff IK: Glioblastoma and other primary brain malignancies in adults: A review. JAMA 329: 574-587, 2023.
4. National Brain Tumor Society: Grade 4-Glioblastoma (GBM). https://braintumor.org/events/glioblastoma-awareness-day/about-glioblastoma/.
5. Butt AM, Jones HC and Abbott NJ: Electrical resistance across the blood-brain barrier in anaesthetized rats: A developmental study. J Physiol 429: 47-62, 1990.
6. Brown LS, Foster CG, Courtney JM, King NE, Howells DW and Sutherland BA: Pericytes and neurovascular function in the healthy and diseased brain. Front Cell Neurosci 13: 282, 2019.
7. Ou A, Yung WKA and Majd N: Molecular mechanisms of treatment resistance in glioblastoma. Int J Mol Sci 22: 351, 2020.
8. Sarkaria JN, Hu LS, Parney IF, Pafundi DH, Brinkmann DH, Laack NN, Giannini C, Burns TC, Kizilbash SH, Laramy JK, *et al*: Is the blood-brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. Neuro Oncol 20: 184-191, 2018.
9. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, Bunnell C, Rue M, Gelman R and Winer E: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 97: 2972-2977, 2003.
10. McCord M, Mukouyama YS, Gilbert MR and Jackson S: Targeting WNT signaling for multifaceted glioblastoma therapy. Front Cell Neurosci 11: 318, 2017.
11. Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, Sabbagh M, Wosik K, Bourbonnière L, Bernard M, *et al*: The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science 334: 1727-1731, 2011.
12. Mo F, Pellerino A, Soffietti R and Rudà R: Blood-brain barrier in brain tumors: Biology and clinical relevance. Int J Mol Sci 22: 12654, 2021.
13. Ommaya AK: Subcutaneous reservoir and pump for sterile access to ventricular cerebrospinal fluid. Lancet 2: 983-984, 1963.
14. Jabbour E, O'Brien S, Kantarjian H, Garcia-Manero G, Ferrajoli A, Ravandi F, Cabanillas M and Thomas DA: Neurologic complications associated with intrathecal liposomal cytarabine given prophylactically in combination with high-dose methotrexate and cytarabine to patients with acute lymphocytic leukemia. Blood 109: 3214-3218, 2007.
15. Siegal T, Horowitz A and Gabizon A: Doxorubicin encapsulated in sterically stabilized liposomes for the treatment of a brain tumor model: Biodistribution and therapeutic efficacy. J Neurosurg 83: 1029-1037, 1995.
16. Pinzón-Daza M, Garzón R, Couraud P, Romero Ia, Weksler B, Ghigo D, Bosia A and Riganti C: The association of statins plus LDL receptor-targeted Liposome-encapsulated doxorubicin increases in vitro drug delivery across blood-brain barrier cells. Br J Pharmacol 167: 1431-1447, 2012.
17. Durmus S, Sparidans RW, Wagenaar E, Beijnen JH and Schinkel AH: Oral availability and brain penetration of the B-RAFV600E inhibitor vemurafenib can be enhanced by the P-GLYCOprotein (ABCB1) and breast cancer resistance protein (ABCG2) inhibitor elacridar. Mol Pharm 9: 3236-3245, 2012.
18. McDannold N, Zhang Y, Supko JG, Power C, Sun T, Peng C, Vykhodtseva N, Golby AJ and Reardon DA: Acoustic feedback enables safe and reliable carboplatin delivery across the blood-brain barrier with a clinical focused ultrasound system and improves survival in a rat glioma model. Theranostics 9: 6284-6299, 2019.
19. Portnow J, Synold TW, Badie B, Tirughana R, Lacey SF, D'Apuzzo M, Metz MZ, Najbauer J, Bedell V, Vo T, *et al*: Neural stem Cell-based anticancer gene therapy: A First-in-Human study in recurrent High-grade glioma patients. Clin Cancer Res 23: 2951-2960, 2017.
20. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, *et al*: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352: 987-996, 2005.
21. Shen Y, Thng DKH, Wong ALA and Toh TB: Mechanistic insights and the clinical prospects of targeted therapies for glioblastoma: A comprehensive review. Exp Hematol Oncol 13: 40, 2024.

22. Fu D, Calvo JA and Samson LD: Balancing repair and tolerance of DNA damage caused by alkylating agents. Nat Rev Cancer 12: 104-120, 2012.
23. Roos WP, Batista LF, Naumann SC, Wick W, Weller M, Menck CF and Kaina B: Apoptosis in malignant glioma cells triggered by the temozolomide-induced DNA lesion O6-methylguanine. Oncogene 26: 186-197, 2007.
24. Kitange GJ, Carlson BL, Schroeder MA, Grogan PT, Lamont JD, Decker PA, Wu W, James CD and Sarkaria JN: Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro Oncol 11: 281-291, 2009.
25. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, *et al*: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352: 997-1003, 2005.
26. Sarkaria JN, Ballman KV, Kizilbash SH, Sulman EP, Giannini C, Mashru SH, Piccioni DE, Friday BEB, Dixon JG, Kabat B, *et al*: Randomized phase II/III trial of veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed glioblastoma (GBM) patients with MGMT promoter hypermethylation (Alliance A071102). J Clin Oncol 40 (Suppl 16): S2001, 2022.
27. Stupp R, Hegi ME, Gorlia T, Erridge SC, Perry J, Hong YK, Aldape KD, Lhermitte B, Pietsch T, Grujicic D, *et al*: Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 15: 1100-1108, 2014.
28. Balana C, De Las Penas R, Sepúlveda JM, Gil-Gil MJ, Luque R, Gallego O, Carrato C, Sanz C, Reynes G, Herrero A, *et al*: Bevacizumab and temozolomide versus temozolomide alone as neoadjuvant treatment in unresected glioblastoma: The GENOM 009 randomized phase II trial. J Neurooncol 127: 569-579, 2016.
29. Shinsato Y, Furukawa T, Yunoue S, Yonezawa H, Minami K, Nishizawa Y, Ikeda R, Kawahara K, Yamamoto M, Hirano H, *et al*: Reduction of MLH1 and PMS2 confers temozolomide resistance and is associated with recurrence of glioblastoma. Oncotarget 4: 2261-2270, 2013.
30. Cahill DP, Levine KK, Betensky RA, Codd PJ, Romany CA, Reavie LB, Batchelor TT, Futreal PA, Stratton MR, Curry WT, *et al*: Loss of the mismatch repair protein MSH6 in human glioblastomas is associated with tumor progression during temozolomide treatment. Clin Cancer Res 13: 2038-2045, 2007.
31. Stark AM, Doukas A, Hugo HH, Hedderich J, Hattermann K, Maximilian Mehdorn H and Held-Feindt J: Expression of DNA mismatch repair proteins MLH1, MSH2, and MSH6 in recurrent glioblastoma. Neurol Res 37: 95-105, 2015.
32. Hunter C, Smith R, Cahill DP, Stephens P, Stevens C, Teague J, Greenman C, Edkins S, Bignell G, Davies H, *et al*: A hypermutation phenotype and somatic MSH6 mutations in recurrent human malignant gliomas after alkylator chemotherapy. Cancer Res 66: 3987-3991, 2006.
33. Leelatian N, Hong CS and Bindra RS: The role of mismatch repair in glioblastoma multiforme treatment response and resistance. Neurosurg Clin N Am 32: 171-180, 2021.
34. Brastianos PK, Kim AE, Giobbie-Hurder A, Lee EQ, Lin NU, Overmoyer B, Wen PY, Nayak L, Cohen JV, Dietrich J, *et al*: Pembrolizumab in brain metastases of diverse histologies: Phase 2 trial results. Nat Med 29: 1728-1737, 2023.
35. Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG and Parada LF: A restricted cell population propagates glioblastoma growth after chemotherapy. Nature 488: 522-526, 2012.
36. Warrier NM, Krishnan RK, Prabhu V, Hariharapura RC, Agarwal P and Kumar P: Survivin inhibition by piperine sensitizes glioblastoma cancer stem cells and leads to better drug response. Int J Mol Sci 23: 7604, 2022.
37. Ahluwalia MS, Reardon DA, Abad AP, Curry WT, Wong ET, Figel SA, Mechtler LL, Peereboom DM, Hutson AD, Withers HG, *et al*: Phase IIa study of SurVaxM plus adjuvant temozolomide for newly diagnosed glioblastoma. J Clin Oncol 41: 1453-1465, 2023.
38. Munoz JL, Walker ND, Scotto KW and Rameshwar P: Temozolomide competes for P-glycoprotein and contributes to chemoresistance in glioblastoma cells. Cancer Lett 367: 69-75, 2015.
39. Oberstadt MC, Bien-Möller S, Weitmann K, Herzog S, Hentschel K, Rimmbach C, Vogelgesang S, Balz E, Fink M, Michael H, *et al*: Epigenetic modulation of the drug resistance genes MGMT, ABCB1 and ABCG2 in glioblastoma multiforme. BMC Cancer 13: 617, 2013.
40. Yan Y, Liu Y, Liang Q and Xu Z: Drug metabolism-related gene ABCA1 augments temozolomide chemoresistance and immune infiltration abundance of M2 macrophages in glioma. Eur J Med Res 28: 373, 2023.
41. Meng J, Qian W, Yang Z, Gong L, Xu D, Huang H, Jiang X, Pu Z, Yin Y and Zou J: p53/E2F7 axis promotes temozolomide chemoresistance in glioblastoma multiforme. BMC Cancer 24: 317, 2024.
42. Karve AS, Desai JM, Gadgil SN, Dave N, Wise-Draper TM, Gudelsky GA, Phoenix TN, DasGupta B, Yogendran L, Sengupta S, *et al*: A Review of approaches to potentiate the activity of temozolomide against glioblastoma to overcome resistance. Int J Mol Sci 25: 3217, 2024.
43. Goenka A, Tiek D, Song X, Huang T, Hu B and Cheng SY: The many facets of therapy resistance and tumor recurrence in glioblastoma. Cells 10: 484, 2021.
44. Persano L, Pistollato F, Rampazzo E, Della Puppa A, Abbadi S, Frasson C, Volpin F, Indraccolo S, Scienza R and Basso G: BMP2 sensitizes glioblastoma stem-like cells to Temozolomide by affecting HIF-1α stability and MGMT expression. Cell Death Dis 3: e412, 2012.
45. Seidel S, Garvalov BK, Wirta V, von Stechow L, Schänzer A, Meletis K, Wolter M, Sommerlad D, Henze AT, Nistér M, *et al*: A hypoxic niche regulates glioblastoma stem cells through hypoxia inducible factor 2 alpha. Brain 133: 983-995, 2010.
46. Ren P, Wang JY, Zeng ZR, Li NX, Chen HL, Peng XG, Bhawal UK and Guo WZ: A novel hypoxia-driven gene signature that can predict the prognosis and drug resistance of gliomas. Front Genet 13: 976356, 2022.
47. Ge X, Pan MH, Wang L, Li W, Jiang C, He J, Abouzid K, Liu LZ, Shi Z and Jiang BH: Hypoxia-mediated mitochondria apoptosis inhibition induces temozolomide treatment resistance through miR-26a/Bad/Bax axis. Cell Death Dis 9: 1128, 2018.
48. Brenner AJ, Sun JD, Floyd J, Hart CP, Eng C, Kroll S, Fichtel L, Gruslova A, Lodi A and Tiziani S: Phase 1/2 study of investigational hypoxia-targeted drug, TH-302, and bevacizumab (bev) in recurrent glioblastoma (GBM) following bev failure. J Clin Oncol 32 (15_Suppl): S2029, 2014.
49. Strowd R, Ellingson B, Raymond C, Yao J, Wen PY, Ahluwalia M, Piotrowski A, Desai A, Clarke JL, Lieberman FS, *et al*: Activity of a first-in-class oral HIF2-alpha inhibitor, PT2385, in patients with first recurrence of glioblastoma. J Neurooncol 165: 101-112, 2023.
50. Lickliter JD, Ruben J, Kichenadasse G, Jennens R, Gzell C, Mason RP, Zhou H, Becker J, Unger E and Stea B: Dodecafluoropentane emulsion as a radiosensitizer in glioblastoma multiforme. Cancer Res Commun 3: 1607-1614, 2023.
51. Jeong W, Park SR, Rapisarda A, Fer N, Kinders RJ, Chen A, Melillo G, Turkbey B, Steinberg SM, Choyke P, *et al*: Weekly EZN-2208 (PEGylated SN-38) in combination with bevacizumab in patients with refractory solid tumors. Invest New Drugs 32: 340-346, 2014.
52. Network TC: Corrigendum: Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 494: 506, 2013.
53. Velpula KK and Tsung AJ: PDK1: A new therapeutic target for glioblastoma? CNS Oncol 3: 177-179, 2014.
54. Velpula KK, Guda MR, Sahu K, Tuszynski J, Asuthkar S, Bach SE, Lathia JD and Tsung AJ: Metabolic targeting of EGFRvIII/PDK1 axis in temozolomide resistant glioblastoma. Oncotarget 8: 35639-35655, 2017.
55. Kaur B, Khwaja FW, Severson EA, Matheny SL, Brat DJ and Van Meir EG: Hypoxia and the hypoxia-inducible-factor pathway in glioma growth and angiogenesis. Neuro Oncol 7: 134-153, 2005.
56. Würth R, Bajetto A, Harrison JK, Barbieri F and Florio T: CXCL12 modulation of CXCR4 and CXCR7 activity in human glioblastoma stem-like cells and regulation of the tumor microenvironment. Front Cell Neurosci 8: 144, 2014.
57. Nogueira L, Ruiz-Ontañon P, Vazquez-Barquero A, Moris F and Fernandez-Luna JL: The NFκB pathway: A therapeutic target in glioblastoma. Oncotarget 2: 646-653, 2011.
58. Pareja F, Macleod D, Shu C, Crary JF, Canoll PD, Ross AH and Siegelin MD: PI3K and Bcl-2 inhibition primes glioblastoma cells to apoptosis through downregulation of Mcl-1 and Phospho-BAD. Mol Cancer Res 12: 987-1001, 2014.
59. Valdés-Rives SA, Casique-Aguirre D, Germán-Castelán L, Velasco-Velázquez MA and González-Arenas A: Apoptotic signaling pathways in glioblastoma and therapeutic implications. BioMed Res Int 2017: 7403747, 2017.

60. Daniele S, Costa B, Zappelli E, Da Pozzo E, Sestito S, Nesi G, Campiglia P, Marinelli L, Novellino E, Rapposelli S and Martini C: Combined inhibition of AKT/mTOR and MDM2 enhances Glioblastoma Multiforme cell apoptosis and differentiation of cancer stem cells. Sci Rep 5: 9956, 2015.
61. Song Z, Pan Y, Ling G, Wang S, Huang M, Jiang X and Ke Y: Escape of U251 glioma cells from temozolomide-induced senescence was modulated by CDK1/survivin signaling. Am J Transl Res 9: 2163-2180, 2017.
62. Josset E, Burckel H, Noël G and Bischoff P: The mTOR inhibitor RAD001 potentiates autophagic cell death induced by temozolomide in a glioblastoma cell line. Anticancer Res 33: 1845-1851, 2013.
63. Zou Y, Chen M, Zhang S, Miao Z, Wang J, Lu X and Zhao X: TRPC5-induced autophagy promotes the TMZ-resistance of glioma cells via the CAMMKβ/AMPKα/mTOR pathway. Oncol Rep 41: 3413-3423, 2019.
64. Wen PY, de Groot JF, Battiste J, Goldlust SA, Garner JS, Friend J, Simpson JA, Damek D, Olivero A and Cloughesy TF: Paxalisib in patients with newly diagnosed glioblastoma with unmethylated MGMT promoter status: Final phase 2 study results. J Clin Oncol 40 (16_suppl): 2047, 2022.
65. Wen PY, Omuro A, Ahluwalia MS, Fathallah-Shaykh HM, Mohile N, Lager JJ, Laird AD, Tang J, Jiang J, Egile C and Cloughesy TF: Phase I dose-escalation study of the PI3K/mTOR inhibitor voxtalisib (SAR245409, XL765) plus temozolomide with or without radiotherapy in patients with high-grade glioma. Neuro Oncol 17: 1275-1283, 2015.
66. Yu Z, Xie G, Zhou G, Cheng Y, Zhang G, Yao G, Chen Y, Li Y and Zhao G: NVP-BEZ235, a novel dual PI3K-mTOR inhibitor displays anti-glioma activity and reduces chemoresistance to temozolomide in human glioma cells. Cancer Lett 367: 58-68, 2015.
67. Xu P, Zhang G, Hou S and Sha LG: MAPK8 mediates resistance to temozolomide and apoptosis of glioblastoma cells through MAPK signaling pathway. Biomed Pharmacother 106: 1419-1427, 2018.
68. Lin CJ, Lee CC, Shih YL, Lin TY, Wang SH, Lin YF and Shih CM: Resveratrol enhances the therapeutic effect of temozolomide against malignant glioma in vitro and in vivo by inhibiting autophagy. Free Radic Biol Med 52: 377-391, 2012.
69. Ma L, Liu J, Zhang X, Qi J, Yu W and Gu Y: p38 MAPK-dependent Nrf2 induction enhances the resistance of glioma cells against TMZ. Med Oncol 32: 69, 2015.
70. Cheng HS, Chong YK, Lim EKY, Lee XY, Pang QY, Novera W, Marvalim C, Lee JXT, Ang BT, Tang C and Tan NS: Dual p38MAPK and MEK inhibition disrupts adaptive chemoresistance in mesenchymal glioblastoma to temozolomide. Neuro Oncol 26: 1247-1261, 2024.
71. Reardon DA, Vredenburgh JJ, Desjardins A, Peters K, Gururangan S, Sampson JH, Marcello J, Herndon JE II, McLendon RE, Janney D, *et al*: Effect of CYP3A-inducing anti-epileptics on sorafenib exposure: Results of a phase II study of sorafenib plus daily temozolomide in adults with recurrent glioblastoma. J Neurooncol 101: 57-66, 2011.
72. Hainsworth JD, Ervin T, Friedman E, Priego V, Murphy PB, Clark BL and Lamar RE: Concurrent radiotherapy and temozolomide followed by temozolomide and sorafenib in the first-line treatment of patients with glioblastoma multiforme. Cancer 116: 3663-3669, 2010.
73. Singh N, Miner A, Hennis L and Mittal S: Mechanisms of temozolomide resistance in glioblastoma-a comprehensive review. Cancer Drug Resist 4: 17-43, 2021.
74. Riganti C, Salaroglio IC, Caldera V, Campia I, Kopecka J, Mellai M, Annovazzi L, Bosia A, Ghigo D and Schiffer D: Temozolomide downregulates P-glycoprotein expression in glioblastoma stem cells by interfering with the Wnt3a/glycogen synthase-3 kinase/β-catenin pathway. Neuro Oncol 15: 1502-1517, 2013.
75. Xu K, Zhang Z, Pei H, Wang H, Li L and Xia Q: FoxO3a induces temozolomide resistance in glioblastoma cells via the regulation of β-catenin nuclear accumulation. Oncol Rep 37: 2391-2397, 2017.
76. Huang M, Zhang D, Wu JY, Xing K, Yeo E, Li C, Zhang L, Holland E, Yao L, Qin L, *et al*: Wnt-mediated endothelial transformation into mesenchymal stem cell-like cells induces chemoresistance in glioblastoma. Sci Transl Med 12: eaay7522, 2020.
77. Wickström M, Dyberg C, Milosevic J, Einvik C, Calero R, Sveinbjörnsson B, Sandén E, Darabi A, Siesjö P, Kool M, *et al*: Wnt/β-catenin pathway regulates MGMT gene expression in cancer and inhibition of Wnt signalling prevents chemoresistance. Nat Commun 6: 8904, 2015.
78. Tomar VS, Patil V and Somasundaram K: Temozolomide induces activation of Wnt/β-catenin signaling in glioma cells via PI3K/Akt pathway: Implications in glioma therapy. Cell Biol Toxicol 36: 273-278, 2020.
79. Lu C, Cui C, Liu B, Zou S, Song H, Tian H, Zhao J and Li Y: FERMT3 contributes to glioblastoma cell proliferation and chemoresistance to temozolomide through integrin mediated Wnt signaling. Neurosci Lett 657: 77-83, 2017.
80. Luo W, Yan D, Song Z, Zhu X, Liu X, Li X and Zhao S: miR-126-3p sensitizes glioblastoma cells to temozolomide by inactivating Wnt/β-catenin signaling via targeting SOX2. Life Sci 226: 98-106, 2019.
81. Zeng A, Yin J, Li Y, Li R, Wang Z, Zhou X, Jin X, Shen F, Yan W and You Y: miR-129-5p targets Wnt5a to block PKC/ERK/NF-κB and JNK pathways in glioblastoma. Cell Death Dis 9: 394, 2018.
82. Zhang KL, Han L, Chen LY, Shi ZD, Yang M, Ren Y, Chen LC, Zhang JX, Pu PY and Kang CS: Blockage of a miR-21/EGFR regulatory feedback loop augments anti-EGFR therapy in glioblastomas. Cancer Lett 342: 139-149, 2014.
83. Huang T, Alvarez AA, Pangeni RP, Horbinski CM, Lu S, Kim SH, James CD, J Raizer J, A Kessler J, Brenann CW, *et al*: A regulatory circuit of miR-125b/miR-20b and Wnt signalling controls glioblastoma phenotypes through FZD6-modulated pathways. Nat Commun 7: 12885, 2016.
84. Chen KC, Chen PH, Ho KH, Shih CM, Chou CM, Cheng CH and Lee CC: IGF-1-enhanced miR-513a-5p signaling desensitizes glioma cells to temozolomide by targeting the NEDD4L-inhibited Wnt/β-catenin pathway. PLoS One 14: e0225913, 2019.
85. Kahlert UD, Suwala AK, Koch K, Natsumeda M, Orr BA, Hayashi M, Maciaczyk J and Eberhart CG: Pharmacologic wnt inhibition reduces proliferation, survival, and clonogenicity of glioblastoma cells. J Neuropathol Exp Neurol 74: 889-900, 2015.
86. Kim Y, Kim KH, Lee J, Lee Y, Kim M, Lee SJ, Park K, Yang H, Jin J, Joo KM, *et al*: Wnt activation is implicated in glioblastoma radioresistance. Lab Invest 92: 466-473, 2012.
87. De Robertis A, Valensin S, Rossi M, Tunici P, Verani M, De Rosa A, Giordano C, Varrone M, Nencini A, Pratelli C, *et al*: Identification and characterization of a small-molecule inhibitor of Wnt signaling in glioblastoma cells. Mol Cancer Ther 12: 1180-1189, 2013.
88. Yoshino T, Ikeda M, Finn RS, Jeffry Evans TR, Weng L, Saito K, Mody K, Tamai T, Paoletti C and Iwasa S: Abstract CT523: An open-label, multicenter, phase 1b/2 Study of E7386 (Wnt/β-catenin pathway inhibitor) + pembrolizumab in patients with pretreated advanced solid tumors. Cancer Res 82 (Suppl): CT523, 2022.
89. Bhat KP, Salazar KL, Balasubramaniyan V, Wani K, Heathcock L, Hollingsworth F, James JD, Gumin J, Diefes KL, Kim SH, *et al*: The transcriptional coactivator TAZ regulates mesenchymal differentiation in malignant glioma. Genes Dev 25: 2594-2609, 2011.
90. Orr BA, Bai H, Odia Y, Jain D, Anders RA and Eberhart CG: Yes-associated protein 1 is widely expressed in human brain tumors and promotes glioblastoma growth. J Neuropathol Exp Neurol 70: 568-577, 2011.
91. Tian T, Li A, Lu H, Luo R, Zhang M and Li Z: TAZ promotes temozolomide resistance by upregulating MCL-1 in human glioma cells. Biochem Biophys Res Commun 463: 638-643, 2015.
92. Casati G, Giunti L, Iorio AL, Marturano A, Galli L and Sardi I: Hippo pathway in regulating drug resistance of glioblastoma. Int J Mol Sci 22: 13431, 2021.
93. Minata M, Audia A, Shi J, Lu S, Bernstock J, Pavlyukov MS, Das A, Kim SH, Shin YJ, Lee Y, *et al*: Phenotypic plasticity of invasive edge glioma stem-like cells in response to ionizing radiation. Cell Rep 26: 1893-1905.e7, 2019.
94. Vigneswaran K, Boyd NH, Oh SY, Lallani S, Boucher A, Neill SG, Olson JJ and Read RD: YAP/TAZ transcriptional coactivators create therapeutic vulnerability to verteporfin in EGFR-mutant glioblastoma. Clin Cancer Res 27: 1553-1569, 2021.
95. Read RD: Repurposing the drug verteporfin as anti-neoplastic therapy for glioblastoma. Neuro Oncol 24: 708-710, 2022.
96. Hagenbeek TJ, Zbieg JR, Hafner M, Mroue R, Lacap JA, Sodir NM, Noland CL, Afghani S, Kishore A, Bhat KP, *et al*: An allosteric pan-TEAD inhibitor blocks oncogenic YAP/TAZ signaling and overcomes KRAS G12C inhibitor resistance. Nat Cancer 4: 812-828, 2023.

97. Lu J, Gao M, He H, Feng L, Gao Z, Cui W, Yang K, Lu J, Zheng Q, Zhu J, *et al*: Abstract 1671: Discovery of ETS-003, a potent and selective YAP/TAZ-TEAD PPI inhibitor with broad anti-tumor activity in Hippo-YAP aberrant cancers. Cancer Res 83 (Suppl): S1671, 2023.
98. Chapeau EA, Sansregret L, Galli GG, Chène P, Wartmann M, Mourikis TP, Jaaks P, Baltschukat S, Barbosa IAM, Bauer D, *et al*: Direct and selective pharmacological disruption of the YAP-TEAD interface by IAG933 inhibits Hippo-dependent and RAS-MAPK-altered cancers. Nat Cancer 5: 1102-1120, 2024.
99. Movahedpour A, Khatami SH, Khorsand M, Salehi M, Savardashtaki A, Mirmajidi SH, Negahdari B, Khanjani N, Naeli P, Vakili O, *et al*: Exosomal noncoding RNAs: Key players in glioblastoma drug resistance. Mol Cell Biochem 476: 4081-4092, 2021.
100. Shea A, Harish V, Afzal Z, Chijioke J, Kedir H, Dusmatova S, Roy A, Ramalinga M, Harris B, Blancato J, *et al*: MicroRNAs in glioblastoma multiforme pathogenesis and therapeutics. Cancer Med 5: 1917-1946, 2016.
101. Xiao S, Yang Z, Qiu X, Lv R, Liu J, Wu M, Liao Y and Liu Q: miR-29c contribute to glioma cells temozolomide sensitivity by targeting O6-methylguanine-DNA methyltransferases indirectely. Oncotarget 7: 50229-50238, 2016.
102. Cunha PP, Costa PM, Morais CM, Lopes IR, Cardoso AM, Cardoso AL, Mano M, Jurado AS and Pedroso de Lima MC: High-throughput screening uncovers miRNAs enhancing glioblastoma cell susceptibility to tyrosine kinase inhibitors. Hum Mol Genet 26: 4375-4387, 2017.
103. Xia Y, Pei T, Zhao J, Wang Z, Shen Y, Yang Y and Liang J: Long noncoding RNA H19: Functions and mechanisms in regulating programmed cell death in cancer. Cell Death Discov 10: 76, 2024.
104. Zhang Z, Yin J, Lu C, Wei Y, Zeng A and You Y: Exosomal transfer of long Non-coding RNA SBF2-AS1 enhances chemoresistance to temozolomide in glioblastoma. J Exp Clin Cancer Res 38: 166, 2019.
105. Li H, Yuan X, Yan D, Li D, Guan F, Dong Y, Wang H, Liu X and Yang B: Long Non-Coding RNA MALAT1 decreases the sensitivity of resistant glioblastoma cell lines to temozolomide. Cell Physiol Biochem 42: 1192-1201, 2017.
106. Amodio N, Raimondi L, Juli G, Stamato MA, Caracciolo D, Tagliaferri P and Tassone P: MALAT1: A druggable long non-coding RNA for targeted anti-cancer approaches. J Hematol Oncol 11: 63, 2018.
107. Yan Y, Xu Z, Chen X, Wang X, Zeng S, Zhao Z, Qian L, Li Z, Wei J, Huo L, *et al*: Novel function of lncRNA ADAMTS9-AS2 in promoting temozolomide resistance in glioblastoma via upregulating the FUS/MDM2 ubiquitination axis. Front Cell Dev Biol 7: 217, 2019.
108. Liao Y, Shen L, Zhao H, Liu Q, Fu J, Guo Y, Peng R and Cheng L: LncRNA CASC2 Interacts With miR-181a to modulate glioma growth and resistance to TMZ through PTEN pathway. J Cell Biochem 118: 1889-1899, 2017.
109. Ahmed SP, Castresana JS and Shahi MH: Role of circular RNA in brain tumor development. Cells 11: 2130, 2022.
110. Ding C, Yi X, Wu X, Bu X, Wang D, Wu Z, Zhang G, Gu J and Kang D: Exosome-mediated transfer of circRNA CircNFIX enhances temozolomide resistance in glioma. Cancer Lett 479: 1-12, 2020.
111. Han C, Wang S, Wang H and Zhang J: Exosomal circ-HIPK3 facilitates tumor progression and temozolomide resistance by regulating miR-421/ZIC5 axis in glioma. Cancer Biother Radiopharm 36: 537-548, 2021.
112. Campelo MM, Reis-das-Mercês L, Vidal AF, da Silva FRP, de Oliveira ACA, Monteiro JRS, Cabral CG, Noronha RCR and Pereira AL: The dual role of circHIPK3 in cancer and its implications for multiple drugs resistance: A systematic review and computational approach. Front Oncol 15: 1547889, 2025.
113. Li X, Wang N, Leng H, Yuan H and Xu L: Hsa_circ_0043949 reinforces temozolomide resistance via upregulating oncogene ITGA1 axis in glioblastoma. Metab Brain Dis 37: 2979-2993, 2022.
114. Wei Y, Lu C, Zhou P, Zhao L, Lyu X, Yin J, Shi Z and You Y: EIF4A3-induced circular RNA ASAP1 promotes tumorigenesis and temozolomide resistance of glioblastoma via NRAS/MEK1/ERK1-2 signaling. Neuro Oncol 23: 611-624, 2021.
115. Hua L, Huang L, Zhang X and Feng H: Downregulation of hsa_circ_0000936 sensitizes resistant glioma cells to temozolomide by sponging miR-1294. J Biosci 45: 101, 2020.
116. Zhao J, Cui X, Zhan Q, Zhang K, Su D, Yang S, Hong B, Wang Q, Ju J, Cheng C, *et al*: CRISPR-Cas9 library screening combined with an exosome-targeted delivery system addresses tumorigenesis/TMZ resistance in the mesenchymal subtype of glioblastoma. Theranostics 14: 2835-2855, 2024.
117. Halasz LM, Soltys SG, Breneman JC, Chan MD, Laack NN, Minniti G and Kirkpatrick JP: Treatment of gliomas: A changing landscape. Int J Radiat Oncol Biol Phys 98: 255-258, 2017.
118. Shaffer R, Nichol AM, Vollans E, Fong M, Nakano S, Moiseenko V, Schmuland M, Ma R, McKenzie M and Otto K: A comparison of volumetric modulated arc therapy and conventional intensity-modulated radiotherapy for frontal and temporal High-grade gliomas. Int J Radiat Oncol Biol Phys 76: 1177-1184, 2010.
119. Wang TJC, Wu CC, Jani A, Estrada J, Ung T, Chow DS, Soun JE, Saad S, Qureshi YH, Gartrell R, *et al*: Hypofractionated radiation therapy versus standard fractionated radiation therapy with concurrent temozolomide in elderly patients with newly diagnosed glioblastoma. Pract Radiat Oncol 6: 306-314, 2016.
120. Gu J, Mu N, Jia B, Guo Q, Pan L, Zhu M, Zhang W, Zhang K, Li W, Li M, *et al*: Targeting radiation-tolerant persister cells as a strategy for inhibiting radioresistance and recurrence in glioblastoma. Neuro Oncol 24: 1056-1070, 2022.
121. Fang X, Huang Z, Zhai K, Huang Q, Tao W, Kim L, Wu Q, Almasan A, Yu JS, Li X, *et al*: Inhibiting DNA-PK induces glioma stem cell differentiation and sensitizes glioblastoma to radiation in mice. Sci Transl Med 13: eabc7275, 2021.
122. Huang ZL, Liu ZG, Lin Q, Tao YL, Li X, Baxter P, Su JM, Adesina AM, Man C, Chintagumpala M, *et al*: Fractionated radiation therapy alters energy metabolism and induces cellular quiescence exit in patient-derived orthotopic xenograft models of high-grade glioma. Transl Oncol 45: 101988, 2024.
123. Osuka S, Zhu D, Zhang Z, Li C, Stackhouse CT, Sampetrean O, Olson JJ, Gillespie GY, Saya H, Willey CD, *et al*: N-cadherin upregulation mediates adaptive radioresistance in glioblastoma. J Clin Invest 131: e136098, 2021.
124. Stackhouse CT, Anderson JC, Yue Z, Nguyen T, Eustace NJ, Langford CP, Wang J, Rowland JR IV, Xing C, Mikhail FM, *et al*: An in vivo model of glioblastoma radiation resistance identifies long noncoding RNAs and targetable kinases. JCI Insight 7: e148717, 2022.
125. Huang RX and Zhou PK: DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduct Target Ther 5: 60, 2020.
126. Bastiancich C, Bastiat G and Lagarce F: Gemcitabine and glioblastoma: Challenges and current perspectives. Drug Discov Today 23: 416-423, 2018.
127. Lesueur P, Chevalier F, El-Habr EA, Junier MP, Chneiweiss H, Castera L, Müller E, Stefan D and Saintigny Y: Radiosensitization effect of talazoparib, a parp inhibitor, on glioblastoma stem cells exposed to low and high linear energy transfer radiation. Sci Rep 8: 3664, 2018.
128. Stea B, Falsey R, Kislin K, Patel J, Glanzberg H, Carey S, Ambrad AA, Meuillet EJ and Martinez JD: Time and dose-dependent radiosensitization of the glioblastoma multiforme U251 cells by the EGF receptor tyrosine kinase inhibitor ZD1839 ('Iressa'). Cancer Lett 202: 43-51, 2003.
129. Lo Cascio C, Margaryan T, Luna-Melendez E, McNamara JB, White CI, Knight W, Ganta S, Opachich Z, Cantoni C, Yoo W, *et al*: Quisinostat is a brain-penetrant radiosensitizer in glioblastoma. JCI Insight 8: e167081, 2023.
130. Galanis E, Anderson SK, Miller CR, Sarkaria JN, Jaeckle K, Buckner JC, Ligon KL, Ballman KV, Moore DF Jr, Nebozhyn M, *et al*: Phase I/II trial of vorinostat combined with temozolomide and radiation therapy for newly diagnosed glioblastoma: Results of Alliance N0874/ABTC 02. Neuro Oncol 20: 546-556, 2018.
131. Compter I, Eekers DBP, Hoeben A, Rouschop KMA, Reymen B, Ackermans L, Beckervordersantforth J, Bauer NJC, Anten MM, Wesseling P, *et al*: Chloroquine combined with concurrent radiotherapy and temozolomide for newly diagnosed glioblastoma: A phase IB trial. Autophagy 17: 2604-2612, 2021.
132. Benej M, Hong X, Vibhute S, Scott S, Wu J, Graves E, Le QT, Koong AC, Giaccia AJ, Yu B, *et al*: Papaverine and its derivatives radiosensitize solid tumors by inhibiting mitochondrial metabolism. Proc Natl Acad Sci USA 115: 10756-10761, 2018.
133. Ali MY, Oliva CR, Noman ASM, Allen BG, Goswami PC, Zakharia Y, Monga V, Spitz DR, Buatti JM and Griguer CE: Radioresistance in glioblastoma and the development of radiosensitizers. Cancers (Basel) 12: 2511, 2020.

134. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, *et al*: Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 17: 98-110, 2010.
135. Szerlip NJ, Pedraza A, Chakravarty D, Azim M, McGuire J, Fang Y, Ozawa T, Holland EC, Huse JT, Jhanwar S, *et al*: Intratumoral heterogeneity of receptor tyrosine kinases EGFR and PDGFRA amplification in glioblastoma defines subpopulations with distinct growth factor response. Proc Natl Acad Sci USA 109: 3041-3046, 2012.
136. Lane R, Cilibrasi C, Chen J, Shah K, Messuti E, Mazarakis NK, Stebbing J, Critchley G, Song E, Simon T, *et al*: PDGF-R inhibition induces glioblastoma cell differentiation via DUSP1/p38MAPK signalling. Oncogene 41: 2749-2763, 2022.
137. Cenciarelli C, Marei HE, Felsani A, Casalbore P, Sica G, Puglisi MA, Cameron AJ, Olivi A and Mangiola A: PDGFRα depletion attenuates glioblastoma stem cells features by modulation of STAT3, RB1 and multiple oncogenic signals. Oncotarget 7: 53047-53063, 2016.
138. MayrL,NeyaziS,SchwarkK,TrissalM,BeckA,LabelleJ,EderSK, Weiler-Wichtl L, Marques JG, de Biagi-Junior CAO, *et al*: Effective targeting of PDGFRA-altered high-grade glioma with avapritinib. Cancer Cell 43: 740-756.e8, 2025.
139. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, *et al*: A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370: 699-708, 2014.
140. Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, Baehring J, Ahluwalia MS, Roth P, Bähr O, *et al*: Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: The CheckMate 143 Phase 3 randomized clinical trial. JAMA Oncol 6: 1003-1010, 2020.
141. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, *et al*: The somatic genomic landscape of glioblastoma. Cell 155: 462-477, 2013.
142. An Z, Aksoy O, Zheng T, Fan QW and Weiss WA: Epidermal growth factor receptor and EGFRvIII in glioblastoma: Signaling pathways and targeted therapies. Oncogene 37: 1561-1575, 2018.
143. Ezzati S, Salib S, Balasubramaniam M and Aboud O: Epidermal growth factor receptor inhibitors in glioblastoma: Current status and future possibilities. Int J Mol Sci 25: 2316, 2024.
144. Guo G, Gong K, Ali S, Ali N, Shallwani S, Hatanpaa KJ, Pan E, Mickey B, Burma S, Wang DH, *et al*: Primary resistance to EGFR inhibition in glioblastoma is mediated by a TNF-JNK-Axl-ERK signaling axis. Nat Neurosci 20: 1074-1084, 2017.
145. Marin BM, Porath KA, Jain S, Kim M, Conage-Pough JE, Oh JH, Miller CL, Talele S, Kitange GJ, Tian S, *et al*: Heterogeneous delivery across the blood-brain barrier limits the efficacy of an EGFR-targeting antibody drug conjugate in glioblastoma. Neuro Oncol 23: 2042-2053, 2021.
146. Hottinger AF, Ben Aissa A, Espeli V, Squiban D, Dunkel N, Vargas MI, Hundsberger T, Mach N, Schaller K, Weber DC, *et al*: Phase I study of sorafenib combined with radiation therapy and temozolomide as first-line treatment of high-grade glioma. Br J Cancer 110: 2655-2661, 2014.
147. Kim JY, Jo Y, Oh HK and Kim EH: Sorafenib increases tumor treating Fields-induced cell death in glioblastoma by inhibiting STAT3. Am J Cancer Res 10: 3475-3486, 2020.
148. Schreck KC, Grossman SA and Pratilas CA: BRAF mutations and the utility of RAF and MEK inhibitors in primary brain tumors. Cancers (Basel) 11: 1262, 2019.
149. Fabro F, Lamfers MLM and Leenstra S: Advancements, challenges, and future directions in tackling glioblastoma resistance to small kinase inhibitors. Cancers (Basel) 14: 600, 2022.
150. Marie Y, Carpentier AF, Omuro AM, Sanson M, Thillet J, Hoang-Xuan K and Delattre JY: EGFR tyrosine kinase domain mutations in human gliomas. Neurology 64: 1444-1445, 2005.
151. Stommel JM, Kimmelman AC, Ying H, Nabioullin R, Ponugoti AH, Wiedemeyer R, Stegh AH, Bradner JE, Ligon KL, Brennan C, *et al*: Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. Science 318: 287-290, 2007.
152. Nathanson DA, Gini B, Mottahedeh J, Visnyei K, Koga T, Gomez G, Eskin A, Hwang K, Wang J, Masui K, *et al*: Targeted therapy resistance mediated by dynamic regulation of extrachromosomal mutant EGFR DNA. Science 343: 72-76, 2014.
153. Day EK, Sosale NG, Xiao A, Zhong Q, Purow B and Lazzara MJ: Glioblastoma cell resistance to EGFR and MET inhibition can be overcome via blockade of FGFR-SPRY2 bypass signaling. Cell Rep 30: 3383-3396.e7, 2020.
154. Chakravarti A, Loeffler JS and Dyson NJ: Insulin-like growth factor receptor I mediates resistance to Anti-epidermal growth factor receptor therapy in primary human glioblastoma cells through continued activation of phosphoinositide 3-kinase signaling. Cancer Res 62: 200-207, 2002.
155. Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR and Yang C: IDH mutation in glioma: Molecular mechanisms and potential therapeutic targets. Br J Cancer 122: 1580-1589, 2020.
156. Fanucci K, Pilat MJ, Shyr D, Shyr Y, Boerner S, Li J, Durecki D, Drappatz J, Puduvalli V, Lieberman FS, *et al*: Multicenter Phase II trial of the PARP inhibitor olaparib in recurrent IDH1- and IDH2-mutant glioma. Cancer Res Commun 3: 192-201, 2023.
157. Lin MD, Tsai AC, Abdullah KG, McBrayer SK and Shi DD: Treatment of IDH-mutant glioma in the INDIGO era. NPJ Precis Oncol 8: 149, 2024.
158. Omuro A, Brandes AA, Carpentier AF, Idbaih A, Reardon DA, Cloughesy T, Sumrall A, Baehring J, van den Bent M, Bähr O, *et al*: Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase III trial. Neuro Oncol 25: 123-134, 2023.
159. Lee AH, Sun L, Mochizuki AY, Reynoso JG, Orpilla J, Chow F, Kienzler JC, Everson RG, Nathanson DA, Bensinger SJ, *et al*: Neoadjuvant PD-1 blockade induces T cell and cDC1 activation but fails to overcome the immunosuppressive tumor associated macrophages in recurrent glioblastoma. Nat Commun 12: 6938, 2021.
160. Lin YJ, Wu CY, Wu JY and Lim M: The role of myeloid cells in GBM immunosuppression. Front Immunol 13: 887781, 2022.
161. Sesé B, Íñiguez-Muñoz S, Ensenyat-Mendez M, Llinàs-Arias P, Ramis G, Orozco JIJ, Fernández de Mattos S, Villalonga P and Marzese DM: Glioblastoma Embryonic-like stem cells exhibit immune-evasive phenotype. Cancers (Basel) 14: 2070, 2022.
162. Chen A, Jiang Y, Li Z, Wu L, Santiago U, Zou H, Cai C, Sharma V, Guan Y, McCarl LH, *et al*: Chitinase-3-like 1 protein complexes modulate macrophage-mediated immune suppression in glioblastoma. J Clin Invest 131: e147552, 2021.
163. Chongsathidkiet P, Jackson C, Koyama S, Loebel F, Cui X, Farber SH, Woroniecka K, Elsamadicy AA, Dechant CA, Kemeny HR, *et al*: Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. Nat Med 24: 1459-1468, 2018.
164. Kang W, Mo Z, Li W, Ma H and Zhang Q: Heterogeneity and individualized treatment of microenvironment in glioblastoma (review). Oncol Rep 50: 217, 2023.
165. Wu A, Maxwell R, Xia Y, Cardarelli P, Oyasu M, Belcaid Z, Kim E, Hung A, Luksik AS, Garzon-Muvdi T, *et al*: Combination anti-CXCR4 and anti-PD-1 immunotherapy provides survival benefit in glioblastoma through immune cell modulation of tumor microenvironment. J Neurooncol 143: 241-249, 2019.