Narrative Review Article

Glucose Metabolism and Antioxidant Alterations in Glioma Stem Cells Facilitating Glioblastoma Recurrence

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ABSTRACT

Glioblastoma (GBM) is the most aggressive primary brain tumor in adults. Its poor prognosis largely arises from its tendency to recur despite standard treatment with surgery, radiotherapy, and temozolomide. Glioblastoma stem cells (GSCs) are a major driver of recurrence because they possess stem-like properties and can regenerate the tumor after resisting treatment. Increasing evidence indicates that metabolic reprogramming within GSCs supports their survival following therapy. GSCs can switch between glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) in response to therapy-induced stress. Unlike bulk GBM cells, which predominantly rely on aerobic glycolysis known as the Warburg effect, GSCs can be glycolytic, OXPHOS-dependent, or hybrid, and can transition between these states under stress. Furthermore, the ability of GSCs to survive and recur also depends on antioxidant pathways that counteract therapy-induced oxidative stress. Key mechanisms include activation of the NRF2 pathway and upregulation of the glutathione and thioredoxin systems. This review synthesizes current literature to highlight how alterations in glucose metabolism and antioxidant reprogramming in GSCs contribute to GBM recurrence. It also discusses key therapeutic challenges, including intratumoral heterogeneity, metabolic state switching, limited drug delivery across the blood-brain barrier, and the risk of toxicity when disrupting metabolic pathways required by normal neural cells.

Keywords: glioblastoma stem cells; metabolic reprogramming; antioxidant pathways; Warburg effect; NRF2 pathway

INTRODUCTION

Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor in adults and is classified by the World Health Organization (WHO) as a grade IV astrocytic glioma (1-2). It accounts for 49% of all primary malignant tumors of the central nervous system and carries a very poor prognosis, with a 5% 5-year survival rate and death typically occurring 15-16 months after diagnosis (3-4). This poor outcome is largely due to the almost inevitable recurrence of GBM after treatment. Standard treatment for GBM consists of the Stupp protocol, which combines surgical resection with fractionated radiotherapy and adjuvant temozolomide chemotherapy. However, this approach is not curative, and nearly all patients experience tumor recurrence (5-7). Furthermore, GBM's heterogeneous nature and immunosuppressive tumor microenvironment limit the effectiveness of targeted and immune-based therapies (8-9).

The tumor microenvironment (TME) facilitates GBM

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recurrence. Hypoxic regions within GBM, characterized by low oxygen levels, are resistant to radiotherapy because oxygen is required to stabilize radiation-induced DNA strand breaks. Normally, cells are vulnerable to radiotherapy because it causes DNA damage that is made irreversible by oxygen fixation (10). Moreover, hypoxia promotes the expression of HIF-1 and DNA repair enzymes. Consequently, not only is the initial DNA damage induced by radiation reduced, but tumor cells are also better equipped to repair any damage that does occur. In addition, the blood-brain barrier (BBB) hinders effective GBM treatment by preventing sufficient drug concentrations from reaching residual tumor cells (11-12).

GBM's tumor microenvironment (TME) is highly immunosuppressive and contains very few functional T cells. As a result, immune checkpoint inhibitors that act by reactivating suppressed anti-tumor T cells have demonstrated minimal benefit in GBM (13). Even when T cells are present in glioblastoma, their function is suppressed by immunosuppressive cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). In addition, tumor cells and immune cells express multiple immune checkpoint molecules, such as PD-L1, CTLA-4, and TIM-3, which further restrain T-cell activation. Beyond checkpoint signaling, the GBM TME expresses immunosuppressive metabolic enzymes, including indoleamine 2,3-dioxygenase (IDO) and arginase, primarily produced by tumor cells. IDO depletes the essential amino acid tryptophan and generates kynurenine, both of which suppress T-cell proliferation and function, while arginase depletes arginine, another amino acid required for T-cell activation. These mechanisms drive T-cell anergy, a state in which immune cells fail to respond effectively to tumor antigens (14).

In particular, within the TME, glioblastoma stem cells (GSCs) are a major driver of recurrence and therapy resistance. They are a subpopulation of tumor cells with stem-like properties that contribute to cellular heterogeneity. GSCs generate a heterogeneous mixture of cells and cellular states, producing a highly variable cellular composition within each tumor and allowing it to continuously survive, adapt, and resist therapy (15-16). Single-cell RNA sequencing studies have revealed that GBM cells can exist in multiple subtypes, including proneural, classical, and mesenchymal, within the same tumor (17). For instance, GSCs have been observed to transition between a proneural subtype, which is more proliferative but therapy-sensitive, and a mesenchymal subtype, which is more invasive and therapy-resistant (18-19). Mesenchymal transition is one mechanism by which tumors resist therapy (20). Standard treatments can kill most tumor cells, but GSCs often survive. After therapy, the tumor microenvironment can become even more conducive to GSC expansion. Dying tumor cells release factors that activate microglia and astrocytes, which subsequently secrete growth factors that promote GSC proliferation and tumor regeneration.

Existing research has characterized the cellular and molecular features of GBM, including heterogeneity and signaling pathways (21-22). While metabolism is increasingly recognized as a driver of therapy resistance, the metabolic reprogramming that occurs specifically within glioblastoma stem cells during recurrence remains incompletely understood (23). Understanding GSC metabolism is critical because these cells survive therapy-induced stress and regenerate the tumor (24). Emerging evidence indicates that GSCs undergo metabolic adaptations that support proliferation and phenotypic plasticity in the post-treatment tumor microenvironment (25).

This review focuses specifically on alterations in glucose metabolism and antioxidant pathways in GSCs. Other metabolic pathways, including lipid and amino acid metabolism, also contribute to GSC function but lie beyond the scope of this paper.

ALTERATIONS IN GLUCOSE METABOLISM IN GLIOMA STEM CELLS

Alterations in GSC glucose metabolism contribute to therapy resistance and, ultimately, GBM recurrence. In bulk GBM cells, a hallmark of glucose metabolism is the Warburg effect, defined as the preference for aerobic glycolysis despite the presence of oxygen. Under normal physiological conditions, cells synthesize most of their ATP through oxidative phosphorylation (OXPHOS). Tumor cells favor glycolysis because it enables rapid ATP generation and supports proliferation. Consequently, GBM cells increase glucose uptake, much of which is converted into lactate. Studies have reported increased expression of glucose transporters (GLUT1 and GLUT3), upregulation of key glycolytic enzymes (HK2, PFKFB3, and PKM2), and elevated lactate production (26-30).

Glycolytic reprogramming in GSCs

Bulk tumor cells use the Warburg effect, whereas GSCs have more metabolic plasticity (Figure 1). While bulk GBM cells depend on aerobic glycolysis,

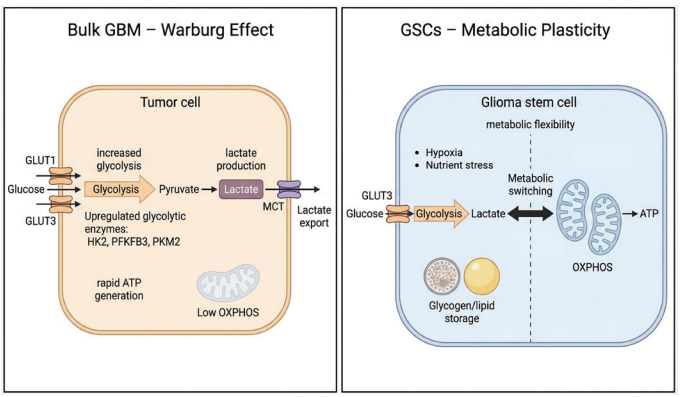

Figure 1. Metabolic differences between bulk glioblastoma (GBM) cells and glioma stem cells (GSCs). *Bulk GBM cells rely primarily on aerobic glycolysis (Warburg effect), whereas GSCs exhibit metabolic flexibility, switching between glycolysis and oxidative phosphorylation (OXPHOS) under stress conditions such as hypoxia. This metabolic plasticity supports survival after therapy and contributes to tumor recurrence.*

many GSCs can shift toward OXPHOS under certain conditions. However, GSCs display marked metabolic flexibility and can retain or upregulate glycolytic pathways under specific microenvironmental conditions, particularly hypoxia and nutrient stress. This flexibility enables continued glucose utilization and metabolic adaptation following therapy, thereby facilitating proliferation and tumor repopulation during recurrence.

Under hypoxic or glucose-restricted conditions, as studied by Fidoamore *et al*. (2017), patient-derived GBM neurospheres enriched for GSCs showed upregulation of glucose transporters, particularly GLUT3, leading to enhanced glucose uptake and increased glycogen and lipid storage for more efficient glucose use. In this study, tumor cells obtained from glioblastoma patients were grown as neurospheres and exposed to hypoxic conditions to mimic the tumor microenvironment. Researchers then measured GLUT3 levels and glucose uptake using western blotting and fluorescent staining techniques (31). These findings suggest that GSCs can enhance glycolytic capacity to sustain energy production under hostile tumor microenvironmental conditions, a feature that supports survival after therapy. However, these conclusions were primarily based on preclinical in vitro experiments.

Sustaining glycolysis and metabolic activities in GSCs

To sustain glycolysis and related metabolic activity, GSCs also rely on overexpression of mitochondrial-cytosolic shuttle systems that transfer NADH and support mitochondrial ATP synthesis. Lv *et al*. (2024) found that GSCs exhibit elevated activity of the malate-aspartate shuttle (MAS) and increased expression of mitochondrial MDH2, an enzyme required for this shuttle. Using patient-derived GSC cultures, the authors applied CRISPR/Cas9 to knock out MDH2 and used RNA sequencing and m6A MeRIP-seq to examine how MDH2 regulates metabolism and gene expression. They also validated the findings in orthotopic mouse xenograft models. When MDH2 was inhibited, GSC proliferation and self-renewal were impaired, and tumor growth was reduced (32).

Furthermore, a recent study by Zhou *et al*. (2025) connects glycolysis to epigenetic and paracrine regulation (33). The authors demonstrated that lactate derived from glycolysis modifies the RNA-binding protein PTBP1 through lysine lactylation, thereby enhancing its RNA-binding capacity. Using patient-derived glioma stem cells, proteomic analysis to detect lactylated proteins, and RNA-binding assays, the researchers showed that this process stabilizes PFKFB4 mRNA and increases glycolysis.

Similarly, GSCs secrete extracellular vesicles (EVs) that transfer miRNAs into neighboring glioma cells, suppressing PTEN and activating PI3K/Akt signaling. This increases glycolytic enzyme activity, including PFK1 and LDHA, and elevates lactate production in recipient cells. The resulting increase in lactate acidifies the microenvironment and promotes invasion and angiogenesis (34-35).

OXPHOS reprogramming in GSCs

As mentioned previously, some subpopulations of GSCs also engage in, and may even depend on, mitochondrial oxidative phosphorylation (OXPHOS). Some GSCs consume high amounts of glucose and produce large amounts of lactate, representing a "glycolytic" phenotype, whereas others show higher oxygen consumption and greater ATP content, representing a mitochondrial or OXPHOS-dominant phenotype (26, 36).

One of the earliest studies comparing GSCs with non-stem glioma cells was conducted by Vlashi *et al*. The authors reported that GSCs consumed less glucose and produced less lactate than other tumor cells while maintaining higher ATP levels (37). These findings suggested that OXPHOS may provide advantages such as enhanced therapy resistance, cellular quiescence, and survival in nutrient-limited microenvironments.

A recent study by Brisudova *et al*. demonstrated that mitochondrial respiration is essential for glioblastoma tumor growth in vivo, showing that GBM cells lacking mitochondrial DNA were unable to form tumors unless they received mitochondria from the host (38).

Beyond tumor initiation, OXPHOS has been linked to therapy resistance in GSCs. A study by Burban *et al*., using the OXPHOS inhibitor mubritinib, showed that pharmacological suppression of mitochondrial respiration sensitized patient-derived GSCs to irradiation. The authors measured effects on cell growth, stemness markers, and apoptosis, and they performed RNA sequencing to examine transcriptional changes after treatment. GSCs that relied on OXPHOS maintained ATP production and survived radiation-induced stress, whereas OXPHOS inhibition enhanced cell death. In the same study, orthotopic mouse xenograft models treated with mubritinib showed an approximately threefold decrease in luciferase activity, a measure of tumor burden, along with improved survival. These results indicate that mitochondrial respiration enables GSCs to withstand genotoxic therapies and contributes to their persistence following treatment (39).

Even during proliferation, single-cell and molecular analyses support an association between elevated OXPHOS activity and aggressive GBM phenotypes. Liu *et al*. (2024) analyzed single-cell RNA sequencing datasets from glioblastoma tumors to identify cellular subpopulations and their metabolic profiles, identifying a highly proliferative GBM subpopulation enriched in G2/M-phase cells that exhibited elevated OXPHOS pathway activity. They further validated these findings by performing NFYB knockdown experiments in glioblastoma cell lines, showing that reducing NFYB decreased OXPHOS activity and suppressed cell proliferation. This metabolic state was regulated by the transcription factor NFYB, whose knockdown significantly reduced proliferation, suggesting that mitochondrial metabolism may drive tumor growth. These findings indicate that OXPHOS upregulation is not restricted to quiescent GSCs but may also support proliferation in aggressive tumor subsets (40). In addition, disruption of mitochondrial regulators has been shown to impair stemness and tumor initiation (41).

Taken together, OXPHOS reprogramming in GSCs primarily supports survival and quiescence while preserving the ability to recur and proliferate. OXPHOS provides metabolic flexibility that enables GSCs to endure therapeutic stress and recur after treatment.

ENHANCED ANTIOXIDANT PATHWAYS

Beyond energy metabolism, the ability of glioma stem cells to survive and recur also depends on antioxidant pathways that counteract therapy-induced oxidative stress (42).

Reactive oxygen species (ROS) are present in healthy brain tissue as by-products of aerobic respiration. ROS include oxygen-derived molecules such as superoxide (O2-·), hydrogen peroxide (H2O2), and hydroxyl radical (·OH) (43-44). They are mainly generated by the mitochondrial electron transport chain, but they can also arise from endogenous sources such as peroxisomal metabolism and from exogenous sources such as ionizing radiation (45-46). At low to moderate levels, ROS can activate signaling pathways, including MAPK and NF-kB, that are involved in immune and stress responses (47-48).

In GBM cells, substantially higher levels of ROS are produced, causing oxidative stress. However, GBM cannot tolerate unchecked oxidative stress. Standard treatments (radiation and temozolomide) exploit this and kill tumor cells via DNA damage, mediated through increased ROS (49-50).

To prevent ROS from reaching damaging concentrations, cells rely on antioxidant systems that include both enzymatic and non-enzymatic antioxidants. For instance, superoxide dismutases (SODs) convert superoxide into H2O2, which is then detoxified by catalase or by glutathione peroxidases in peroxisomes. These enzymes are supported by small-molecule antioxidants such as glutathione (GSH), thioredoxin (Trx), and vitamins C and E, as well as carotenoids (51).

However, in GSCs, ROS levels are lower than in the bulk tumor population. Thus, although treatment initially increases oxidative stress and eliminates many bulk tumor cells, it can favor the survival of GSCs (52).

This section examines how GSCs exploit antioxidant pathways to maintain low ROS levels and thereby promote recurrence.

NRF2 pathway

The nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that regulates antioxidant metabolism by binding to antioxidant response elements (AREs) in gene promoters and inducing detoxifying and cytoprotective genes (53-54). Under normal conditions, KEAP1 binds NRF2 in the cytoplasm and targets it for degradation. In bulk glioblastoma cells, however, NRF2 is often aberrantly activated and accumulates in the

nucleus, promoting survival under stressful conditions such as therapy or hypoxia (55-57). This difference in NRF2 regulation between normal conditions and in GSCs is shown in Figure 2.

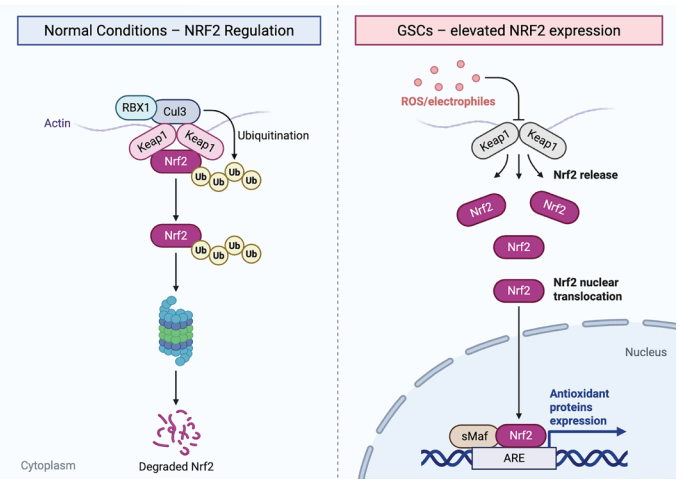

Figure 2. NRF2 antioxidant pathway alteration in glioblastoma (GBM) and glioma stem cells (GSCs). *Under normal conditions, NRF2 is degraded by KEAP1, whereas in GBM and especially GSCs, NRF2 accumulates in the nucleus and activates antioxidant gene expression, promoting survival, stemness, and therapy resistance.*

In GSCs, NRF2 expression is typically elevated compared with that in bulk glioma cells (58). In addition, expression of NRF2 target antioxidant genes is increased, indicating that GSCs rely heavily on NRF2-driven redox defenses to maintain viability under stress (59). Knocking down NRF2 using lentiviral shRNA in patient-derived GSCs reduced self-renewal, stemness marker expression (SOX2 and BMI1), proliferation, and in vivo tumor-initiating capacity (60). The study used GSC cultures derived from multiple patient tumors, and experiments were repeated at least three times for statistical analysis. Because the findings were supported by both in vitro stem-cell assays and in vivo xenograft experiments, the evidence is relatively strong at the preclinical level, although the number of patient-derived cell lines was limited and the results have not yet been validated in clinical studies.

Glutathione and thioredoxin

Glioblastoma stem cells use glutathione (GSH) and thioredoxin (Trx) antioxidant systems to counteract increased ROS levels (61). GSCs upregulate these two thiol-based pathways to maintain intracellular ROS below cytotoxic thresholds even under oxidative stress.

GSH is one of the most abundant intracellular antioxidants and plays a central role in neutralizing ROS. When oxidized, GSH is converted to glutathione disulfide (GSSG) and then recycled back to its reduced form using NADPH. In GSCs, the GSH pathway is often upregulated through increased expression of enzymes involved in GSH synthesis and detoxification, thereby increasing the capacity to neutralize ROS and prevent oxidative damage (62). For example, the mitochondrial enzyme ALDH1L2 (aldehyde dehydrogenase 1 family member L2), which generates NADPH for GSH regeneration, is overexpressed in GSCs. CRISPR/Cas9 knockout of ALDH1L2 in an in vitro glioblastoma cell model derived from the human U251 cell line reduced total NADPH, elevated ROS levels, and impaired GSC formation (63).

The Trx system is composed of thioredoxin and thioredoxin reductase (TrxR) (64). Inhibition of TrxR has been shown to be toxic to GSCs. The TrxR inhibitor auranofin induces cell death in GSC cultures and is accompanied by an increase in apoptosis markers (61). In particular, GSCs activate the GSH system when TrxR is inhibited, as auranofin treatment induces compensatory upregulation of glutathione-related pathways. Simultaneously targeting both the Trx and GSH pathways yields synergistic anti-GSC effects, achieving far lower IC50 values than targeting either pathway alone. These findings illustrate that GSCs use both the GSH and Trx systems to maintain redox balance and that co-inhibition may push ROS to lethal levels. Together, these studies support the idea that antioxidant pathway reprogramming enables GSCs to survive increased therapy-induced ROS, persist as a residual population, and ultimately contribute to tumor recurrence.

CONCLUSION

Glioma stem cells drive recurrence after resisting standard treatment, in part because of their metabolic alterations and, in particular, their ability to switch between different metabolic programs. Bulk GBM often displays aerobic glycolysis characteristic of the Warburg effect, whereas GSCs can be glycolytic, OXPHOS-dependent, or hybrid, and can transition between these states under stress. This adaptability allows GSCs to preserve ATP production when one pathway is compromised. Importantly, GSCs that rely on

either glycolysis or OXPHOS can repopulate the tumor, suggesting that recurrence is driven, at least in part, by the ability of GSCs to transition between metabolic states.

Antioxidant metabolism reprogramming is crucial, as radiotherapy and temozolomide induce DNA damage through increased ROS production. However, GSCs maintain lower intracellular ROS levels than bulk tumor cells. This is achieved through activation of antioxidant programs, including NRF2 signaling and the glutathione (GSH) and thioredoxin (Trx) systems.

The connection between glucose metabolism and antioxidant pathways lies in the fact that metabolic rewiring provides reducing power in the form of NADPH to keep antioxidant systems active. When therapy elevates ROS, surviving GSCs appear to shift toward NADPH-generating pathways, which sustain glutathione and thioredoxin recycling. In parallel, GSCs are able to keep ROS low enough to preserve stemness and DNA repair capacity.

These insights highlight key challenges in tackling recurrent GBM. First, heterogeneity and plasticity mean that effective therapies must account for transitions between these states. One study demonstrated that targeting metabolic plasticity in glioma stem cells can impair their survival. Using a c-Src-inhibiting peptide (TAT-Cx43(266-283)) in human GSCs and an orthotopic xenograft model, the authors showed that inhibiting a central regulatory node suppressed both glycolysis and OXPHOS without inducing compensatory metabolic switching. This reduced GSC viability and decreased expression of metabolic proteins such as HK2 and GLUT3 in vivo, supporting the idea that blocking metabolic state transitions may be more effective than targeting a single metabolic pathway in preventing GBM recurrence (65).

Second, the blood-brain barrier limits delivery of metabolic inhibitors at effective concentrations, particularly to hypoxic and perivascular GSC niches. Current studies explore convection-enhanced delivery (CED) as a strategy to bypass the BBB (66). In 2025, a phase 1 dose-escalation study delivered 186Re nanoliposomes via CED to recurrent GBM tumors, illustrating how local delivery can achieve intratumoral distribution. Notably, toxicity was not higher than that of external beam radiation therapy, and patient survival exceeded the standard of care for recurrent glioblastoma (67). These findings suggest that improving drug delivery remains a promising area for therapeutic progress in GBM.

Third, metabolic and redox pathways are connected to normal brain function, which raises concerns about toxicity. The pathways altered in GSCs are also central to normal neural physiology. Neurons generate most of their ATP through mitochondrial OXPHOS, and impaired mitochondrial function is linked to neurological dysfunction and neurodegeneration (68). Similarly, antioxidant systems are essential in the central nervous system, as astrocytes maintain high glutathione concentrations that protect brain tissue from oxidative stress, while thioredoxin and thioredoxin reductase pathways are important for redox homeostasis and neuronal viability (69-70). Studies have produced conflicting results. For example, one study using the complex I inhibitor mubritinib demonstrated reduced self-renewal and tumorigenic capacity of GSCs, as well as radiosensitization in vivo, while showing minimal toxicity to normal cells (71). In contrast, motexafin gadolinium, designed to disrupt oxidative stress responses and enhance radiation-induced damage, was evaluated in combination with radiotherapy and temozolomide in newly diagnosed GBM. Treatment-related adverse events, including rare but severe toxicities, were observed, and overall survival benefits were limited (72).

Current studies suggest that targeting metabolic plasticity may limit GSC survival by preventing compensation between glycolysis and OXPHOS. However, most approaches remain preclinical and do not yet account for the complexity of conditions in patients. Future work should focus on identifying metabolic regulators of state transitions and on developing strategies that can cross the BBB and selectively disrupt GSC metabolism while minimizing toxicity to normal neural cells.

In conclusion, this review addresses a gap in the literature by synthesizing research on how alterations in glucose metabolism and antioxidant pathways in GSCs interact to promote GBM recurrence. The available evidence suggests that these processes are closely linked, as metabolic pathways provide both energy and redox balance for stem cell survival. However, much of the current evidence is derived from preclinical models, including in vitro cell culture systems, patient-derived neurospheres, and xenograft mouse models, which may oversimplify the tumor microenvironment compared with that in patients. In addition, many studies involve relatively small numbers of primary cells or cell lines, and differences between experimental models may contribute to conflicting conclusions in this field.

Despite these limitations, the current body of evidence supports the idea that therapies targeting a single metabolic pathway may be insufficient, as GSCs can compensate by switching to alternative metabolic states. Overall, GSC survival appears to require both sustained energy production and redox homeostasis, maintained through NRF2 signaling and antioxidant systems (GSH/Trx) supported by NADPH-generating glucose metabolism. Future progress will likely come from (1) mapping specific metabolic state transitions in GSCs, (2) validating metabolic biomarkers, and (3) designing combination strategies that simultaneously limit metabolic flexibility and collapse a specific pathway.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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