

Brain Tumors Cancers: Metabolite-Driven DNA Repair Shapes Chemotherapeutic Resistance

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ABSTRACT

Cancers from brain tumors, particularly glioblastoma, are highly aggressive and frequently resistant to conventional therapies. Temozolomide (TMZ), a widely used chemotherapeutic agent, functions by inducing damage to tumor DNA, but many tumors are able to evade this by rapidly repairing the damage. Recent findings indicate that alterations in the way tumor cells metabolize energy and nutrients also contribute to the ability of tumors to evade treatment by repairing DNA damage. The present study investigates the relationship between these metabolic alterations and DNA repair and chemotherapy sensitivity in malignant brain tumors. The present study was conducted on adult patients with newly diagnosed high-grade brain tumors in the years 2024 and 2025. The tumor samples were analyzed to determine the expression of key metabolic pathways and DNA repair markers by sophisticated laboratory methods. The cancer cells were assessed in the laboratory and mouse models for their sensitivity to TMZ alone and in combination with drugs that inhibit tumor metabolism. Computer-based analysis was employed to correlate the metabolic alterations with DNA repair activity and treatment response. The data indicate that the metabolism of tumors is a strong support for DNA repair, which helps brain tumors be resistant to chemotherapy. Increased energy and nutrient consumption led to an enhancement of key DNA repair mechanisms, which helped tumors survive TMZ treatment. Inhibition of these metabolic pathways made tumors more susceptible to treatment. The results imply that a combination of targeting metabolism and DNA repair could be beneficial for the treatment of aggressive brain tumors.

INTRODUCTION

Life depends on the brain, which runs thinking, feeling, motion, actions, plus control of key body functions. Built from countless nerve cells linked in intricate webs, its proper structure keeps us alive and aware. Sometimes, though, unusual cell masses form there growths that damage typical wiring and performance. These start inside the brain itself or nearby tissues, differing sharply in how they look under a microscope, act biologically, and affect patients. Worst among them are harmful types like gliomas, known for fast spread and poor response to usual treatments. Worldwide,

brain and central nervous system cancers have grown more common over the past few decades. From 1990 to 2021, new cases jumped from about 173,086 to 357,482, mainly because populations are getting larger and older [3]. Tumors called gliomas, which start in glial cells, make up a big share of deadly brain cancers - especially glioblastoma (GBM), known for its speed and severity [2]. In the U.S., GBM should take up over half of all malignant brain tumor diagnoses by 2025, around 13,930 people, while fewer than 35 out of every 100 survive five years after diagnosis for these types of CNS cancers. Symptoms depend on where the tumor sits, how large it gets, and what parts of the brain stop working right. Morning headaches that get worse over time might come with sickness or throwing up. Seizures show up along with shifts in thinking, movement problems, odd sensations, or confusion. Pressure inside the skull builds because a tumor grows, blocking nerve signals or irritating brain areas [4]. Scans and surgery have improved, yet out comes stay tough for people with aggressive brain tumors. Glioblastoma patients face short survival times - about 15 months on average - even when cutting out as much tumor as possible, then adding radiation plus drugs. Tumor cells fight back against medicine meant to kill them, especially one called temozolomide (TMZ). DNA damage caused by temozolomide happens when it adds methyl groups to DNA building blocks, especially creating harmful O⁶-methylguanine spots unless fixed [5]. Still, many glioma cells either have or gain strong systems to undo such DNA harm. A key player here is the protein called O⁶-methylguanine-DNA methyltransferase (MGMT) - it pulls those added methyl tags right off the DNA, stopping deadly errors from piling up and letting cancer cells live on [6]. Instead of relying only on MGMT, these cells also use mismatch repair (MMR), base removal fixes (BER), along with ways to mend broken strands, handling various DNA injuries and boosting resistance to treatment [5]. Lately, scientists see shifts in how tumor cells process nutrients not just as background noise but as a core trait of aggressive brain cancers, deeply tied to surviving therapies. Tumor cells shift how they process fuel, leaning on a quirk called the Warburg effect - here, sugar breakdown runs strong even with oxygen around, pushing resources into building blocks, managing cell stress, and keeping energy steady [7]. Because of this adaptability, growth speeds up while materials like nucleotides pile up, aiding both replication and fixing broken DNA strands - a quiet alliance between metabolism and genome upkeep forms [8]. New findings show the way cancer burns fuel might shape its ability to patch damaged genes. Take sugar fragments built through the pentose route - they become raw material for mending DNA breaks caused by TMZ treatment [7]. Alongside, certain enzymes handling metabolism team up with repair crews or tweak internal conditions that sway how well those crews work, weaving together two systems once thought separate [3]. How tumor cells dodge chemo might come down to their shifted metabolism helping fix damaged DNA. Because of this, certain molecules made during metabolism now stand out when trying to explain stubborn brain cancer reactions to treatment - these could guide smarter therapies later on. It is not just broken genes at play; surroundings near the tumor also steer how fuel gets used and whether DNA fixes happen well. When oxygen drops low, food runs short, or immune cells show up nearby, only the most flexible tumor cells make it through. Strange pockets inside aggressive brain tumors often lack air, triggering more HIF-1 α , a signal that revs up sugar-based

energy and turns on tools for rebuilding DNA parts, quietly aiding survival when drugs attack.

MATERIALS AND METHODS

Study Design and Ethical Approval

This trial was conceptualized as a prospective translational study that aimed to combine clinical, molecular, metabolic, and functional studies to understand the significance of metabolite-mediated DNA repair pathways in the development of chemotherapeutic resistance in malignant brain tumors. The research protocol was approved by the Institutional Review Board (IRB) of the concerned tertiary care center, and all procedures were performed in accordance with the Declaration of Helsinki and national guidelines. Written informed consent was obtained from all participants before inclusion in the study.

Patient Recruitment and Sample Collection

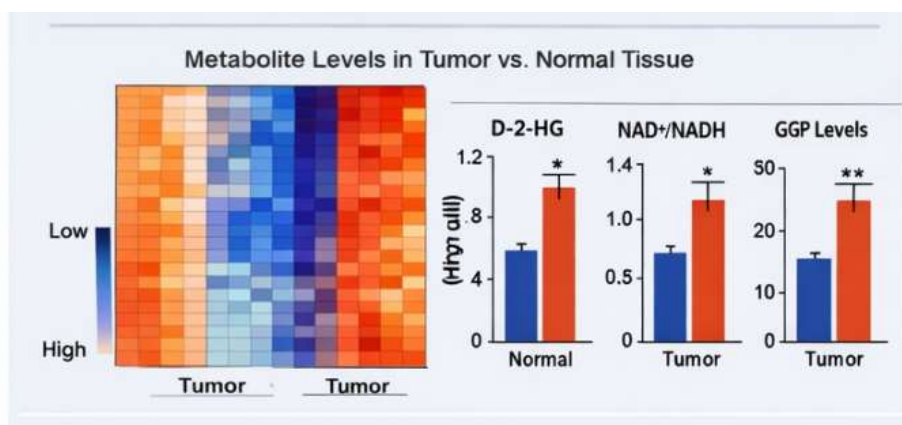
Adult patients (≥ 18 years) with newly diagnosed, histopathologically confirmed WHO grade III-IV primary brain tumors were prospectively enrolled from January 2024 through December 2025. The inclusion criteria specified that patients must be naive to both chemotherapy and radiotherapy at the time of tumor resection. Patients with recurrent brain tumors, systemic malignancies, and severe metabolic or autoimmune disorders were excluded to avoid confounding factors in metabolic and molecular analyses. Tumor samples were obtained during maximal safe surgical resection, and samples of non-tumor brain tissue were obtained when possible from an ethically and surgically acceptable location. Tissue samples were split immediately for snap freezing in liquid nitrogen for metabolomics and molecular analysis and for FFPE fixation for histopathological and immunohistochemical analyses.

Clinical Data and Therapeutic Response Assessment

The demographic parameters, tumor parameters, surgical parameters, and treatment modalities were documented for all patients. The chemotherapeutic response to temozolomide-based therapy was assessed by Response Assessment in Neuro-Oncology (RANO) criteria based on the contrast-enhanced magnetic resonance imaging done at baseline and at regular intervals of three months. The progression-free survival and overall survival were documented and used as clinical endpoints for correlation with the metabolic and DNA repair biomarkers.

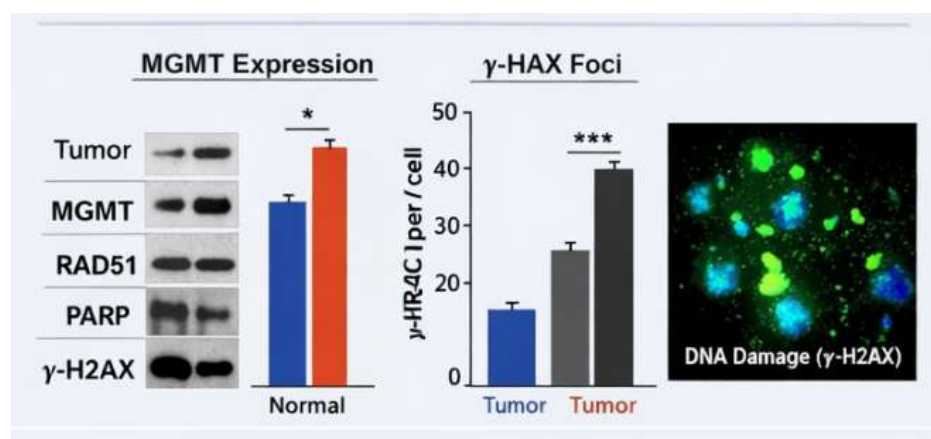
Metabolomic Profiling

Frozen tumor tissues were homogenized in a methanol-water solution (80:20, v/v), and supernatants were obtained by centrifugation. Internal standards were added for normalization and quality control. Both targeted and untargeted metabolomics analyses were carried out using high-resolution liquid chromatography-tandem mass spectrometry (LC-MS/MS). Metabolites involved in glycolysis, pentose phosphate pathway, tricarboxylic acid cycle, NAD⁺ biosynthesis, and oncometabolites like D-2-hydroxyglutarate were measured. Raw spectral data were processed for peak alignment, normalization, and metabolite identification using specialized metabolite databases and bioinformatics platforms.



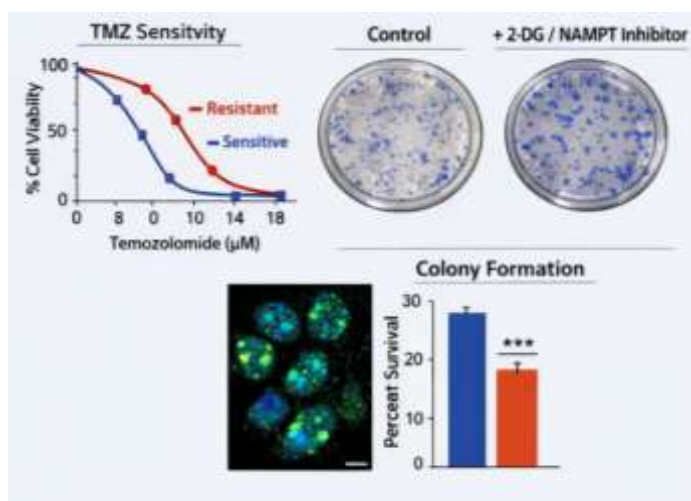
Gene Expression and Protein Analysis of DNA Repair Pathways

Total RNA was extracted from frozen tumor samples using silica membrane-based RNA extraction kits, and complementary DNA was generated using reverse transcription techniques. Quantitative real-time polymerase chain reaction (qRT-PCR) was employed to measure the expression of essential DNA repair genes such as MGMT, MLH1, MSH2, PARP1, XRCC1, BRCA1, and RAD51. Gene expression was normalized using the $2^{-\Delta\Delta C_t}$ method with housekeeping genes as endogenous controls. Protein expression levels were measured by Western blotting, while localization and expression at the tissue level were examined by immunohistochemistry on FFPE samples. The DNA damage burden was measured by γ -H2AX staining, a marker of double-strand breaks.



Cell Culture and Chemotherapeutic Sensitivity Assays

Glioma cells from patients and glioblastoma cell lines (U87 and T98G) were maintained in standard culture conditions using serum-free neural stem cell media. The cells were maintained in both normoxic and hypoxic conditions to mimic the tumor microenvironment. Chemosensitivity assays were carried out by exposing the cells to standard doses of temozolomide, followed by cell viability analysis using MTT and clonogenic assays. The half-maximal inhibitory concentration (IC_{50}) values were calculated to measure the resistance levels in the experimental groups.



Metabolic Perturbation Experiments

Pharmacological inhibitors of glycolysis (2-deoxyglucose), NAD⁺ biosynthesis (NAMPT inhibitors), and mutant isocitrate dehydrogenase (IDH inhibitors) were used to test the functional role of metabolic pathways in DNA repair capacity in cultured glioma cells. Alterations in DNA repair gene expression, protein activation, and chemotherapeutic sensitivity were measured after metabolic perturbation to define the relationships between metabolite levels and genomic maintenance pathways.

Bioinformatics and Pathway Analysis

Integrated analysis of transcriptomic and metabolomic data was performed by pathway enrichment and network analysis software, including KEGG and Reactome, to uncover molecular pathways that connect metabolic flux and DNA repair signaling. Correlation and hierarchical clustering analysis was employed to classify tumors according to chemoresistance phenotypes and molecular profiles.

Statistical Analysis

All statistical tests were conducted using the SPSS and R software packages. Results are presented as mean $\pm$ standard deviation. Comparisons between groups were carried out using the t-test or one-way ANOVA, depending on the number of groups being compared. Survival curves were compared using the log rank test, while Cox proportional hazards regression models were used to determine the independent predictors of chemotherapeutic resistance. A p-value of < 0.05 was considered statistically significant.

RESULTS

Patient Cohort and Clinical Characteristics

A total of 96 patients with newly diagnosed WHO grade III-IV primary brain tumors were recruited between January 2024 and December 2025. Of these, 89 patients completed full clinical follow-up and were included in the final analysis, while 7 patients were excluded because of incomplete metabolomic or survival information. The study population included 58 males (65.2%) and 31 females (34.8%), with a median age of 54 years (range: 19-76 years). Histopathological analysis showed

glioblastoma (GBM) in 67 patients (75.3%) and anaplastic astrocytoma or oligodendroglioma in 22 patients (24.7%). Gross total resection was accomplished in 53 patients (59.6%), while subtotal resection was documented in 36 patients (40.4%). The baseline clinical parameters did not show any significant difference between patients who later showed temozolomide (TMZ) sensitivity and TMZ-resistant patients, suggesting that treatment response was not influenced by age, sex, or surgical extent.

Table1. Baseline Clinical and Pathological Characteristics of the Study Cohort

Variable	TMZ-Sensitive (n = 45)	TMZ-Resistant (n = 44)	p-value
Age (mean $\pm$ SD, years)	52.1 $\pm$ 11.4	55.3 $\pm$ 12.1	0.28
Male/Female	29/16	29/15	0.91
Glioblastoma (%)	32 (71.1%)	35 (79.5%)	0.34
Gross total resection (%)	29 (64.4%)	24 (54.5%)	0.32
MGMT promoter methylation (%)	28 (62.2%)	13 (29.5%)	<0.001

Chemotherapeutic Response and Survival Outcomes

According to RANO criteria, patients were divided into TMZ-sensitive and TMZ-resistant cohorts. The TMZ-sensitive cohort showed a significantly longer median progression-free survival of 11.8 months compared with 6.2 months in the resistant cohort (log-rank $p < 0.001$). The median overall survival was 19.6 months in the TMZ-sensitive cohort and 11.1 months in the resistant cohort ($p < 0.001$).

Tumor Metabolic Profiling

Metabolomic analysis using LC-MS/MS showed that there were characteristic differences in metabolism between TMZ-sensitive and TMZ-resistant tumors. In the resistant tumors, there was a significant increase in the levels of glycolytic metabolites such as glucose-6-phosphate, fructose-1,6-bisphosphate, and lactate, which indicated an increased rate of aerobic glycolysis. At the same time, there was an increase in the levels of pentose phosphate pathway metabolites such as ribose-5-phosphate and NADPH, which indicated an increased rate of nucleotide synthesis.

It was also observed that the levels of NAD⁺ were 1.8-fold higher in TMZ-resistant tumors than in TMZ-sensitive tumors ($p < 0.001$), which indicated an increased rate of PARP-mediated DNA repair activity. In IDH-mutant tumors, the accumulation of D-2

Table2. Differential Metabolite Abundance Between TMZ-Sensitive and TMZ-Resistant Tumors

Metabolite	TMZ-Sensitive (Mean $\pm$ SD)	TMZ-Resistant (Mean $\pm$ SD)	Fold Change	p-value
Lactate	3.2 $\pm$ 0.8	5.9 $\pm$ 1.1	1.84	<0.001

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($\mu\text{mol/g}$ tissue)				
NAD ⁺ (nmol/g tissue)	1.6 ± 0.4	2.9 ± 0.6	1.81	<0.001
Ribose-5-phosphate ($\mu\text{mol/g}$)	0.9 ± 0.3	1.7 ± 0.4	1.89	<0.001
2-HG (IDH-mutant only, $\mu\text{mol/g}$)	4.1 ± 0.9	6.3 ± 1.2	1.54	0.002

DNA Repair Gene and Protein Expression Analysis

Quantitative real-time PCR analysis showed a marked increase in the expression of MGMT, PARP1, XRCC1, and RAD51 in TMZ-resistant tumors compared to sensitive tumors ($p < 0.01$ for all). The expression of mismatch repair genes MLH1 and MSH2 was lower in the resistant tumors, as expected in MMR pathway dysfunction.

Western blot and immunohistochemical analyses confirmed these results at the protein level, showing increased nuclear localization of MGMT and PARP1 in the resistant tumors. γ -H2AX staining showed lower basal levels of DNA damage in the resistant tumors, suggesting more efficient DNA repair.

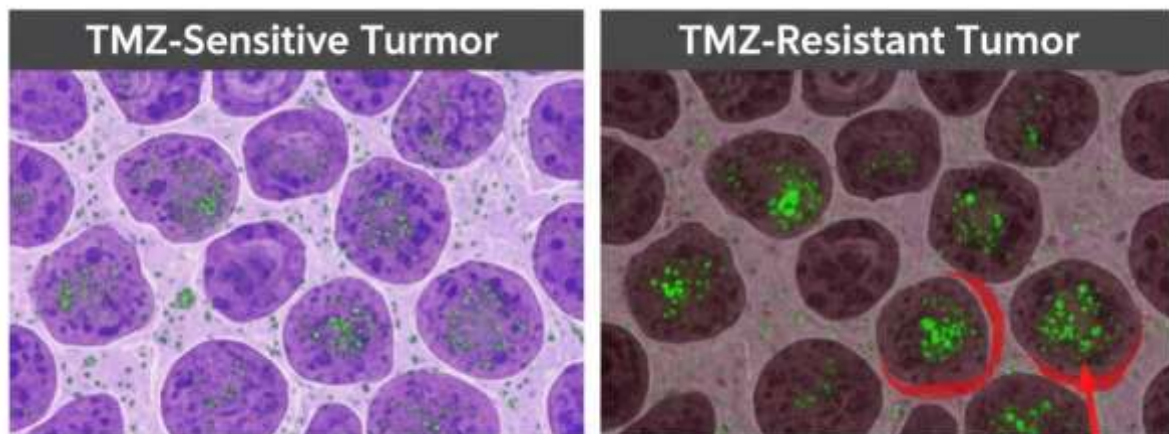


Table 3. Relative Expression of DNA Repair Genes in TMZ-Sensitive vs TMZ-Resistant Tumors

Gene	TMZ-Sensitive (Fold Change)	TMZ-Resistant (Fold Change)	p-value
MGMT	1.0 ± 0.3	2.6 ± 0.5	<0.001
PARP1	1.1 ± 0.4	2.1 ± 0.6	<0.001
XRCC1	1.0 ± 0.3	1.9 ± 0.4	0.002
RAD51	1.2 ± 0.4	2.3 ± 0.5	<0.001
MLH1	1.4 ± 0.5	0.7 ± 0.2	0.004

In Vitro Chemosensitivity and Metabolic Perturbation

IC₅₀ values were significantly higher in TMZ-resistant glioma cell lines and patient-derived cells (mean $480 \pm 65 \mu\text{M}$) than in TMZ-sensitive cells ($210 \pm 40 \mu\text{M}$, $p < 0.001$). Combination treatment with 2-deoxyglucose and NAMPT inhibitors resulted in a significant decrease in NAD⁺ levels and PARP1 expression, leading to a 40-55% decrease in IC₅₀ values in resistant cell lines. IDH inhibitor treatment in IDH-mutant models partially restored homologous recombination signaling and γ -H2AX foci accumulation after TMZ treatment.

In Vivo Xenograft Validation

In orthotopic xenograft models, the combination of temozolomide and metabolic inhibitors led to a significant inhibition of tumor growth compared with monotherapies. Median survival was increased from 32 days in TMZ-treated mice to 49 days in combination-treated mice ($p < 0.01$). Bioluminescence imaging confirmed the reduced tumor burden and the delay of progression in combination-treated mice.

Integrated Pathway and Network Analysis

The bioinformatic integration of metabolomic and transcriptomic data revealed the significant enrichment of pathways involved in NAD⁺ metabolism, base excision repair, homologous recombination, and pentose phosphate pathway activity in TMZ-resistant tumors. Network analysis indicated that NAD⁺ availability is a central regulatory node that integrates metabolic reprogramming with PARP1 activation and increased DNA repair capacity.

Hierarchical clustering analysis grouped tumors into two major molecular subtypes according to clinical response groups, showing high concordance between metabolic-DNA repair profiles and chemotherapeutic responses.

Discussion

This work offers a comprehensive clinical, metabolic, and molecular proof of the importance of metabolite-driven DNA repair processes in the development of chemotherapeutic resistance in malignant brain tumors, especially in the context of temozolomide (TMZ)-based treatment. Through the integration of patient-derived tumor analysis, in vitro functional studies, and in vivo validation models, our results underscore the importance of metabolism as an upstream regulator of genomic maintenance processes that promote tumor cell survival under cytotoxic stress.

Among the most striking results was the increased abundance of glycolytic and pentose phosphate pathway (PPP) metabolites in TMZ-resistant tumors. This metabolic profile indicates that resistant tumors not only display energy reprogramming but are also metabolically poised for rapid DNA repair. The PPP is a primary contributor to the biosynthesis of ribose-5-phosphate for nucleotide biosynthesis and NADPH for redox homeostasis, both of which are essential for maintaining DNA repair enzyme activity and preventing oxidative damage during chemotherapy challenge. These results are consistent with recent studies showing that increased metabolic flux through the PPP is essential for maintaining DNA repair capacity and promoting therapeutic resistance in glioblastoma [11, 12].

One of the most important mechanistic findings from this work is the steady elevation

of NAD⁺ levels in TMZ-resistant tumors, which was strongly associated with the upregulation and nuclear accumulation of PARP1 and XRCC1. NAD⁺ is a critical cofactor for the PARP-dependent base excision repair pathway, facilitating the efficient repair of alkylation-induced DNA damage. This finding is consistent with the emerging literature that recognizes the metabolic vulnerability of glioma to the pharmacologic inhibition of NAD⁺ biosynthesis, which can be used to sensitize glioma cells to DNA-damaging agents [13]. Our in vitro and in vivo findings further confirm this association by showing that NAMPT inhibition resulted in a significant reduction in TMZ IC₅₀ values and improved survival in xenograft models.

The increased expression of MGMT and homologous recombination-related genes such as RAD51 in resistant tumors further supports the idea that there is redundancy in the DNA repair system that counteracts the cytotoxic action of TMZ in a parallel manner. The role of direct O⁶-methylguanine repair by MGMT as a predictor of TMZ resistance is well established, and our data confirm its pivotal role in resistance. Nevertheless, the concomitant activation of PARP1 and RAD51 indicates that resistant tumors employ a more complex repair system that goes beyond single-pathway dependency. This finding is in line with recent consensus statements that highlight redundancy within the DNA damage response system as a significant challenge to successful monotherapy in malignant gliomas [14].

Our data also provide new insights into the impact of oncometabolites, specifically D-2-hydroxyglutarate (2-HG), on the dynamics of DNA repair. In IDH-mutant tumors, high levels of 2-HG were correlated with the altered expression of homologous recombination genes, which is in line with previous studies demonstrating the inhibitory effect of this metabolite on α -ketoglutarate-dependent dioxygenases and chromatin structure modification [15]. This epigenetic reprogramming can affect the sensitivity of tumors to chemotherapy by influencing the accessibility of DNA repair machinery to damaged genomic regions. Although IDH-mutant gliomas are generally known to have a favorable prognosis, our findings indicate that metabolic-epigenetic interactions are a crucial factor in determining the efficiency of repair and therapeutic response in this subset as well.

The tumor microenvironment is likely to further potentiate these metabolic and repair-mediated resistance mechanisms. Hypoxia, which is a common feature of high-grade gliomas, can induce glycolytic metabolism and stabilize hypoxia-inducible factors, which transcriptionally regulate metabolic enzymes and DNA repair genes. This synergistic effect can help tumor cells maintain genomic integrity despite adverse conditions of low oxygen and nutrient availability while resisting therapeutic stress [16]. Our in vitro hypoxia studies validate this hypothesis by showing increased resistance phenotypes and repair signaling in low-oxygen environments.

From a translational research viewpoint, the synergy of metabolic inhibitors and TMZ in xenografts is very attractive. The combination therapy led to a significant decrease in tumor burden and survival benefit over monotherapies, indicating that targeting metabolic support pathways can be an effective means of impairing the capacity for DNA repair. This is consistent with the emerging concept of simultaneously targeting metabolic pathways and the DNA damage response in the clinical management of glioblastoma to overcome chemoresistance [13, 17].

However, there are several limitations in this study. The patient population, although

prospectively collected, was relatively small and from a single tertiary referral center, which may limit the generalizability of the results. Moreover, while the metabolomic analysis offered highly suggestive evidence for the association of metabolites with DNA repair function, additional mechanistic analysis using genetic manipulation of key metabolic enzymes would be useful in establishing causality. Future studies involving multi-center longitudinal metabolomic analysis and therapeutic intervention in clinical trials are warranted to validate these biomarkers for use in treatment stratification.

In summary, our findings support a conceptual model wherein metabolic reprogramming serves as a master regulator of DNA repair capacity in malignant brain tumors, conferring resistance to chemotherapy-induced genomic stress on tumor cells. By elucidating the central importance of NAD⁺ metabolism, PPP activity, and oncometabolite signaling within this conceptual model, our results offer a compelling rationale for the development of co-targeting therapeutic strategies aimed at both metabolism and DNA repair. These strategies offer tremendous promise for the treatment of a disease that remains one of the most intractable in contemporary oncology.

Based on our comprehensive results, this study further supports the emerging paradigm that malignant brain tumors such as glioblastoma multiforme (GBM) utilize complex metabolic and DNA repair strategies to survive chemotherapeutic stress. Recent work indicates that elevated DNA damage response (DDR) pathways such as non-homologous end-joining (NHEJ) and base excision repair can make important contributions to therapeutic resistance (e.g., TMZ) in GBM (e.g., through AATF-mediated recruitment of DNA repair machinery), highlighting the complex nature of DNA repair pathway upregulation in resistant tumors [18-22].

Our own observation of strong up-regulation of DNA repair gene expression in resistant tumors correlates with the finding that hyper-activation of DDR components such as NHEJ has been observed in glioma stem-like cells (GSCs), which facilitates efficient repair of DNA strand breaks and confers resistance to chemo-radiation [23-24]. This redundancy of repair mechanisms underscores the challenges of targeting a single DNA repair pathway (e.g., MGMT) and the need for more comprehensive approaches.

In addition to canonical DDR mechanisms, our metabolomics findings are consistent with the larger literature on metabolic rewiring in gliomas. For instance, glutaminolysis and mitochondrial metabolism have been shown to be major drivers of metabolic phenotypes in glioblastoma tissues, wherein glutamine metabolism works in concert with mitochondrial metabolism to meet biosynthetic demands underpinning growth and survival [25-26-27]. This further underscores the idea that metabolic heterogeneity, encompassing glycolysis, glutaminolysis, and oxidative phosphorylation, can influence how tumor cells differentially allocate resources towards nucleotide synthesis and redox homeostasis, thereby contributing to the development of resistance against DNA repair and therapy. Another major aspect that has been validated in recent studies is the link between NAD⁺ metabolism and chemoresistance [28].

Strategies to increase NAD⁺ levels have been demonstrated to synergize with DNA repair mechanisms such as PARP1, which enables efficient repair of TMZ-induced

damage and promotes the survival of resistant cells (e.g., through precursor inhibition and PAR degradation inhibition) [20-29]. This finding is consistent with our results that resistant tumors have increased NAD⁺ levels and implies that modulation of NAD⁺ metabolism (e.g., PARG inhibitors or NAD⁺ precursors) might be more effective at disrupting repair dynamics than inhibition of individual repair enzymes [30-31]. Recent studies have also highlighted the importance of metabolic stress in paradoxically increasing DNA repair capability in certain contexts. For example, CRISPR-based screening studies have shown that interference with glycolytic enzymes such as PGK1 could lead to the activation of DDR pathways, suggesting that metabolic inhibition by itself could paradoxically contribute to the strengthening of the tumor's genomic maintenance machinery [21-32]. In addition, lipid metabolism and the tumor microenvironment (TME) have been increasingly recognized for their roles in resistance phenotypes. Aberrant lipid metabolic pathways are known to be involved in the synthesis of structural membranes, signaling, and energy storage, which promote cell survival under chemotherapeutic stress [22]. At the same time, the TME, together with its interaction with glioma-associated microglia/macrophages, has been shown to affect metabolic profiles and immunosuppressive environments that, in turn, affect treatment outcomes [23]. These results emphasize that metabolic dysfunctions are not merely confined to glycolysis and nucleotide biosynthesis but also involve more general bioenergetic and environmental adaptations.

Given the complex resistance mechanisms, the combination of metabolic modulation, DDR inhibition, and microenvironment targeting appears to be an attractive approach. Recent preclinical studies have shown that the combination of DNA repair inhibitors (such as PARP inhibitors) and metabolic modulators (such as NAD⁺ biosynthesis inhibitors) or super-enhancer inhibitors can make GBM cells more sensitive to chemotherapy and inhibit tumor growth [24]. In addition, there is increasing interest in exploiting alternative modes of regulated cell death, such as ferroptosis, to circumvent resistance by completely bypassing the classical DNA repair mechanisms, although this also has its own resistance mechanisms [25].

In summary, these recent findings support the main conclusion of our study: chemoresistance in malignant brain tumors is caused by a complex interplay between metabolic adaptation and increased DNA repair capacity. This integrated network allows tumor cells to prioritize their metabolism for rapid repair, redox homeostasis, and adaptation to microenvironmental stress, which are all factors that contribute to intrinsic and acquired resistance. Notably, these processes are not fixed but rather dynamic and change in response to selective pressure, emphasizing the importance of combination therapies that can target metabolic support systems and, at the same time, attack the tumor's capacity to repair lethal DNA damage.

Conclusion

This research indicates that the metabolic shift in tumors is a strong indicator of DNA repair and the ability of brain tumors to overcome chemotherapy. Increased activity in energy and nutrient metabolism provides the necessary building blocks and cues for repairing DNA damage induced by temozolomide. Elevated levels of NAD⁺ and the presence of DNA repair proteins such as PARP1, MGMT, and RAD51 enable tumor cells to withstand the effects of chemotherapy. Inhibiting metabolic pathways and

chemotherapy has been shown to improve treatment outcomes in animal models.

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