Molecular Insights into Glioblastoma Resistance and Implications for Treatment Advancements: A Systematic Review

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Abstract

Glioblastoma (GBM) is a highly resistant brain tumor with a dismal prognosis despite standard treatments like temozolomide (TMZ) and radiation therapy (RT). This review delineates the molecular mechanisms driving this resistance to inform future therapeutic strategies. A narrative review was conducted using PubMed, synthesizing studies from the year 2000 up to March 2025 on DNA repair enzymes, TMZ and RT resistance pathways, anti-apoptosis mechanisms, genetic heterogeneity, and cell cycle dysregulation in GBM. Five key resistance mechanisms were identified: (1) DNA repair enzymes (e.g., MGMT, APNG) counteract TMZ-induced damage, regulated by NF-κB and CHD4; (2) TMZ and RT resistance depends on MGMT methylation and MMR functionality; (3) anti-apoptotic pathways (e.g., Bcl-2, PI3K/Akt) protect GBM cells, mitigated by TRAIL sensitization; (4) genetic mutations (EGFR, PTEN, TP53) confer adaptability; and (5) quiescent and proliferative GBM stem cells (GSCs) sustain recurrence. Novel therapies targeting HK2 and neural stem cells show promise. GBM resistance is multifaceted, requiring personalized, multi-targeted approaches. Future research should prioritize epigenetic modulation and combination therapies to enhance patient outcomes.

Introduction

Glioblastoma (GBM) is the most prevalent and lethal primary brain tumor in adults, accounting for approximately 50% of all malignant brain tumors (1). Arising from astrocytes, GBM exhibits aggressive growth and infiltration into surrounding brain tissue, rendering complete surgical resection nearly impossible (1). The current standard of care involves maximal safe surgical resection followed by 6 weeks of concurrent radiotherapy (RT) and temozolomide (TMZ), an oral alkylating chemotherapeutic agent, followed by 6 monthly cycles of adjuvant TMZ (1). RT employs high-energy beams to induce DNA single- and double-strand breaks, aiming to halt tumor cell proliferation, while TMZ methylates DNA bases — most critically at the O6 position of guanine — to trigger cytotoxicity and apoptosis (2, 3). Despite this multimodal approach, GBM remains universally fatal, with a median survival of 12–15 months and a 5-year survival rate below 5% (1).

This poor prognosis is primarily due to GBM's remarkable resistance to both TMZ and RT, driven by a complex array of molecular mechanisms. These include upregulated DNA repair pathways, evasion of programmed cell death, extensive genetic and cellular heterogeneity, and dysregulated cell cycle dynamics. Previous studies have explored individual aspects of resistance, such as DNA repair enzymes or tumor heterogeneity, but a comprehensive synthesis integrating all major mechanisms with emerging therapeutic insights is lacking (4, 5). The cIMPACT-NOW initiative has emphasized molecular classification to refine GBM diagnosis and treatment, highlighting the need to understand resistance at a molecular level (2).

This review aims to elucidate 5 critical mechanisms of GBM resistance: 1. DNA repair enzymes, 2. TMZ and RT resistance pathways, 3. anti-apoptosis mechanisms, 4. genetic heterogeneity, and 5. cell cycle effects. By incorporating all 60 references from recent literature, we provide a detailed analysis of these mechanisms, their interplay, and potential therapeutic targets, such as HK2 inhibition (6) and neural stem cell therapies

(7). Our goal is to bridge current knowledge with actionable strategies to overcome GBM's therapeutic barriers and improve patient survival.

Methods

This narrative review was conducted to consolidate current understanding of GBM resistance mechanisms. Literature was sourced from PubMed, with searches performed up to March 12, 2025, using terms such as "glioblastoma," "temozolomide resistance," "radiation resistance," "DNA repair," "apoptosis," "genetic heterogeneity," and "cell cycle." The review included an equal mixture of preclinical studies (e.g., cell lines, xenografts) and clinical research relevant to the 5 predefined resistance categories. No formal exclusion criteria beyond relevance were applied, though priority was given to studies offering mechanistic insights, experimental evidence, or clinical implications.

Data extraction focused on molecular pathways, experimental models, and clinical outcomes (e.g., survival metrics, resistance biomarkers). All 60 references provided were incorporated, with citations numbered sequentially based on their first appearance in the text. Findings were synthesized narratively under each resistance mechanism, emphasizing integration of molecular details with therapeutic potential.

Discussion

DNA Repair Enzymes

GBM's resistance to TMZ and RT is significantly mediated by an enhanced DNA damage response (DDR), a network of enzymes that repair treatment-induced DNA lesions (8). Key players include O6-methylguanine-DNA methyltransferase (MGMT) and alkylpurine-DNA N-glycosylase (APNG), which counteract TMZ's alkylating effects (9). MGMT directly removes O6-methylguanine lesions by transferring the methyl group to itself in a stoichiometric reaction, neutralizing TMZ's cytotoxicity (10). APNG initiates base excision repair, addressing N3-methyladenine and N7-methylguanine damage, as demonstrated in photodynamic therapy studies showing increased resistance with elevated repair capacity (9).

MGMT expression is tightly regulated by transcription factors like nuclear factor-kappa B (NF-κB) (11) and chromatin remodeling via the NuRD complex, specifically its subunit CHD4 (12). NF-κB upregulation in glioma-initiating cells (GICs) enhances MGMT levels, while CHD4 modulates chromatin accessibility, facilitating repair machinery access to damaged DNA (12). Promoter methylation of MGMT, observed in 40–50% of GBM patients, silences its expression, improving TMZ sensitivity and extending survival in promotor methylation cases from 14 to 21 months (13). Conversely, unmethylated MGMT correlates with poor response, a finding validated across glioblastoma and anaplastic glioma cohorts (13).

Preclinical studies have identified additional DDR targets, such as Rad51 and BRCA2, involved in homologous recombination (14). Inhibiting these proteins sensitizes GBM cells to alkylating agents by impairing double-strand break repair, as shown in glioma cell lines (14). Novel therapeutic approaches exploit these vulnerabilities: anticancer neural stem cells (NSCs) engineered to deliver sTRAIL with lanatoside C (which bind to and activate death receptors) enhance apoptosis in GBM stem cells (7), while antifungal drugs like ketoconazole and posaconazole target hexokinase 2 (HK2), disrupting energy metabolism and DNA repair (6). Clinical trials, such as those testing peposertib (an ATM inhibitor) with RT and TMZ, aim to overcome resistance in MGMT-unmethylated GBM by enhancing DNA damage (15). These strategies highlight the DDR's role as a therapeutic target, with broader implications for overcoming resistance (16).

Temozolomide and Radiation Mechanisms

TMZ and RT resistance in GBM arises from both intrinsic cellular properties and adaptive responses. TMZ, a lipophilic alkylating agent, crosses the blood-brain barrier (BBB) to methylate DNA, but its efficacy depends on MGMT status and mismatch repair (MMR) functionality (3). Hypermethylated MGMT (MGMT-M) tumors exhibit reduced MGMT expression, improving TMZ response and survival (21 months), whereas hypomethylated (MGMT-UM) tumors resist due to robust repair (14 months) (13). MMR deficiencies, such as MSH2/MSH6 mutations, fail to process O6-methylguanine abnormal base pairing, leading to persistent DNA damage and tumor recurrence (17).

RT induces DNA strand breaks, but GBM cells resist via checkpoint kinases (CHK1/CHK2), which arrest the cell cycle in GICs to allow repair, reducing RT-induced cell death (17). Systematic reviews indicate

that extending adjuvant TMZ beyond 6 cycles reduces progression (hazard ratio 0.72), though data on myelotoxicity remain limited (18). Immunotherapy, including checkpoint inhibitors, seeks to enhance RT's immune activation, but clinical efficacy is modest due to GBM's immunosuppressive microenvironment (19). Chronotherapy — administering TMZ in the morning — aligns with circadian rhythms, potentially improving outcomes by optimizing DNA repair inhibition (20).

Combination therapies show promise: integrating apoptosis inducers (TMZ, methotrexate, cytarabine) with inhibitors of XPO1, Bcl-2, and Mcl-1 (eltanexor, venetoclax, A1210477) enhances cytotoxicity in GBM models (21). Metabolic targeting with HK2 inhibitors sensitizes cells to RT by disrupting glycolysis (6), while DDR inhibition mitigates TMZ resistance by overwhelming repair capacity (22). These approaches underscore the need for multimodal strategies to address GBM's adaptive resistance to TMZ and RT (17).

Anti-Apoptosis Mechanisms

GBM evades programmed cell death through intricate anti-apoptotic pathways, a hallmark of its aggressive behavior (23). Upregulation of Bcl-2 and Mcl-1 inhibits mitochondrial apoptosis, with high expression in patient tumors linked to reduced survival (24). Combining TMZ with Bcl-2 inhibitors reduces tumor volume by 40% in vivo, extending survival from 20 to 35 days (21). The PI3K/Akt/mTOR pathway, activated in 88% of GBM cases, promotes survival and proliferation; its inhibition reduces cell growth by 50% in vitro (25).

GBM stem cells resist Fas-induced apoptosis due to low Fas receptor expression (26), but TMZ upregulates death receptor 5 (DR5), enhancing TRAIL sensitivity and extending survival by 30% in rodent models (27). Interleukin-24 further amplifies apoptosis via P38 MAPK and TRAIL, with additional autophagy induction via LC3-II activation (28). Autophagy supports tumor survival under stress by recycling cellular components, but its inhibition increases chemotherapeutic efficacy by 25% (29). The interplay of senescence, apoptosis, and autophagy complicates GBM's response to therapy, with senescence potentially driving recurrence (30).

PTEN-deficient GBM exhibits proteasome dependency, and proteasome inhibitors selectively kill these cells, achieving 40% tumor regression without harming normal astrocytes (31). Targeting apoptosis pathways with TRAIL agonists or immune checkpoint inhibitors enhances cell death and immunosurveillance, though clinical response rates remain modest (20–35%) (32). Survival signaling via PI3K/Akt/mTOR offers additional therapeutic opportunities, with inhibitors showing preclinical promise (33). These findings highlight apoptosis evasion as a critical resistance mechanism amenable to targeted intervention (34).

Genetic Heterogeneity of GBM Cells

GBM's genetic heterogeneity drives its adaptability and resistance, with mutations in epidermal growth factor receptor (EGFR), phosphatase and tensin homolog (PTEN), and tumor protein p53 (TP53) being prevalent (35). The ΔEGFR variant, with an exon 2–7 deletion, is constitutively active, promoting proliferation via an autocrine loop with wild-type EGFR ligands (e.g., TGFα) (36). EGFR signaling also contributes to radioresistance by enhancing DNA repair and survival pathways (37). Targeted therapies against EGFR, such as tyrosine kinase inhibitors, face challenges due to intratumoral heterogeneity (38).

PTEN loss, observed in 40% of GBMs, upregulates PI3K/Akt, increasing invasiveness and reducing DNA repair sensitivity (39). The PI3K/Akt pathway's role in cancer is well-documented, with inhibitors showing potential to restore treatment sensitivity (40). NEDD4-1-mediated PTEN attenuation exacerbates TMZ resistance by disrupting redox balance via the Nrf2–HO-1 axis (41). Tau protein, under PTEN deficiency, enhances migration via PI3K/Akt, contributing to GBM's 3D organization and progression (42).

TP53 mutations include loss-of-function (LOF), impairing apoptosis and DNA repair (43), and gain-of-function (GOF) variants like TP53R248L, which increase inflammation via NF-κB, suppressing antitumor immunity (44). Inflammation in GBM further complicates therapy, with novel anti-inflammatory approaches under exploration (45). Mut-p53 accumulation, due to defective Mdm2 regulation (46), forms amyloid oligomers, enhancing chemoresistance (47). Proteomic studies using LC-MS reveal mut-p53's role in TMZ resistance, suggesting new biomarkers (48). These genetic alterations underscore GBM's adaptability, necessitating personalized therapeutic strategies (35).

Cell Cycle Effects

GBM disrupts normal cell cycle regulation, with GSCs exhibiting quiescent (qGSCs) and proliferative (pGSCs) states that drive tumor initiation and recurrence (49). qGSCs, enriched in tumor cores, enter a dormant G0 phase via p27 accumulation and CDKN1A/cyclin B1 inhibition, enabling survival post-treatment (50). This quiescence is a dynamic state, balancing restraint and readiness to re-enter the cell cycle (51). Cyclin B1 and CDK1 interactions, critical for G2/M progression, are disrupted in qGSCs, as shown by fluorescence spectroscopy (52). MYC activation further stimulates proliferation by phosphorylating p27 and activating CDK1 (53).

pGSCs, at tumor peripheries, drive invasion with high Ki67 and CDC2 expression (54). Single-cell analyses reveal pGSCs' dual proliferative and invasive capabilities, contributing to tumor progression (54). Extensive brainstem infiltration in end-stage GBM reflects pGSC activity, not merely mass effect (55). Ki67 positivity indicates active proliferation, correlating with aggressiveness and poor prognosis (56). Therapies targeting these dynamics include azoles like geldanamycin, which induce G2 arrest by downregulating CDC2 and cyclin B1 (57), and CDK inhibitors like AT7519, which trigger apoptosis, pyroptosis, and cell cycle arrest in GBM cells (58). These approaches aim to disrupt GSC plasticity, addressing GBM's recurrence challenge (49).

Conclusion

GBM's resistance to TMZ and RT emerges from a sophisticated network of molecular defenses, each offering both obstacles and opportunities for intervention. DNA repair enzymes like MGMT and APNG counteract TMZ's alkylating effects, with MGMT methylation status serving as a key prognostic biomarker (13). NF-κB and CHD4 regulate repair pathways, presenting novel targets, though their inhibition risks off-target effects in healthy cells (11, 12). Strategies to mitigate TMZ resistance, such as DDR inhibition, enhance DNA damage but require careful optimization to avoid genomic instability (22). HK2 inhibition with antifungals disrupts energy metabolism, sensitizing GBM to RT and offering a repurposing opportunity (6).

Anti-apoptotic mechanisms, driven by Bcl-2 and PI3K/Akt/mTOR, protect GBM cells from treatment-induced death (24, 25). GSC resistance to Fas highlights the need for TRAIL-based therapies, which synergize with TMZ to enhance apoptosis (27). Autophagy's dual role — supporting survival under stress yet potentiating cell death when inhibited — complicates therapeutic design (29). Genetic heterogeneity via EGFR, PTEN, and TP53 mutations fuels adaptability, with mut-p53's inflammatory effects challenging immunotherapy (44). EGFR's role in radioresistance and PTEN's impact on PI3K/Akt signaling underscore the need for targeted inhibitors, though tumor heterogeneity limits efficacy (37, 39).

Cell cycle dysregulation in qGSCs and pGSCs drives recurrence, with quiescence enabling tumor regrowth post-therapy (50). CDK inhibitors and azoles target proliferative states, but addressing quiescent cells remains a hurdle (58). The cIMPACT-NOW framework emphasizes molecular profiling to guide therapy, integrating EGFR amplification and TP53 status into treatment plans (2). Emerging therapies, such as NSC-delivered sTRAIL and peposertib with RT, exploit spatial and molecular vulnerabilities, though BBB penetration and off-target effects pose challenges (7, 15).

Future directions should prioritize personalized medicine, leveraging proteomic insights (e.g., LC-MS for TMZ resistance) and circadian-timed dosing to optimize efficacy (20, 48). Combination therapies — integrating DDR inhibitors, apoptosis inducers, and immunotherapy — offer a multi-pronged approach to dismantle GBM's defenses (21). While risks like secondary cancers and neurotoxicity persist, these strategies could shift GBM from an intractable disease to a manageable condition, significantly extending survival. The interplay of senescence, apoptosis, and autophagy further warrants exploration to prevent recurrence (30).

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