Ferroptosis and Oxidative Stress

Science Exploration

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Beyond ferroptosis induction: Defining ferroptosis vulnerability in glioblastoma

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Abstract

Glioblastoma (GBM) is the most lethal primary brain tumor, with minimal therapeutic progress over the past two decades. A defining feature of GBM is its intrinsic resistance to apoptosis, prompting interest in activating alternative cell death pathways such as ferroptosis, an iron-dependent process driven by lipid peroxidation. In GBM, ferroptosis represents a context-dependent vulnerability that arises directly from tumor-specific lipid metabolic reprogramming. Here, we outline a unifying framework in which ferroptosis sensitivity is governed by three interdependent axes: availability of oxidizable lipids, redox buffering, and iron handling. Genetic alterations common in GBM, such as *CDKN2A* loss, *EGFR* amplification or mutation, and *PTEN* loss, reshape these axes to either suppress or promote ferroptotic cell death. This susceptibility is further modulated by cellular state and the tumor microenvironment. Effective therapeutic targeting will require biomarker-driven patient stratification, rational combination strategies, and the development of brain-penetrant agents with tumor-selective activity. Together, this framework positions ferroptosis not as a universally inducible death pathway in GBM, but as a context-dependent vulnerability that can be therapeutically exploited in tumors already poised near the ferroptosis threshold.

Keywords: Glioblastoma, lipid metabolism, ferroptosis, cell death

1. Introduction

Glioblastoma (GBM) is one of the most treatment-resistant human cancers, with survival largely unchanged despite decades of progress in understanding the molecular basis of this disease[1-3]. Classified as a World Health Organization (WHO) grade 4 astrocytic tumor in the 2021 CNS classification, primary GBM is almost exclusively isocitrate dehydrogenase (IDH) wildtype and is defined by various molecular alterations, including Epidermal Growth Factor Receptor (*EGFR*) amplifications, Cyclin Dependent Kinase Inhibitor 2A/B (*CDKN2A/B*) homozygous deletion, and Phosphatase and Tensin homolog deleted from chromosome ten (*PTEN*) loss[4-7]. The current standard of care for newly diagnosed GBM is maximal tumor resection followed by concurrent and adjuvant chemotherapy combined with radiotherapy, which has extended median overall survival from 3-4 months to 14.6 months[1], a figure that has remained largely unchanged for nearly two decades. In part, this therapeutic stagnation may reflect a disconnect between treatment mechanisms and tumor biology. Radiotherapy and most conventional chemotherapies rely on the induction of apoptosis[8,9], whereas GBM exhibits profound resistance to apoptotic cell death[10]. Multiple mechanisms contribute to this resistance, including disruption of tumor protein 53 (TP53) signaling, overexpression of anti-apoptotic B-cell lymphoma 2 (BCL2) family members, and the persistence of quiescent, therapy-refractory glioma stem-like cells[11]. Compounding this challenge, GBM exhibits profound inter- and intra-tumoral heterogeneity. Tumors differ substantially between patients at the intertumoral level in their genetic, transcriptional, and metabolic programs[12], resulting in variable therapeutic vulnerabilities. Furthermore, individual tumors contain diverse cellular populations that recapitulate distinct neurodevelopmental lineages, as determined using single-cell profiling, each with unique functional properties and treatment sensitivities[7,13-15]. Together, cellular heterogeneity and apoptotic resistance limit the efficacy of conventional therapies, suggesting that alternative, non-apoptotic forms of regulated cell death may offer a more effective therapeutic strategy.

Considering these findings, ferroptosis has emerged as a compelling candidate for GBM. Ferroptosis is an iron-dependent form of cell death caused by the accumulation of toxic lipid peroxides, linking its execution directly to lipid metabolism[16-21]. This is highly relevant in GBM, where genetic and non-genetic remodeling of lipid metabolism contributes to tumor progression and therapeutic

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resistance[12,22,23]. Importantly, not all GBMs are equally sensitive to ferroptosis. Rather, tumors exist along a spectrum of sensitivities defined by their proximity to a ferroptosis threshold[12,18,24-27], the point at which lipid peroxide accumulation overwhelms antioxidant defenses and triggers cell death.

How should we think about ferroptosis sensitivity in GBM? In this review, we propose a unifying framework in which ferroptosis sensitivity in GBM is governed by three axes: lipid availability, redox buffering, and iron handling. We apply this framework to examine how ferroptosis vulnerability is established and modulated in GBM. We discuss how GBM-specific molecular lesions, transcriptional states, and tumor microenvironmental factors converge on the three core axes to position tumors along the ferroptosis threshold (Figure 1). We further explore how this conceptual model can inform biomarker-driven patient stratification, rational combination therapies, and the development of brain-penetrant, tumor-selective therapeutics. By framing ferroptosis as a context-dependent vulnerability rather than a universal mechanism of cell death, we aim to provide a conceptual framework for identifying clinically actionable strategies to overcome apoptotic resistance in GBM.

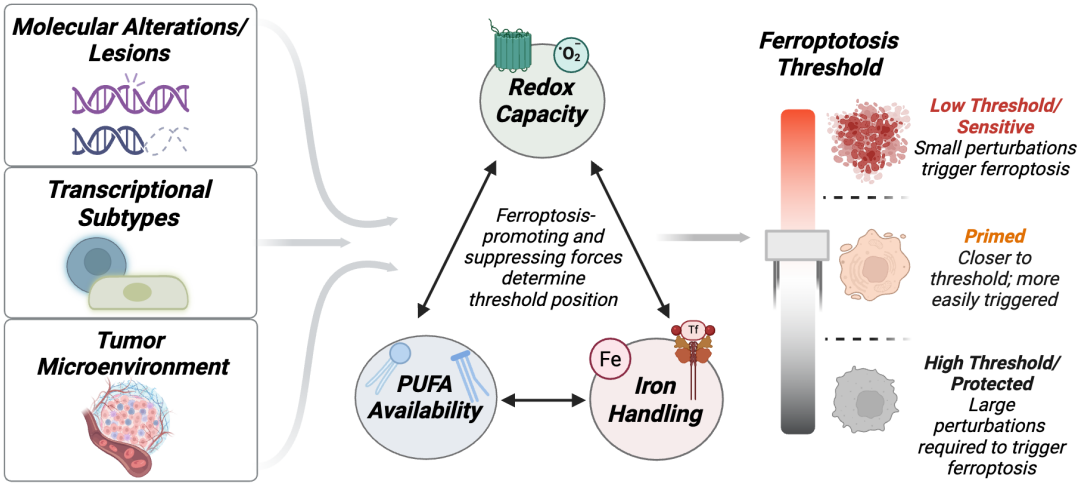


Figure 1. Determinants of the ferroptosis threshold in Glioblastoma. Conceptual model illustrating how upstream tumor features converge on three interdependent axes, Oxidizable Lipid (PUFA) Availability, Redox Capacity, and Iron Handling, to set a cell's ferroptosis threshold. Molecular alterations/lesions, transcriptional subtypes, and the tumor microenvironment (left) feed into this triad, where opposing ferroptosis-promoting and -suppressing forces dynamically determine threshold position. The net output (right) places tumor cells along a continuum of ferroptotic susceptibility: a low threshold/sensitive state, in which minor perturbations are sufficient to trigger ferroptosis; a primed intermediate state, positioned closer to the threshold and more readily triggered; and a high threshold/protected state, requiring large perturbations to induce ferroptosis. Created in BioRender. Salinas, J. (2026) https://BioRender.com/vea0ke4. PUFA: polyunsaturated fatty acid; Tf: transferrin.

2. Intrinsic Determinants of the Ferroptosis Threshold in GBM

First, we will describe the cell autonomous regulators that contribute to ferroptosis in GBM. Across the three axes of the framework proposed in this review, GBM-specific metabolic enzyme expression, genetic alterations, and transcriptional programs collectively determine where a tumor sits relative to the ferroptosis threshold (Figure 2), a point at which pro-ferroptotic pressures (oxidizable lipid abundance, labile iron pool) exceed the protective capacity (antioxidant buffering, lipid sequestration), thus sensitizing cells to ferroptosis-induced cell death. Critically, these determinants are not uniformly distributed: they vary between GBM molecular subtypes, between individual tumors, and between cell populations within a single tumor. Understanding this intrinsic heterogeneity may help identify patients who are most likely to respond to ferroptosis-inducing therapy and predict resistance mechanisms that could be co-targeted.

2.1 Lipid availability, redox buffering, and iron handling

A key requirement for ferroptosis is the presence of oxidizable phospholipid substrates[16,17,28]. Consequently, GBM susceptibility is influenced by metabolic programs that determine the availability or generation of oxidizable fatty acids that are incorporated into phospholipid membranes or sequestered in neutral lipids[29,30]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) activates the polyunsaturated fatty acids arachidonic acid (AA, 20:4) and adrenic acid (AdA, 22:4) to CoA thioesters[31], which are then esterified into membrane phospholipids, thus generating oxidizable substrates for lipid peroxidation[17,19,32,33]. ACSL4 is required for ferroptosis when glutathione peroxidase 4 (GPX4) is inactivated, at least in cultured cells[34]. Likewise, GBMs may exhibit resistance to ferroptosis due to reduced ACSL4 expression across a panel of human glioma tissues and cells[26]. This ferroptosis resistance correlated with elevated GPX4 expression and reduced 12/15-hydroxyeicosatetraenoic acid (HETE) lipid peroxide levels. Overexpression of ACSL4 decreased expression of GPX4, increased 12/15-HETE lipid peroxide levels, and decreased cell viability[26]. These findings position ACSL4 as a key determinant of whether GBM cells accumulate polyunsaturated fatty acid (PUFA)-containing phospholipid substrates.

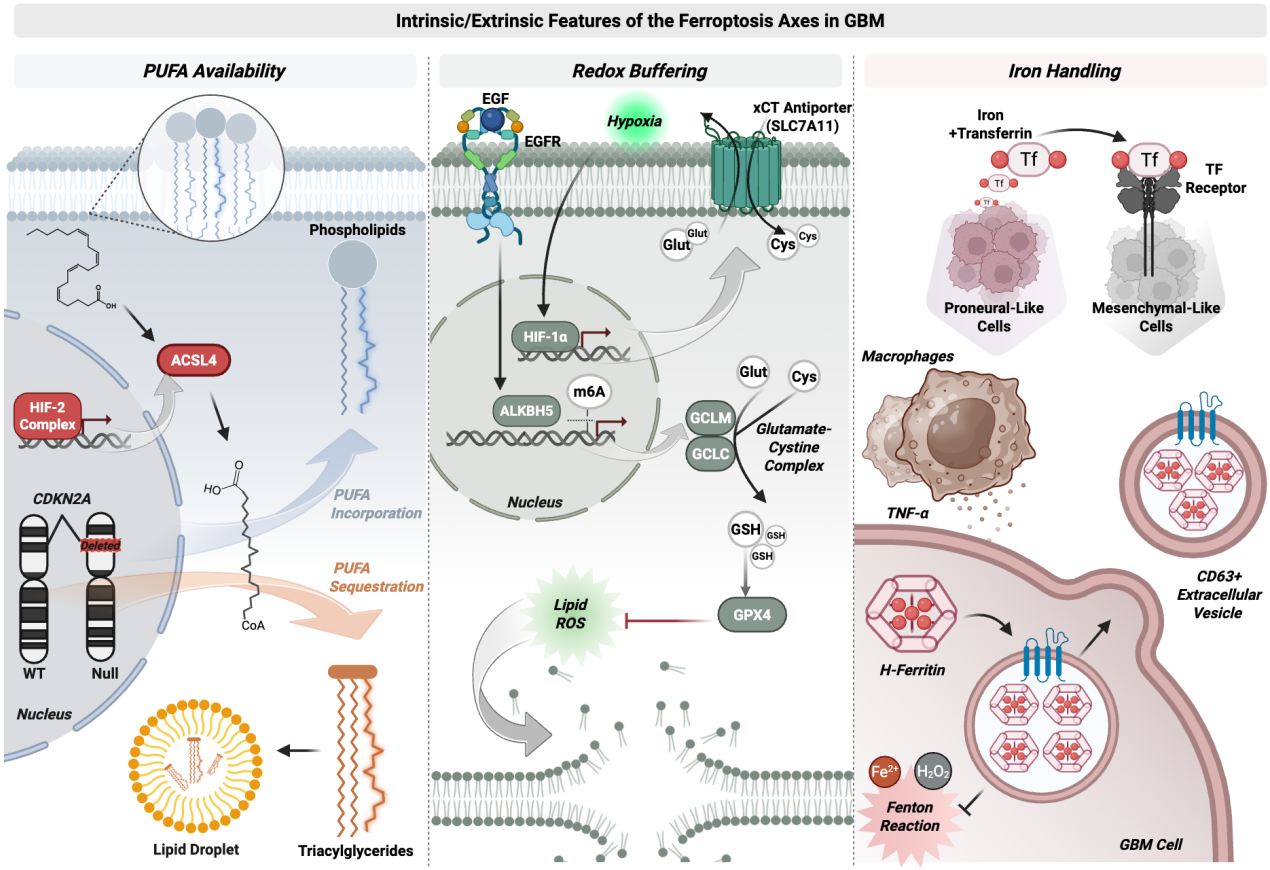


Figure 2. Intrinsic and extrinsic regulators of ferroptosis susceptibility in Glioblastoma. Schematic overview of the major regulatory axes that collectively establish the ferroptosis threshold in GBM, organized by oxidizable lipid availability, redox buffering, and iron handling. Lipid availability (left): GBM cells regulate ferroptotic susceptibility through control of PUFA metabolism and membrane lipid composition. ACSL4 promotes PUFA-CoA activation and incorporation into phospholipids, enhancing substrates for lipid peroxidation, whereas alternative sequestration of PUFAs into TAGs within lipid droplets limits ferroptotic propagation. This lipid partitioning program is influenced by oncogenic alterations, including *CDKN2A* loss and HIF-2–dependent transcriptional regulation. Redox buffering (center): GBM cells maintain protection from ferroptosis through coordinated antioxidant systems that limit lipid ROS accumulation. Hypoxia-responsive pathways regulate redox adaptation, including glutamate-cystine transport, GSH synthesis, and GPX4-mediated detoxification of lipid peroxides. Iron handling (right): Iron availability represents a critical determinant of ferroptotic sensitivity, with GBM cell states exhibiting distinct mechanisms of iron uptake, storage, and utilization. Tf-mediated iron acquisition, ferritin-based sequestration, and regulation of the labile iron pool influence iron-dependent lipid peroxidation, which can be modulated by the TIME or cellular subtype. Together, these interconnected axes establish the ferroptotic threshold of GBM cells and represent potential therapeutic vulnerabilities for selectively inducing ferroptotic cell death. Created in BioRender. Salinas, J. (2026) https://BioRender.com/1corsnp. GBM: glioblastoma; PUFA: polyunsaturated fatty acid; HIF: hypoxia inducible factor; ACSL4: acyl-CoA synthetase long-chain family member 4; CDKN2A: cyclin dependent kinase inhibitor 2A; EGFR: epidermal growth factor receptor; m^6A: N^6-methyladenosine; GSH: glutathione; ROS: reactive oxygen species; GPX4: glutathione peroxidase 4; Tf: transferrin; TAGs: triacylglycerides; TIME: tumor immune microenvironment.

In contrast to ACSL4-mediated membrane PUFA loading, GBM cells can actively buffer ferroptosis susceptibility by sequestering oxidizable lipids away from plasma membrane phospholipids in lipid droplets[12,35]. Lipid droplets (LDs) serve as a protective store for PUFAs that have been sequestered into neutral triacylglycerides (TAG) and are physically compartmentalized away from phospholipid incorporation that may occur via ACSL4, suppressing ferroptosis[35-37]. Lipid droplet accumulation is a key feature of GBM[38-40]. Under periods of energy deprivation (low glucose conditions), GBM cells deplete TAG-containing lipid droplets to release fatty acids for mitochondrial oxidation. Furthermore, inhibiting fatty acid oxidation or autophagy leads to increased accumulation of TAG-containing lipid droplets[38,40]. Thus, GBM cells do not simply lack the ability to execute ferroptosis, but instead these tumors have a lipidome that reflects the sequestration of lipids away from peroxidation-susceptible membrane components and towards protective lipid droplets.

Another mechanism of protection that GBM tumors exhibit against ferroptosis is reduced mitochondrial lipid peroxidation. Unbiased RNAi screening in GBM patient-derived orthotopic xenografts (PDOXs) identified medium-chain acyl-CoA dehydrogenase (MCAD) as important for GBM tumor growth[36], with immunohistochemistry confirming heightened expression of MCAD in GBM tumors compared to normal brain[41]. MCAD catalyzes the first step of medium chain FA (MCFA) oxidation. Depletion of MCAD induced lipid peroxidation and oxidative stress via accumulation of unmetabolized MCFAs in the mitochondria in both *in vitro* and *in vivo* systems.

This led to structural damage within the mitochondria, and ultimately cell death that was rescued with the ferroptosis-specific small molecule inhibitor ferrostatin-1, implicating MCFA oxidation as a potential ferroptosis-buffering strategy in GBM[41]. These findings suggest that mitochondrial fatty acid oxidation may act as a metabolic sink to prevent the accumulation of peroxidation prone lipid species in GBM.

While lipid availability determines the availability of ferroptosis substrates, ferroptotic execution additionally depends on whether antioxidant systems can effectively neutralize the accumulation of oxidizable lipid species. Outside of lipid-level defenses (e.g., decreased oxidizable PUFAs in the phospholipid (PL) membrane, increased TAG-containing LDs), tumors also possess multiple enzymatic antioxidant systems that are relevant to GBM biology. The cystine/glutamate antiporter xCT (SLC7A11) exchanges extracellular cystine for intracellular glutamate at the plasma membrane[42,43]. Inside the cell, cystine is reduced to cysteine and used to synthesize glutathione (GSH), a critical antioxidant[43]. GBM tumors exhibit increased SLC7A11 expression, thus enabling resistance to oxidative stress[44,45]. In GBM patients, increased SLC7A11 expression correlated with poorer prognosis, with high-SLC7A11 patients having both shorter progression-free and overall survival[45]. Wild-type p53 negatively regulates SLC7A11 expression, with stabilization of p53 leading to decreased ferroptosis sensitivity in response to cystine deprivation[46]. This was found to be associated with slower depletion of intracellular glutathione and reduced accumulation of reactive oxygen species (ROS)[46]. These observations suggest that GBM cells may protect themselves against ferroptosis through cystine-dependent glutathione buffering.

In addition to cytosolic glutathione buffering, GBM cells can also engage mitochondrial antioxidant systems to influence ferroptosis susceptibility. Dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme involved in de novo pyrimidine synthesis, regulates mitochondrial lipid peroxidation[47-50]. DHODH reduces ubiquinone to ubiquinol within the inner mitochondrial membrane and may limit mitochondrial lipid peroxidation and ferroptosis under certain conditions[51,52]. In GBM, depletion of proline-rich protein 11 (PRR11) sensitized recurrent tumor cells to temozolomide (TMZ) by disrupting PRR11-mediated stabilization of DHODH, increasing lipid peroxidation and ferroptotic cell death[53]. These findings suggest that DHODH may contribute to ferroptosis resistance in at least a subset of GBMs and may be particularly relevant in recurrent or therapy-resistant disease.

Iron handling represents a third major determinant of the ferroptosis threshold in GBM through regulating catalytic iron required for lipid peroxidation. Ferritin-mediated sequestration serves as a protective mechanism, with disruption of ferritin regulation increasing iron-dependent oxidative stress. In GBM models, tripartite motif-containing protein 7 (TRIM7) regulates nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, with loss of TRIM7 leading to enhanced ferritin degradation, increased intracellular iron availability, and increased lipid peroxidation[54]. These factors sensitized GBM cells to ferroptosis-mediated cell death[54]. Similarly, alterations in ferritin heavy chain 1 (FTH1)-mediated iron sequestration increase ferroptosis sensitivity[55]. Mechanistically, disruption of FTH1 regulation was associated with increased iron-dependent oxidative stress, elevated lipid peroxidation, and impaired tumor cell survival under ferroptotic pressure[55].

Viewed through the lens of the three-axis framework, these findings reveal that GBM suppresses ferroptosis through coordinated regulation of both lipid availability and redox buffering. Oxidizable PUFAs are diverted away from peroxidation-susceptible membrane phospholipids and into protective storage or metabolic clearance pathways, while glutathione-dependent antioxidant systems, together with other mitochondrial redox pathways, help neutralize lipid peroxide accumulation. Together, these mechanisms maintain GBM cells below the ferroptosis threshold and constitute major determinants of intrinsic ferroptosis resistance.

2.2 Gene regulatory programs shaping ferroptosis sensitivity in GBM

In GBM, ferroptosis sensitivity is not exclusively determined by a single enzyme. Coordinated transcriptional and post-transcriptional programs can also regulate the antioxidant systems that define the redox buffering axis, thereby influencing how close tumor cells are to the ferroptosis threshold. These regulatory networks frequently contribute to resistance against both standard therapies and ferroptosis-inducing agents.

Among the transcriptional regulators of ferroptosis, the NFE2-like bZIP transcription factor 2 (NFE2L2, NRF2) pathway represents a central mechanism by which GBM coordinates redox defense, with NRF2 acting as a key regulator in redox-dependent events[56-58]. Under oxidative stress, NRF2 uncouples from Kelch-like ECH-associated protein 1 (KEAP1) and translocates to the nucleus, where it induces the transcription of genes containing antioxidant response elements (AREs)[57]. Compared to non-cancerous brain tissue, GBM tissue exhibited elevated NRF2 levels, which correlated with poorer clinical outcomes and overall reduced survival[59]. Genetic activation of NRF2 or loss of KEAP1 increased SLC7A11 expression and promoted glioma cell proliferation, whereas NRF2 suppression sensitized glioma cells to ferroptosis through increased ROS accumulation[59]. SRC proto-oncogene, non-receptor tyrosine kinase (SRC) signaling promoted NRF2 stabilization by activating the mTORC1-p62-KEAP1 (mechanistic target of rapamycin complex 1-p62-KEAP1) axis, leading to transcriptional upregulation of ferroptosis-defense genes including SLC7A11 and GPX4[27]. SRC inhibition with dasatinib, a multi-tyrosine kinase inhibitor, released the sequestration of KEAP1 and sensitized GBM cells to ionizing radiation (IR)-induced ferroptosis[27]. Collectively, these findings suggest that NRF2 functions as an important regulator of ferroptosis resistance in GBM by reinforcing antioxidant capacity and cystine-dependent redox buffering, although the specific contribution of individual downstream ferroptosis regulators remains context-dependent.

Beyond transcriptional regulation, GBM cells employ post-transcriptional mechanisms that influence ferroptosis-associated pathways, including regulation of RNA stability, protein expression, and antioxidant capacity. These mechanisms can alter the ability of tumor cells to maintain redox homeostasis and survive oxidative stress. For example, Fragile-X mental retardation autosomal 1 (FXR1), an RNA-binding protein, bound and stabilized *GPX4* mRNA in TMZ-resistant glioma cells[60]. Increased FXR1 expression was associated with TMZ resistance, whereas *FXR1* silencing reduced GPX4 expression and sensitized glioma cells to TMZ treatment, accompanied by increased ferroptotic vulnerability[60]. These findings suggest that post-transcriptional regulation of antioxidant defense pathways may contribute to ferroptosis resistance in therapy-resistant GBM states. NF-κB activating protein (NKAP), another RNA binding protein, was also found to modulate ferroptosis sensitivity in GBM by stabilizing *SLC7A11* mRNA[61]. NKAP knockdown sensitized cells to ferroptosis both *in vitro* and *in vivo*, while overexpression of NKAP promoted resistance to ferroptosis through positive regulation of SLC7A11. This regulation was weakened in a post-transcriptional manner, with NKAP regulating *SLC7A11* mRNA splicing through N^6-methyladenosine (m^6A) modifications[61].

Solute carrier family 10 member 3 (SLC10A3) is upregulated in low-grade gliomas (LGG) and GBM patient tissue and is correlated with poorer patient prognosis[62]. SLC10A3 regulated glioma growth and ferroptosis sensitivity via signal transducer and activator of transcription 3 (STAT3) phosphorylation and downstream GPX4 suppression. Silencing of *SLC10A3* induced ferroptosis in GBM both *in vitro* and *in vivo*[62]. Finally, selenoprotein P (SeP), a selenium-containing protein, was associated with ferroptosis sensitivity through suppressing GPX4 in GBM[63]. Knockdown of SeP in cultured GBM cells decreased GPX4 protein levels and increased RSL3-induced cell death. This cell death was rescued by supplementing cells with selenite, suggesting that SeP regulates GPX4 by acting as a selenium storage system in GBM[63]. Together, these transcriptional and post-transcriptional programs constitute an important redox buffering axis in GBM. Whether through NRF2-driven transcriptional amplification of SLC7A11 and GPX4, SRC-mediated KEAP1 sequestration, *GPX4* mRNA stabilization by FXR1, or selenoprotein P-dependent selenium supply to GPX enzymes, the net effect is the same: GBM cells maintain a constitutively elevated antioxidant capacity that raises the lipid peroxide accumulation required to trigger ferroptosis.

2.3 Genetic alterations rewire the ferroptosis axes

Canonical GBM driver alterations promote proliferation and survival and at the same time establish baseline ferroptosis susceptibility by regulating lipid metabolism, antioxidant capacity, and iron utilization. Among recurrent genetic alterations in primary GBM, cyclin-dependent kinase inhibitor 2A (*CDKN2A*) deletion has emerged as an important determinant of ferroptosis sensitivity[12]. Through integrated lipidomic, transcriptomic, and genomic profiling of more than 150 patient-derived GBM tumors, *CDKN2A* deletion was associated with redistribution of oxidizable PUFAs from protective TAG-containing lipid droplets into peroxidation-susceptible membrane phospholipids. As a consequence, *CDKN2A*-null GBMs exhibited elevated basal lipid peroxidation and increased ferroptosis sensitivity, whereas *CDKN2A* wild-type tumors remained comparatively resistant due to PUFA-TAG buffering. The *CDKN2A* locus encodes several different products, including p16 and p14. Re-expression of p16, but not p14, restored the *CDKN2A* wild-type lipid phenotype and ferroptosis resistance, revealing a link between a canonical cell-cycle regulator and the ferroptotic lipid landscape[12]. Together, these findings identify *CDKN2A* loss as both a mechanistic determinant and a potential biomarker of ferroptosis sensitivity, demonstrating that this common tumor suppressor alteration positions GBM cells closer to the ferroptosis threshold through lipidome remodeling.

In contrast to *CDKN2A*-mediated lipid remodeling, other GBM driver alterations may regulate ferroptosis by modulating redox buffering pathways. For example, epidermal growth factor receptor (*EGFR*) amplification, present in ~ 50% of GBM tumors[64], reduces ferroptosis sensitivity by enhancing glutathione synthesis and boosting redox buffering pathways[65]. EGFR signaling repressed m^6A mRNA levels in GBM cells grown in culture, whereas genetic and pharmacologic suppression of EGFR signaling elevated m^6A levels. Mechanistically, EGFR promoted ferroptosis resistance by increasing the nuclear localization of the RNA demethylase ALKBH5. Nuclear ALKBH5 reduced m^6A levels and post-transcriptionally regulated GCLM, a rate-limiting enzyme in glutathione synthesis. Depletion of ALKBH5 and GCLM led to ferroptosis, establishing a link between EGFR signaling, m^6A demethylation, and ferroptosis[65].

Phosphatase and tensin homolog deleted from chromosome ten (*PTEN*) loss occurs in ~ 36% of primary GBM tumors[66]. This mutation constitutively activates the PI3K/AKT/mTOR pathway[67]. There is no evidence linking PTEN status to ferroptosis susceptibility in GBM. However, in other tumors, PTEN loss promotes ferroptosis resistance by reinforcing redox buffering pathways. In non-GBM models, *PTEN* deletion increased SLC7A11 expression and reduced ferroptosis sensitivity, an effect reversed by AKT inhibition through suppression of NRF2 and SLC7A11 expression[68]. Consistent with a role for PI3K/AKT signaling in ferroptosis regulation, inhibition of the AKT/mTOR pathway in GBM using the sterol regulatory element-binding protein (SREBP) inhibitor Fatostatin induced ferroptosis by suppressing GPX4 synthesis[69]. Together, these findings suggest that PTEN loss may influence ferroptosis susceptibility, at least in part, through AKT-NRF2-SLC7A11-mediated regulation of antioxidant defenses.

Gain of function mutations in IDH produce the oncometabolite 2-hydroxyglutarate (2-HG)[70] and reshape multiple processes relevant to ferroptosis, including lipid metabolism, NADPH utilization, and oxidative stress responses. IDH mutations are present in approximately 80% of grade II/III gliomas, as well as a subset of secondary GBMs[71], and have context-dependent effects on ferroptosis susceptibility that remain incompletely resolved.

Mutant IDH may promote ferroptosis sensitivity in some cancers. Consumption of NADPH by the mutant IDH protein compromises *de novo* lipogenesis, resulting in increased dependence on exogenous lipids for growth[72]. Consistent with this concept, HT-1080 fibrosarcoma cells, a commonly used ferroptosis model harboring an endogenous IDH1 mutation, had reduced ferroptosis sensitivity following deletion of mutant *IDH1* and re-sensitization following re-expression of mutant (but not wild-type) IDH1[73]. Furthermore, 2-HG itself appeared to mediate this phenotype, as pharmacologic inhibition of mutant IDH1 or overexpression of D-2HG dehydrogenase reduced ferroptosis sensitivity[73]. These findings suggest that mutant IDH can create a metabolic state permissive for ferroptosis at least in some cellular contexts.

However, this relationship is not universal, and in other settings the metabolic and signaling consequences of mutant IDH can instead suppress ferroptosis. Gene expression profiling of LGG harboring the IDH mutation identified elevated PI3K/AKT activation as a critical node in these tumors[74]. AKT activation suppressed NRF2-dependent oxidative stress responses and reduced lipid peroxidation, whereas AKT inhibition enhanced TMZ-induced ferroptosis[74]. Similarly, IDH-mutant gliomas were resistant to oncolytic herpes simplex virus (oHSV)-induced ferroptosis because they failed to engage reductive carboxylation and lipid biosynthetic programs observed in IDH-wildtype tumors[75]. Pharmacologic inhibition of mutant IDH restored this metabolic flexibility and enhanced oHSV efficacy[75]. Collectively, these findings suggest that IDH mutations do not exert a uniform effect on ferroptosis susceptibility. Rather, mutant IDH appears to influence ferroptotic vulnerability through complex effects on lipid metabolism, redox homeostasis, and metabolic substrate utilization, with the ultimate outcome dependent on cellular and therapeutic context.

Together, these findings suggest that common GBM driver alterations establish baseline ferroptosis susceptibility by reshaping lipid metabolism, redox buffering, and metabolic state. Consequently, ferroptosis sensitivity may emerge not as a universal property of glioma, but as a genetically encoded vulnerability that varies across molecular subtypes and therapeutic contexts. Rather than inducing ferroptosis indiscriminately, greater opportunity may lie in identifying tumors already positioned near the ferroptosis threshold and selectively pushing them beyond it.

2.4 Cell state identity as a determinant of ferroptosis sensitivity in glioma

Beyond genetic lesions, ferroptosis susceptibility may also relate to transcriptional cell state identity. GBM transcriptional subtypes and cellular states are associated with distinct metabolic programs, antioxidant capacity, and iron utilization, suggesting that ferroptosis vulnerability may shift as tumors transition between developmental and therapy-induced states. Initial work highlighted three main subtypes in GBM: proneural (PN), classical (CL), and mesenchymal (MES)[7]. PN gliomas express neural development genes, CL gliomas have high levels of *EGFR* amplifications, EGFRvIII mutations, and deletions of *CDKN2A*, and MES gliomas are defined by high expression of immune-associated genes and immune cell infiltration[7]. Further single-cell RNA sequencing (scRNA-seq) has uncovered more nuanced cellular states at the intra-tumoral level, with seminal work defining four primary, highly plastic transcriptional states mirroring different neural developmental stages[13,14,76,77]. These states include the neural progenitor-like (NPC-like) state, the oligodendrocyte progenitor-like (OPC-like) state, the astrocyte-like (AC-like) state, and the MES-like state, with newer refinements expanding on this work[13-15,78]. Collectively, these subtypes and states contribute to tumor plasticity, treatment resistance, and recurrence.

Molecular factors are important for maintaining tumor heterogeneity between the PN and MES subtypes of GBM. For example, PN glioma cells secreted dopamine (DA) and transferrin (TF), thus inducing proliferation of MES cells but sensitizing them to ferroptosis[79]. In cell culture, PN glioma-derived TF stimulated MES glioma proliferation in an iron-dependent manner. Furthermore, DA acted in an autocrine manner by inducing PN-glioma growth while inducing TF-receptor 1 expression in MES glioma cells to increase iron uptake, thus enhancing susceptibility to ferroptosis[79]. In an independent study, PN and MES GBM cell lines were exposed to ferric ammonium citrate (FAC)-mediated iron overload and erastin[24]. The PN cell line increased metabolic turnover, while the MES cell line did not show any significant changes. The MES cell line had higher basal levels of glutathione and could upregulate GPX4 levels after FAC treatment relative to the PN cell line[24]. While these observations suggest that PN, not MES, GBM may be more sensitive to ferroptosis, it is important to note that only two cell lines were examined in the absence of inter-tumoral crosstalk. These apparently conflicting findings may reflect differences in experimental systems, iron availability, and the relative engagement of lipid availability, redox buffering, and iron handling programs rather than a fixed ferroptosis phenotype associated with any single transcriptional subtype.

Recent work has expanded on the link between transcriptional identity and ferroptosis vulnerability. In genetically engineered mouse models of glioma, patient-derived cell lines, and *ex vivo* slice cultures generated from patient-derived GBM samples, Notch activation upon tumor initiation induced a quiescent AC-like glioma phenotype[80]. This phenotype was accompanied by alterations in mitochondrial function, increasing ROS generation, increased lipid peroxidation, and ultimately sensitivity to GPX4-inhibition-mediated ferroptosis[80]. The association between AC-like gliomas and ferroptosis vulnerability has also been found in diffuse midline gliomas, a pediatric brain tumor with a median survival of 9-12 months from diagnosis[81]. Gene set enrichment analysis revealed that AC-like diffuse glioma cells were enriched for genes associated with the epithelial-mesenchymal transition (EMT) and immune cell signaling. Treatment of these cells with RSL3 induced lipid peroxidation and cell death, which was rescued by ferrostatin-1[81]. Critically, the transcriptional subtype data reveal that the three axes of ferroptosis sensitivity are not independent

features of individual genetic alterations but are co-regulated as integrated phenotypic programs. The MES state simultaneously upregulates redox buffering (NRF2/GPX4/GSH) and lipid storage (lipid droplet formation), while the PN and AC-like states exhibit comparatively lower antioxidant tone and higher membrane lipid peroxidation susceptibility[80,81]. This suggests that the ferroptosis threshold is not simply the sum of individual molecular alterations but an emergent property of larger transcriptional states and profiles.

3. Extrinsic Signals Dynamically Shift the Three Ferroptosis Axes in GBM

Although intrinsic programs establish baseline ferroptosis susceptibility, GBM cells exist within a highly dynamic tumor microenvironment (TME) that continuously reshapes lipid metabolism, antioxidant defense, and iron availability (Figure 2). Each of the extrinsic signals reviewed in this section may dynamically recalibrate one or more of the three primary axes. Hypoxia and HIF signaling mainly modulate the redox buffering axis through transcriptional regulation of SLC7A11. The immune microenvironment acts on all three axes simultaneously: tumor associated macrophages (TAMs) sequester iron to suppress the iron handling axis, IFN-γ from $CD8^+$ T cells suppresses SLC7A11 to reduce redox buffering, and ferroptotic damage associated molecular patterns (DAMPs) reshape immune cell composition in ways that feed back onto lipid oxidation. Standard-of-care therapies have also been proposed to engage this framework: TMZ has been proposed to expand labile iron pools (iron handling) while depleting GSH (redox buffering), and radiation amplifies ROS-driven lipid peroxidation (lipid availability). Recognizing which axis each extrinsic input targets is essential for designing combination approaches that achieve convergent, rather than redundant, pressure on the ferroptosis threshold.

3.1 Hypoxia and hypoxia inducible factor (HIF)

Hypoxia is a common feature of GBM tumors and has been observed in the necrotic tumor core and pseudopalisading regions[82-84]. The relationship between hypoxia and ferroptosis is context-dependent, showing opposite effects depending on the degree and duration of HIF activation.

Chronic hypoxia suppresses ferroptosis via the PI3K/AKT/HIF-1α axis, with HIF directly binding to the *SLC7A11* promoter and upregulating SLC7A11 expression, thus increasing cystine import and glutathione biosynthesis[85]. This mechanism was validated in GBM cell lines and orthotopic xenograft models, where hypoxia significantly decreased the potency of erastin and sulfasalazine, an antirheumatic drug that inhibits SLC7A11 function. Combined inhibition of HIF and SLC7A11 synergistically increased ferroptosis sensitivity[85], which could be of therapeutic relevance given the hypoxic nature of GBM tumor cores.

Prolyly Hydroxylase (PHD) hydroxylates HIF, targeting it for degredation. Roxadustat is a PHD small-molecule inhibitor, thus stabilizing HIF[86]. Treatment of GBM cells with Roxadustat both *in vitro* and *in vivo* induced ferroptosis[87]. Cell death was accompanied by increases in lipid peroxidation and cellular iron but was blocked by ferrostatin-1 and glutathione. Interestingly, cells that were resistant to TMZ-induced apoptosis appeared exceptionally susceptible to Roxadustat-induced ferroptosis, whereas TMZ-sensitive cells were more resistance to Roxadustat[87]. Mechanistically, Roxadustat drove ferroptosis via HIF-2α (but not HIF-1α), which upregulated lipid regulatory genes involved in PUFA-phospholipid generation[87]. These results illustrate how HIF-driven ferroptosis may be isoform dependent, with HIF-1α suppressing ferroptosis via SLC7A11 and HIF-2α promoting ferroptosis sensitivity through modulation of lipid metabolic genes. Taken together, the effect of hypoxia illustrates how a single microenvironmental factor can simultaneously modulate all three ferroptosis axes.

3.2 The tumor-immune microenvironment (TIME)

Ferroptosis susceptibility in GBM is not determined solely by tumor-intrinsic programs but is continuously reshaped by the TIME. Immune cells, inflammatory signaling, and metabolic competition within the TIME dynamically modulate the three major ferroptosis-regulatory axes, lipid metabolism, redox buffering capacity, and iron handling, thereby shifting tumor cells toward or away from the ferroptosis threshold. TAMs comprise roughly 30-50% of tumor cellular mass, with 15% of that mass derived from microglia and 85% from peripheral-derived monocytes recruited by tumor-derived cytokines[88,89]. One mechanism by which the TIME suppresses ferroptosis in GBM is through reinforcement of tumor antioxidant defenses and redox buffering capacity. Ferroptosis-related gene expression in GBM tumor cells positively correlates with M2 macrophage infiltration in scRNA-seq and with The Cancer Genome Atlas (TCGA)/The Chinese Glioma Genome Atlas (CGGA) bulk expression data[90]. Eight ferroptosis-related risk genes are upregulated in high-risk GBM, with three of those genes (Aurora A kinase (*AURKA*), heat shock factor binding protein 1 (*HSBP1*), and nicotinamide N-methyltransferase (*NNMT*)) promoting the polarization of M1 macrophages to M2 macrophages and inhibiting ferroptosis in GBM cells[90]. In another study, programmed cell death (PCD) status was analyzed across a 1,750 patient glioma RNA-sequencing cohort, and ferroptosis was found to be the most enriched PCD process[25]. Furthermore, gene signatures related to ferroptosis were highly correlated with malignant progression, decreased survival, and decreased antitumor immunity. In both *in vitro* and *in vivo* experimentation, inhibiting ferroptosis in GBM altered the immunosuppressive phenotype of TAMs and improved the efficacy of anti-programmed cell death protein and ligand (anti-PD1/L1) immunotherapy in a GBM xenograft model[25]. The indoleamine 2,3-dioxygenase 1 (IDO1)-tryptophan axis provides another layer of complexity within the TIME. IDO1 is an enzyme highly expressed in GBM patients that is involved in tryptophan catabolism and has immunosuppressive abilities[91]. In glioma cells, IDO1 overexpression suppresses ferroptosis, reduces ROS, and decreases lipid peroxide generation[92]. Mechanistically, IDO1

promoted expression and nuclear translocation of the aryl hydrocarbon receptor (AhR) at the promoter regions of the FTO alpha-ketoglutarate-dependent dioxygenase (*FTO*) gene, an m^{6}A eraser enzyme, thus increasing m^{6}A methylation and the stability of *SLC7A11* transcripts[92]. This finding potentially connects the tryptophan immunosuppressive axis with ferroptosis evasion in GBM, a finding with translational relevance given the use of IDO1 inhibitors in clinical trials for several cancers[93-95]. Collectively, these findings suggest that immunosuppressive signaling within the TIME may stabilize the redox axis of ferroptosis resistance in GBM by sustaining glutathione metabolism and limiting lipid peroxide accumulation.

The TIME may also directly modulate the iron axis of ferroptosis susceptibility. In addition to redox regulation, TAMs regulate iron homeostasis[96]. TAMs render GBM less susceptible to ferroptosis by altering the iron status of these tumors. Co-culture of TAMs with GL261 GBM cells decreased ferritin heavy chain 1 (FTH1) and total iron levels in the GL261 tumor cells. Mechanistically, TAMs released extracellular vesicles containing iron-rich FTH1, which was mediated by TNF-α secretion from TAMs[96]. This suggests that the TIME may actively regulate whether tumor cells accumulate sufficient labile iron to sensitize them to ferroptosis.

Ferroptotic tumor cells may also reciprocally remodel the immune microenvironment by releasing oxidized lipids and DAMPs. Counterbalancing the immunosuppressive circuit, *in vitro* GBM spheroids undergoing ferroptosis release DAMPs and lipid peroxidation products that can trigger M1 repolarization and enhanced CD4$^+$ T cell infiltration in a peripheral blood mononuclear cell (PBMC)-spheroid co-culture[97]. Adenosine triphosphate (ATP) was a candidate DAMP released during ferroptosis, with CD4$^+$ T cells exhibiting a greater response to extracellular ATP than CD8$^+$ T cells. Together, the combination of ferroptosis induction with immunotherapy may improve patient outcomes in GBM, with a therapeutic challenge being to reverse the immunosuppressive TAM phenotype whilst simultaneously engaging potential T-cell recruiting properties of ferroptosis-induced cell death[97]. These findings suggest that lipid peroxidation products generated during ferroptosis may function both as executioners of tumor cell death and as immunologic signaling molecules capable of reshaping the inflammatory landscape of GBM.

Collectively, these findings support a model in which the TIME does not simply regulate immune interactions with GBM but actively modulates ferroptotic susceptibility. Through modulation of antioxidant buffering, lipid peroxide signaling, and iron availability, immune and stromal components reshape the ferroptosis threshold for GBM. These interactions may help explain why ferroptosis-inducing therapies exhibit highly context-dependent effects and suggest that successful therapeutic strategies will likely require simultaneous modulation of both tumor-intrinsic metabolic programs and the surrounding immune landscape.

3.3 TMZ and IR reshape the ferroptotic vulnerability in GBM

Although the canonical mechanisms of radiotherapy and TMZ center on DNA damage, emerging evidence suggests that these therapies also reshape cellular redox states and may influence ferroptotic susceptibility in cancer[98-100]. By increasing ROS, perturbing iron metabolism, and imposing stress on antioxidant buffering systems, these standard-of-care therapies may push GBM cells closer to the ferroptosis threshold, creating potential therapeutic windows for ferroptosis-targeting strategies. However, whether these treatments directly engage ferroptotic cell death pathways or instead generate secondary oxidative stress that sensitizes cells to ferroptosis remains an important unresolved question.

Radiotherapy provides one example of standard-of-care-induced ferroptosis vulnerability. Treatment of HT-1080 cells with differing doses of radiation synergized with ferroptosis-inducing agents to trigger cell death[98]. This was associated with increased lipid peroxidation, which was rescued by the ferroptosis inhibitor ferrostatin-1. Interestingly, the synergistic effects of ferroptosis-inducing agents and radiation were independent of DNA damage, as co-treatment did not increase DNA damage signal relative to radiation alone[98]. These findings in HT-1080 cells were also recapitulated in GBM. Analysis of TCGA data further suggested a role of *SLC7A11* as a feature of radioresistance in gliomas, leading to the question of whether combining small molecule ferroptosis inducers and radiation may have therapeutic benefit[98]. In *ex vivo* samples of human glioma, radiation treatment increased ROS in slice cultures, which further increased upon co-treatment with a ferroptosis inducer[98]. These results suggest the potential of combining ferroptosis agents with radiation; however, the mixed response to radiation suggests better stratification of gliomas to identify which tumors may be most sensitive to the proposed treatment.

In contrast to radiation, the relationship between TMZ and ferroptosis remains more mechanistically ambiguous. One study proposed that TMZ induces ferroptosis through a divalent metal transporter (DMT1, also known as solute carrier family 11 member 2, SLC11A2)-dependent iron accumulation pathway[99]. Upon TMZ treatment, investigators found that GBM cells increased labile iron pools, byproducts of lipid peroxidation (malondialdehyde, MDA), and release of lactate dehydrogenase (LDH), all while depleting glutathione. Short interfering RNA (siRNA)-mediated silencing of *DMT1* reversed the increase in ferroptosis markers, establishing DMT1-iron overload as a potential contributor towards the antitumor activity of TMZ outside of its canonical DNA alkylating function[99]. However, whether these findings represent direct ferroptotic execution or a secondary consequence of TMZ-induced oxidative stress remains unresolved, particularly given that DNA damage remains the dominant mechanism underlying TMZ activity and that ferroptosis validation criteria have not been uniformly applied across models.

The above distinction may be of relevance in the context of TMZ resistance. Despite TMZ being a standard-of-care therapy for GBM, TMZ treatment only improves median survival by ~ 2 months, largely due to the ability of the tumor to develop resistance to the

drug[101]. TMZ analogs and imidazotetrazine alkylating agents have been developed to overcome TMZ-resistance[100]. Conjugation of chlorambucil, a nitrogen mustard alkylating agent, to an imidazotetrazine group resulted in a compound called QX302, which exhibited significant antitumor effects on O-6 methylguanine-DNA methyltransferase (MGMT) overexpressing glioma cells in culture. Furthermore, treatment with QX302 increased levels of ROS, expanded the labile iron, and induced lipid peroxidation. Compared to TMZ, QX302 more robustly induced ferroptosis across multiple GBM cell lines, and downregulated both SLC7A11 and acyl-CoA synthetase long chain family member 3 (ACSL3), a metabolic enzyme that activates long-chain fatty acids, at the mRNA and protein levels[100]. These findings suggest that next-generation alkylating agents may achieve therapeutic benefit by coupling DNA damage with enhanced disruption of lipid redox homeostasis.

Collectively, current evidence supports a model in which radiotherapy and alkylating therapies can remodel ferroptotic susceptibility in GBM by altering oxidative stress, iron availability, and antioxidant capacity. Rather than functioning as classical ferroptosis inducers, these treatments may transiently lower the ferroptosis threshold, creating context-dependent vulnerabilities that can be exploited through rational combination with ferroptosis-targeting therapies.

4. Therapeutic Targeting of Ferroptosis

The goal of ferroptosis-based therapies is to be tumor-selective and exploit tumors already positioned near the ferroptosis threshold. Successful therapeutic exploitation of ferroptosis will likely require identifying tumors that already exist near the ferroptosis threshold and selecting interventions capable of further destabilizing their antioxidant, lipid metabolic, or iron-handling networks. This is all while overcoming the constraints imposed by GBM biology, which include bypassing the blood-brain barrier, the brain TME, and the heterogeneous inter- and intra-tumoral landscape (Figure 3). Although ferroptosis-regulatory pathways can be conceptually divided into redox buffering, lipid metabolism, and iron handling, therapeutic strategies often perturb multiple axes simultaneously. This combinatorial disruption may be particularly important in GBM, where tumor cells exhibit substantial metabolic plasticity and may compensate for inhibition of any single ferroptosis pathway in isolation.

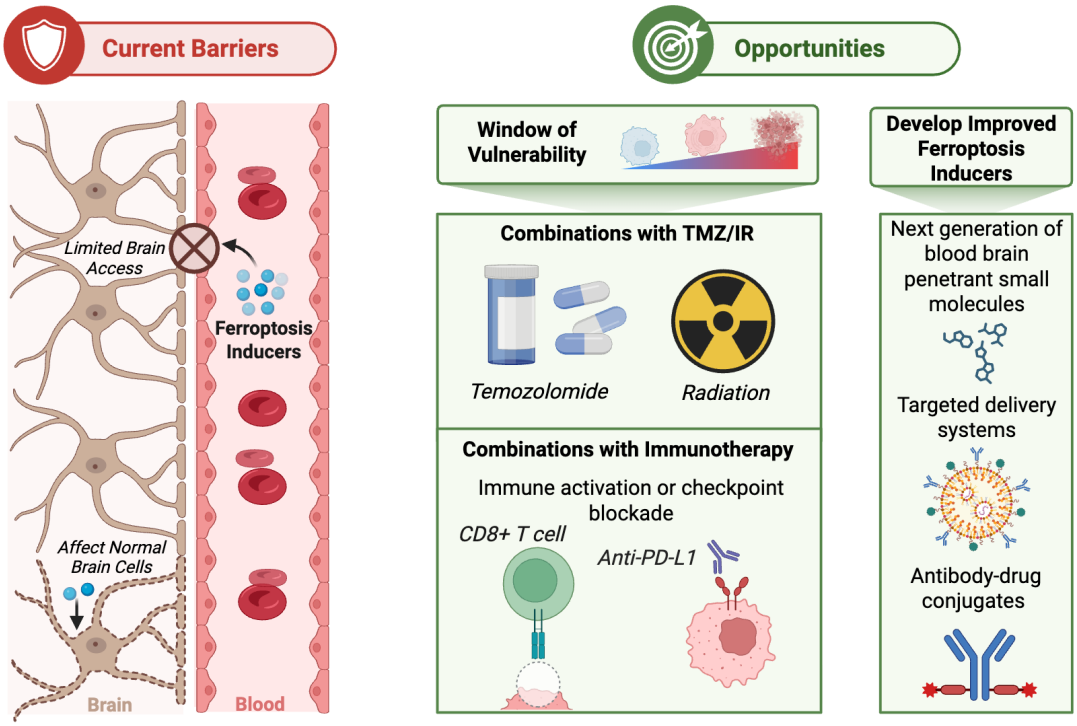


Figure 3. Barriers and opportunities for therapeutic ferroptosis induction in glioblastoma. Schematic outlining key challenges and potential strategies for harnessing ferroptosis as a therapeutic approach in glioblastoma. Current barriers (left): The blood-brain barrier restricts access of ferroptosis-inducing agents to brain tumor tissue, while limited specificity raises concern for off-target effects on normal brain cells. Opportunities (right): Potential strategies include identifying a therapeutic window of vulnerability and pursuing rational combination approaches, pairing ferroptosis induction with standard-of-care TMZ/IR or with immunotherapy, building on existing ferroptosis-inducing modalities such as small molecules, targeted delivery systems (nanoparticles, exosomes), and ADCs. Created in BioRender. Salinas, J. (2026) https://BioRender.com/is0kctq. TMZ/IR: temozolomide/radiation; ADCs: antibody-drug conjugates; Anti-PD1/L1: anti-programmed cell death protein and ligand.

4.1 Targeting redox buffering to lower the ferroptosis threshold

The most direct strategy for ferroptosis induction involves disrupting the antioxidant systems that maintain tumor cells below the ferroptosis threshold. Although many foundational ferroptosis-inducing compounds were initially characterized outside of GBM,

these studies provided critical insights into the conserved redox buffering mechanisms that influence ferroptosis susceptibility across cancers. In GBM, where subsets of tumors exhibit elevated basal lipid peroxidation, ROS stress, and metabolic dependence on antioxidant defenses, these pathways may represent exploitable liabilities capable of pushing already primed tumors beyond the threshold for ferroptotic execution.

Ferroptosis inducers have been validated across multiple cancer types and have been utilized as proof-of-concept tools for core targets[102-106]. Class I ferroptosis inducers such as erastin and its analogue imidazole ketone erastin (IKE) inhibit SLC7A11 to inhibit cystine import and prevent glutathione synthesis[107]. Because glutathione availability is a primary determinant of GPX4 activity, these compounds effectively reduce the capacity of cells to detoxify lipid peroxides. This mechanism may be particularly relevant in GBM subpopulations that exhibit elevated oxidative stress or dependence on cystine metabolism to maintain survival. As mentioned, sulfasalazine has a similar mechanism; however, systemic toxicity (such as anorexia and gastrointestinal effects) for doses tested in phase 1/2 clinical trials limited the clinical efficacy of this compound in malignant gliomas[108]. Class II ferroptosis inducers such as RSL3, ML162, and ML210 have been widely used as pharmacological compounds to perturb GPX4-dependent ferroptosis; however, none of these compounds have been approved for human use and have been primarily utilized in both *in vitro* and *in vivo* preclinical studies[102,106,109]. GPX4 inhibition is especially conceptually important in GBM because subsets of GBM cells exist in a state of elevated basal lipid peroxidation, potentially rendering them disproportionately dependent on GPX4-mediated detoxification for survival. The withanolide C28 steroidal lactone withaferin A (WA) induces ferroptosis in a dose-dependent manner in both neuroblastoma cell lines and xenograft models[110]. Lastly, FIN56 is another compound that has been identified as inducing ferroptosis across a panel of cell lines[111,112]. This compound is considered a Class III ferroptosis inducer and promotes the degradation of GPX4[111]. Whilst GPX4 inhibition may offer one avenue for inducing ferroptosis, conventional GPX4 inhibitors have limited therapeutic efficacy due to poor pharmacokinetics and the necessity of GPX4 for normal tissue[102,104,106,113-115].

Sorafenib (SRF) is another compound not specifically designed to induce ferroptosis but that may induce ferroptosis[116]. SRF is a small molecule kinase inhibitor and has been clinically approved to treat advanced hepatocellular carcinoma[117]. The role of SRF in ferroptosis is mixed. SRF may induce ferroptosis by suppressing SLC7A11 expression[116], but this appears to be cell-line or cell-type-specific[118]. These conflicting findings further emphasize that ferroptosis susceptibility is highly context-dependent and likely determined by the pre-existing metabolic and lipid state of individual tumors rather than exposure to a ferroptosis-inducing agent alone.

Although many canonical ferroptosis inducers were initially characterized outside of GBM, lipidomic and transcriptional analyses in GBM support the relevance of these pathways within the CNS context. *CDKN2A*-deleted tumors, mesenchymal-like cellular states, and therapy-exposed recurrent GBM have all been associated with elevated oxidative stress or altered lipid metabolism that may increase reliance on glutathione- and GPX4-dependent buffering systems. These observations provide a mechanistic rationale for adapting redox-targeting ferroptosis strategies specifically to biomarker-defined GBM subpopulations.

4.2 Targeting lipid availability and peroxidation

Because ferroptosis requires membrane phospholipid peroxidation, therapeutic approaches that increase the abundance or oxidation of PUFA-containing phospholipids may selectively sensitize GBM cells to ferroptotic execution. PLs containing AA or AdA are highly susceptible to lipid peroxidation[19,119]. In chronic myeloid leukemia cells, ACSL4 and lysophosphatidylcholine acyltransferase 3 (LPCAT3) catalyze PUFA (e.g., AA and AdA) activation and insertion into membrane lyso-PLs, respectively. These PUFA-containing PLs can be oxidized by lipoxygenases (LOXs) to form PL hydroperoxides, cascading into membrane peroxide formation and ferroptosis[120]. Therefore, in ACSL4- and LPCAT3-high tumors, providing PUFA substrates to be incorporated into the PL membrane could increase the likelihood of ferroptosis execution. These observations are particularly relevant in GBM, where transcriptional states, *CDKN2A* loss, and lipid droplet dynamics reshape the balance between PUFA storage and membrane incorporation.

DHODH inhibition can simultaneously decrease pyrimidine synthesis and shut down the CoQ10 antioxidant pathway[121]. Intriguingly, DHODH inhibition not only suppresses mitochondrial antioxidant defense but can also alter phospholipid remodeling. Inhibition of DHODH reduced CDP-choline levels and decreased the synthesis of phosphatidylcholine (PC) via the Kennedy pathway; as a compensatory mechanism, cells increased the generation of very long chain polyunsaturated fatty acid containing PC from phosphatidylethanolamines (PEs), which increased $CD8^+$ T cell infiltration and IFN-γ secretion, which enhanced anti-tumor PD-1 blockade *in vivo*[122]. Increased PUFA-PCs could also prime tumors for ferroptosis. Elevated DHODH expression in neuroblastoma correlates with poorer prognosis, making it a compelling target in brain cancers[123].

Recent GBM-specific therapeutic approaches have attempted to directly amplify phospholipid peroxidation within tumors. Using a genome-wide CRISPR-Cas9 screen in the presence of RSL3, ALOX15 was identified as an essential driver of ferroptosis in GBM cells[124]. ALOX15 promoted ferroptosis through increasing peroxidation of PUFAs. To activate this pathway therapeutically, angiopep-2-modified macrophage membrane-coated biomimetic nanoparticles (Ang-MMsaNPs) were developed by encapsulating a small activating RNA (saRNA) of ALOX15 in mesoporous polydopamine (MPDA) and coating with a modified MM[124]. Small activating RNAs are small, double-stranded RNAs that target the promoter of the gene of interest[125,126]. Mechanistically, the Ang-MMsaNPs

caused mitochondrial abnormalities, thus increasing peroxidation and ferroptosis in GBM cells. Preclinical evaluation of Ang-MMsaNPs in GBM orthotopic xenografts showed that Ang-MMsaNPs induced negligible toxic effects on the liver or hematological factors and seemed to decrease tumor volume and increase overall survival. Ang-MMsaNP-treated tumors had increased ALOX15 protein expression and increased ACSL4 expression, as well as increased markers of lipid peroxidation. Ang-MMsaNP could also be combined synergistically with RT to prolong survival and further decrease tumor growth relative to single agent treatment[124]. Importantly, this strategy exploits a pre-existing lipid vulnerability rather than relying solely on generalized oxidative stress.

4.3 Exploiting iron pools and microenvironmental ferroptosis induction

Ferroptosis requires redox-active iron. Multiple emerging GBM-directed therapies therefore aim to amplify ferroptosis through iron delivery, immune-mediated signaling, or simultaneous disruption of multiple ferroptosis axes.

Angiopep-2-modifications have also been utilized to engineer exosome-conjugated magnetic nanoparticles to target both the DHODH and GPX4 axes[127]. Magnetic iron oxide nanoparticles were engineered to simultaneously inhibit GPX4 and DHODH while releasing iron within GBM cells, thereby disrupting both the redox buffering and iron handling axes[127]. These combinatorial nanoparticle systems may be particularly effective because they simultaneously destabilize multiple ferroptosis axes.

Ferroptosis induction may also synergize with immune modulation within the GBM microenvironment. IFN-γ released by activated T cells can induce ferroptosis in cancer cells; to target this phenomenon, a biomimetic microglial membrane-coated Fe_3O_4 nanoparticle was designed to deliver siPD-L1 (Fe_3O_4-siPD-L1@M-BV2) to deplete PD-L1[128]. This compound utilized siRNA to interfere with PD-L1 protein synthesis using an iron (II, III) oxide (Fe_3O_4) nanoparticle to increase siPD-L1 delivery and prevent degradation. Furthermore, this nanoparticle increased intracellular iron, which provided substrates for ferroptosis. To increase blood-brain barrier (BBB) penetration, the nanoparticles were coated with microglial membranes (M-BV2). These modifications showed that Fe_3O_4-siPD-L1@M-BV2 were mainly distributed in the brain and liver of GBM orthotopic xenograft models, with treatment significantly increasing iron content, polarizing M2 type microglia to M1 type microglia, increasing IFN-γ, TNF-α and IL-12, and decreasing tumor growth[128]. Disrupting stress granules sensitized glioma stem cells to IR/TMZ by recruiting iron-related proteins[129]. Mechanistically, stress granule proteins directly interacted with the ferritin light chain in an IR/TMZ-induced manner. IR/TMZ treatment induced the oxidation of stress-granule proteins, which promoted binding to the ferritin light chain, caused ferritin sequestration in stress granules, suppressed iron accumulation, and inhibited ferroptosis in glioma stem cells[129]. This phenotype was reversed by disrupting the interaction between the stress granule proteins and ferritin light chain, thus restoring iron-mediated ferroptosis and re-sensitizing glioma stem cells (both *in vitro* and *in vivo*) to TMZ/IR[129].

Engineered bacterial outer membrane vesicles (OMV-C-C) expressing cell penetrating peptides (CPP) and chlorotoxin (CLT) provide an alternative approach to synthetic nanoparticles[130]. CPP and CLT were co-expressed on the surface of OMV-C-C, with CLT enabling specific targeting of the OMV-C-C to GBM. OMV-C-C crossed the BBB and decreased tumor growth in an orthotopic xenograft model of GBM by increasing the infiltration of $CD8^+$ T cells. Interestingly, BBB penetration was attributed to CPP-mediated transcytosis, as transport was reduced by inhibitors of transcytotic pathways; however, the specific endothelial receptor or transport machinery responsible was not identified. Lastly, $CD8^+$ T cell release of IFN-γ induced ferroptosis through SLC7A11 and GPX4 downregulation, increasing lipid peroxidation[130]. Together, these approaches suggest that ferroptosis induction may be most effective when integrated with immune activation and localized iron amplification rather than as isolated monotherapy.

4.4 Combination therapy to modulate ferroptotic vulnerability

The maximal therapeutic benefit of ferroptosis induction in GBM will likely emerge not from constitutive ferroptosis activation alone, but from exploiting transient windows of vulnerability created by standard therapy. As noted above, it has been proposed that TMZ can prime cells for ferroptosis by depleting glutathione, increasing ROS, and reducing GPX4 activity. Radiotherapy may transiently shift GBM cells closer to the ferroptosis threshold through oxidative membrane damage. Lastly, the ferroptosis-IFN-γ-system x_c^- axis provides a positive feedback loop that can increase $CD8^+$ T cell infiltration and induce tumor ferroptosis. Collectively, these findings suggest that conventional therapies can synergize with ferroptosis induction and actively create temporally restricted ferroptotic vulnerabilities that can be therapeutically exploited.

5. Future Perspectives-Towards Clinical Translation

Despite preclinical evidence supporting ferroptosis as a therapeutic vulnerability in GBM, clinical translation remains limited by a central challenge: ferroptosis susceptibility is neither static nor universal across tumors. Rather, GBM cells occupy dynamic positions regarding ferroptosis sensitivity, where proximity to the ferroptosis threshold is governed by the interplay between lipid composition, antioxidant buffering capacity, and iron handling (Figure 1). Translating ferroptosis into an effective therapeutic strategy will require identifying tumors already poised near this threshold and selectively pushing them beyond it while sparing normal brain tissue.

5.1 Defining the ferroptosis threshold in GBM

As discussed previously, GBM ferroptosis sensitivity is heterogeneous and depends on many genetic and non-genetic factors. One implication of this is that GBM tumors are unlikely to respond uniformly to ferroptosis-inducing therapies. Instead, sensitivity will reflect the cumulative state of the three ferroptosis-regulatory axes: lipid availability, redox buffering capacity, and iron metabolism. Biomarkers capable of measuring these states may therefore identify tumors intrinsically poised for ferroptotic collapse and help guide patient selection.

Among these axes, lipid remodeling may represent the most immediate determinant of ferroptotic priming in GBM. At the genetic level, *CDKN2A* deletion status has emerged as the most immediately actionable biomarker, validated through lipidomic and functional testing in over 150 GBM tumors and derivative preclinical *in vivo* and *in vitro* models[12]. Here, *CDKN2A*-deleted GBMs were found to display increased levels of basal lipid peroxidation due to a preferential shuttling of PUFAs towards oxidizable membrane phospholipids, thus sensitizing these tumors to GPX4 inhibition. Since *CDKN2A* deletion is routinely tested for after surgical resection, this biomarker could be integrated into clinical trial eligibility[12].

In parallel, tumors vary substantially in their antioxidant buffering capacity, which determines their ability to neutralize lipid peroxide accumulation. Furthermore, iron availability represents the third major determinant of ferroptosis susceptibility and may be particularly dynamic within the GBM microenvironment[79,96,129]. At the transcriptional level, GBM subtype and cellular state identity potentially dictate sensitivity to ferroptosis and could be considered as an additional co-stratification variable[24,79,131]. Ferroptosis-gene signatures have been identified and validated in TCGA and CGGA cohorts as stratifying patients by predicted immunotherapy response and could also be leveraged in the context of ferroptosis-inducing therapies[132].

Importantly, no single biomarker is likely to fully predict ferroptosis sensitivity in GBM. Rather, clinically useful stratification will likely require integrated assessment across all three ferroptotic axes. Combining genomic alterations, transcriptional state identity, lipidomic profiling, and ferroptosis-associated gene signatures may provide a more accurate representation of where individual tumors reside relative to the ferroptosis threshold.

5.2 Therapeutic selectivity and the constraint of the Central Nervous System (CNS)

The ferroptosis threshold model also highlights a major therapeutic challenge unique to GBM: the same lipid-rich environment that predisposes tumor cells to ferroptosis also renders normal CNS tissue vulnerable to oxidative membrane damage. Successful clinical translation will therefore depend on inducing ferroptosis in tumor cells while sparing surrounding neural and endothelial cells.

As mentioned previously, the BBB is a formidable physical barrier to ferroptosis-inducing therapies. Conventional small molecule ferroptosis inducers, such as RSL3, ML162, and erastin, offer limited tumor penetration due to poor BBB crossing efficiency and unfavorable pharmacokinetics[133]. Furthermore, a critical constraint of ferroptosis inducers is that they must cross the BBB without inducing ferroptosis in the endothelial cells that line the BBB. This is a high bar because ferroptosis is induced by diverse brain injuries[134-136]. In zebrafish cerebrovascular endothelial cells, BBB disruption was induced upon hypoxic treatment by activating ferroptosis-related genes, inhibiting SLC7A11 activity, and increasing lipid peroxidation and ROS[137]. These effects were reversed with ferrostatin-1 treatment. Thus, there is the concern that doses sufficient to induce GBM ferroptosis may paradoxically compromise the structure that must be passed to successfully deliver drugs to the tumor.

Neurons may also be ferroptosis-sensitive due to their high PUFA content, elevated metabolic demand, and dependence on GPX4-mediated lipid peroxide detoxification. Conditional ablation of *Gpx4* in neurons resulted in rapid motor neuron degeneration and paralysis in mice[138]. Spinal cord sections from *Gpx4* neuronal KO mice showed increased astrogliosis, increased lipid peroxidation, and mitochondrial damage[138]. In human dopaminergic neuronal models, endogenous levels of alpha-synuclein can determine the sensitivity of neurons to ferroptosis, with increased levels corresponding to an increase in lipid peroxidation and thus ferroptosis[139]. Furthermore, neurons are rich in phospholipids that contain PUFAs to regulate membrane fluidity and signaling[140,141]; however, this also renders them more vulnerable to ferroptosis. Thus, catastrophic side effects could emerge when targeting ferroptosis in GBM, ranging from neurodegeneration to undesired endothelial cell BBB disruption and inflammatory necrosis.

Collectively, these challenges reinforce the need for ferroptosis-inducing strategies that are biomarker-guided, spatially restricted, and temporally coordinated with therapies that transiently destabilize tumor redox homeostasis. In this context, the goal is not universal ferroptosis induction, but selective collapse of tumors already positioned near the ferroptosis threshold[10,64,142-154].

5.3 Antibody-drug conjugates (ADCs) as a tumor-specific delivery strategy

ADCs couple tumor-antigen targeting antibodies to cytotoxic payloads via a chemical linker, restricting payload release to target cells[142,143]. This strategy may be particularly attractive for ferroptosis induction in GBM, where the susceptibility of normal CNS cells to lipid peroxidation may constrain the therapeutic window of systemically administered ferroptosis-inducing agents. Because ADC selectivity is strongly influenced by target-antigen expression, identifying tumor-enriched surface antigens is central to adapting this approach to GBM.

B7-H3 (CD276) represents one potential target, as it is highly expressed in GBM tumor cells, with minimal to no expression in normal brain tissue[10]. B7-H3 directed conjugates have already demonstrated GBM-selective activity in preclinical models[10,144,145], providing proof of principle that this antigen can be exploited for tumor-directed payload delivery. Notably, a B7-H3 targeted MMP-2 nanoparticle-antibody conjugate enhanced IFN-γ driven ferroptosis in orthotopic GBM models, while limiting activation outside the tumor microenvironment[144]. EGFRvIII, a tumor-specific EGFR variant absent from normal tissue, offers another potential target, although its heterogeneous expression within a tumor may limit its efficacy as a sole antigen[64,146]. EGFR- and EGFRvIII-directed ADCs, including AMG 595 and depatuxizumab mafodotin, have reached clinical testing in GBM[147-151], establishing the feasibility of antibody-directed payload delivery against these antigens. However, heterogeneous antigen expression and payload-associated toxicities observed with these agents highlight the importance of both antigen and payload selection when designing GBM-directed ADCs.

Importantly, dedicated ferroptosis-inducing agents have begun to be evaluated as ADC payloads outside the CNS. A trastuzumab-RSL3 conjugate induced ferroptosis in HER2-expressing breast cancer cells[152]. Sulfasalazine (SAS) has similarly been incorporated into an FGFR4-targeted ADC that induced ferroptosis in hepatocellular carcinoma[153], while a bispecific Cadherin-17/Guanylyl cyclase C (CDH17/GUCY2C) ADC carrying RSL3 enhanced internalization and inhibited colorectal tumor growth in cell culture and *in vivo*[154]. These studies provide proof of principle that agents targeting GPX4 or system Xc^- can be incorporated into tumor-directed delivery platforms while retaining ferroptosis-inducing activity. They also raise the possibility that payload selection could be guided by a tumor's position along the three-axis ferroptosis framework, with different ferroptotic vulnerabilities potentially favoring distinct payload mechanisms.

Despite this promising precedent, there are no reported GBM-targeted ADCs carrying a dedicated ferroptosis-inducing payload. Nevertheless, the availability of GBM-enriched surface antigens, prior experience with ADC-based delivery in GBM, and proof-of-concept ferroptosis-inducing ADCs in other cancers collectively provide a rationale for this approach. Translating ferroptosis-targeted ADCs to GBM will require a coordinated selection of a sufficiently abundant and homogeneous tumor antigen, a ferroptotic payload matched to the underlying tumor vulnerability, and linker and conjugate properties that enable effective tumor delivery while limiting exposure to normal CNS tissue.

6. Concluding Remarks

Ferroptosis represents more than an additional cell death mechanism that can be activated in GBM; it provides a conceptual framework for understanding how lipid metabolism, antioxidant defenses, and iron handling converge to create therapeutically exploitable vulnerabilities within defined subsets of GBM tumors and states. The evidence reviewed here supports a model in which GBM cells traverse a dynamic ferroptotic landscape shaped by three interdependent axes: lipid availability, redox buffering capacity, and iron handling. Genetic alterations, transcriptional states, microenvironmental signals, and therapeutic exposures continuously shift tumor cells toward or away from the threshold of ferroptosis, generating heterogeneous and context-dependent ferroptosis susceptibility. Advances in nanoparticle-based delivery systems, biomarker-guided patient stratification, and rational combination strategies involving radiotherapy, chemotherapy, and immunotherapy suggest ferroptosis-based approaches may be approaching clinical feasibility. Furthermore, targeted therapeutic delivery strategies such as ADCs offer a complementary route to tumor-selective ferroptosis induction, as discussed in detail in Section 5.3. This may be particularly valuable for overcoming the CNS-selectivity barriers outlined above.

Significant but addressable challenges remain (Figure 3). Moving ferroptosis toward clinical translation in GBM will require biomarker-driven therapeutic strategies that identify tumors intrinsically positioned near the ferroptosis threshold. Based on the evidence reviewed here, one of the most actionable approaches may involve combining therapies already associated with ferroptotic priming, including TMZ, IR, and immunotherapy, with brain penetrant ferroptosis inducers in *CDKN2A*-deleted GBM, a molecular subset with a strong mechanistic rationale and a profound unmet clinical need. Integrating measurements of PUFA-phospholipid abundance, ACSL4 and GPX4 expression, transcriptional state identity, and ferroptosis-associated gene signatures may further refine patient selection and therapeutic response. Equally important will be the development of optimized BBB-penetrant agents capable of selectively targeting tumor cells while minimizing ferroptosis-associated toxicity within normal CNS tissue.

More broadly, ferroptosis may represent only one mechanism within a larger landscape of non-apoptotic, metabolism-linked cell death vulnerabilities in GBM. The same adaptations that render GBM resistant to apoptosis, including metabolic plasticity and lipid remodeling, may simultaneously generate other dependencies that can be therapeutically exploited. Emerging evidence suggests that multiple non-apoptotic cell death mechanisms may intersect through shared control of reactive oxygen species, mitochondrial dysfunction, and lipid metabolic homeostasis[155,156]. In this context, ferroptosis may serve not only as a therapeutic target itself but also as a broader framework for understanding how treatment-resistant GBM tumors become vulnerable through the same metabolic adaptations that sustain them during stress.

As the field moves forward, the central challenge will be to identify additional regulated cell death mechanisms and determine how specific molecular subsets or cell states of GBM become selectively vulnerable to them. Defining these context-dependent liabilities,

and therapeutically exploiting them with sufficient precision within the constraints of the CNS, may ultimately provide a path toward overcoming the profound treatment resistance that has historically defined GBM.

Declarations

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Authors contribution

Minami JK: Conceptualization, visualization, investigation, writing-original draft, writing-review & editing.
Salinas JJ: Conceptualization, visualization, writing-review & editing.
Loo CE: Investigation.
Lee WC, Dixon SJ: Writing-review & editing.
Nathanson DA: Conceptualization, writing-review & editing.

Conflicts of interest

David A Nathanson is a co-founder of Trethera Corporation and holds equity in the company. David A Nathanson is a co-founder of Katmai Pharmaceuticals and holds equity in and has consulting agreements with the company. David A Nathanson is an inventor on intellectual property related to ferroptosis. Scott J Dixon is an Editorial Board member of FOS. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-996. [DOI][PubMed]
2. Chen J, Li Y, Yu TS, McKay RM, Burns DK, Kernie SG, et al. A restricted cell population propagates glioblastoma growth after chemotherapy. Nature. 2012;488(7412):522-526. [DOI][PubMed][PMC]
3. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006;444(7120):756-760. [DOI][PubMed]
4. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. Neuro Oncol. 2021;23(8):1231-1251. [DOI][PubMed][PMC]
5. Wu W, Klockow JL, Zhang M, Lafortune F, Chang E, Jin L, et al. Glioblastoma multiforme (GBM): An overview of current therapies and mechanisms of resistance. Pharmacol Res. 2021;171:105780. [DOI][PubMed][PMC]
6. Brennan CW, Verhaak RGW, McKenna A, Campos B, Noushmehr H, Salama SR, et al. The somatic genomic landscape of glioblastoma. Cell. 2013;155(2):462-477. [DOI][PubMed][PMC]
7. Verhaak RGW, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant

subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010;17(1):98-110. [DOI][PubMed][PMC]
8. Wyllie AH, Kerr JFR, Currie AR. Cell death: The significance of apoptosis. Int Rev Cytol. 1980;68:251-306. [DOI][PubMed]
9. Hannun YA. Apoptosis and the dilemma of cancer chemotherapy. Blood. 1997;89(6):1845-1853. [DOI][PubMed]
10. Fernandez EG, Mai WX, Song K, Bayley NA, Kim J, Zhu H, et al. Integrated molecular and functional characterization of the intrinsic apoptotic machinery identifies therapeutic vulnerabilities in glioma. Nat Commun. 2024;15:10089. [DOI][PubMed][PMC]
11. Ziegler DS, Kung AL, Kieran MW. Anti-apoptosis mechanisms in malignant gliomas. J Clin Oncol. 2008;26(3):493-500. [DOI][PubMed]
12. Minami JK, Morrow D, Bayley NA, Fernandez EG, Salinas JJ, Tse C, et al. CDKN2A deletion remodels lipid metabolism to prime glioblastoma for ferroptosis. Cancer Cell. 2023;41(6):1048-1060.e9. [DOI][PubMed][PMC]
13. Neftel C, Laffy J, Filbin MG, Hara T, Shore ME, Rahme GJ, et al. An integrative model of cellular states, plasticity, and genetics for glioblastoma. Cell. 2019;178(4):835-849.e21. [DOI][PubMed][PMC]
14. Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science. 2014;344(6190):1396-1401. [DOI][PubMed][PMC]
15. Greenwald AC, Darnell NG, Hoefflin R, Simkin D, Mount CW, Gonzalez Castro LN, et al. Integrative spatial analysis reveals a multi-layered organization of glioblastoma. Cell. 2024;187(10):2485-2501.e26. [DOI][PubMed][PMC]
16. Lee WC, Dixon SJ. Mechanisms of ferroptosis sensitization and resistance. Dev Cell. 2025;60(7):982-993. [DOI][PubMed][PMC]
17. Pope LE, Dixon SJ. Regulation of ferroptosis by lipid metabolism. Trends Cell Biol. 2023;33(12):1077-1087. [DOI][PubMed][PMC]
18. Magtanong L, Mueller GD, Williams KJ, Billmann M, Chan K, Armenta DA, et al. Context-dependent regulation of ferroptosis sensitivity. Cell Chem Biol. 2022;29(9):1409-1418.e6. [DOI][PubMed][PMC]
19. Liang D, Minikes AM, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. Mol Cell. 2022;82(12):2215-2227. [DOI][PubMed][PMC]
20. Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. Cell. 2022;185(14):2401-2421. [DOI][PubMed][PMC]
21. Kagan VE, Mao G, Qu F, Angeli JPF, Doll S, St Croix C, et al. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017;13(1):81-90. [DOI][PubMed][PMC]
22. Mashayekhi S, Majedi H, Dehpour AR, Dehghan S, Jafarian M, Hadjighassem M, et al. Ferroptosis as a therapeutic target in glioblastoma: Mechanisms and emerging strategies. Mol Ther Nucleic Acids. 2025;36(3):102649. [DOI][PubMed][PMC]
23. Sun H, Zhang J, Qi H, Jiang D, Hu C, Mao C, et al. Ioning out glioblastoma: Ferroptosis mechanisms and therapeutic frontiers. Cell Death Discov. 2025;11(1):407. [DOI][PubMed][PMC]
24. D'Aprile S, Denaro S, Lavoro A, Candido S, Giallongo S, Torrisi F, et al. Glioblastoma mesenchymal subtype enhances antioxidant defence to reduce susceptibility to ferroptosis. Sci Rep. 2024;14:20770. [DOI][PubMed][PMC]
25. Liu T, Zhu C, Chen X, Guan G, Zou C, Shen S, et al. Ferroptosis, as the most enriched programmed cell death process in glioma, induces immunosuppression and immunotherapy resistance. Neuro Oncol. 2022;24(7):1113-1125. [DOI][PubMed][PMC]
26. Cheng J, Fan YQ, Liu BH, Zhou H, Wang JM, Chen QX. ACSL4 suppresses glioma cells proliferation via activating ferroptosis. Oncol Rep. 2020;43(1):147-158. [DOI][PubMed][PMC]
27. Cirotti C, Taddei I, Contadini C, di Girolamo C, Pepe G, De Bardi M, et al. NRF2 connects Src tyrosine kinase to ferroptosis resistance in glioblastoma. Life Sci Alliance. 2024;7(1):e202302205. [DOI][PubMed][PMC]
28. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: A regulated cell death nexus linking metabolism, redox biology, and disease. Cell. 2017;171(2):273-285. [DOI][PubMed][PMC]
29. Magtanong L, Ko PJ, To M, Cao JY, Forcina GC, Tarangelo A, et al. Exogenous monounsaturated fatty acids promote a ferroptosis-resistant cell state. Cell Chem Biol. 2019;26(3):420-432.e9. [DOI][PubMed][PMC]
30. Li Z, Lange M, Dixon SJ, Olzmann JA. Lipid quality control and ferroptosis: From concept to mechanism. Annu Rev Biochem. 2024;93:499-528. [DOI][PubMed][PMC]
31. Klett EL, Chen S, Yechoor A, Lih FB, Coleman RA. Long-chain acyl-CoA synthetase isoforms differ in preferences for eicosanoid species and long-chain fatty acids. J Lipid Res. 2017;58(5):884-894. [DOI][PubMed][PMC]
32. Yuan H, Li X, Zhang X, Kang R, Tang D. Identification of ACSL4 as a biomarker and contributor of ferroptosis. Biochem Biophys Res Commun. 2016;478(3):1338-1343. [DOI][PubMed]
33. von Krusenstiern AN, Robson RN, Qian N, Qiu B, Hu F, Reznik E, et al. Identification of essential sites of lipid peroxidation in ferroptosis. Nat Chem Biol. 2023;19(6):719-730. [DOI][PubMed][PMC]
34. Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, et al. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017;13(1):91-98. [DOI][PubMed][PMC]
35. Bezawork-Geleta A, Dimou J, Watt MJ. Lipid droplets and ferroptosis as new players in brain cancer glioblastoma progression and therapeutic resistance. Front Oncol. 2022;12:1085034. [DOI][PubMed][PMC]
36. Kim JW, Lee JY, Oh M, Lee EW. An integrated view of lipid metabolism in ferroptosis revisited via lipidomic analysis. Exp Mol Med. 2023;55(8):1620-1631. [DOI][PubMed][PMC]
37. Pan D, Jiao M, Zhu Y, Hu M, Li F, Yu J, et al. DGAT1 inhibition induces ferroptosis and enhances cancer immunotherapy efficacy. Cancer Res. 2026;86(12):3026-3039. [DOI][PubMed][PMC]
38. Cheng X, Geng F, Pan M, Wu X, Zhong Y, Wang C, et al. Targeting DGAT1 ameliorates glioblastoma by increasing fat catabolism and

oxidative stress. Cell Metab. 2020;32(2):229-242.e8. [DOI][PubMed][PMC]
39. Geng F, Guo D. Lipid droplets, potential biomarker and metabolic target in glioblastoma. Intern Med Rev. 2017;3(5):10.18103/imr.v3i5.443. [DOI][PubMed][PMC]
40. Wu X, Geng F, Cheng X, Guo Q, Zhong Y, Cloughesy TF, et al. Lipid droplets maintain energy homeostasis and glioblastoma growth via autophagic release of stored fatty acids. iScience. 2020;23(10):101569. [DOI][PubMed][PMC]
41. Puca F, Yu F, Bartolacci C, Pettazzoni P, Carugo A, Huang-Hobbs E, et al. Medium-chain acyl-CoA dehydrogenase protects mitochondria from lipid peroxidation in glioblastoma. Cancer Discov. 2021;11(11):2904-2923. [DOI][PubMed][PMC]
42. Yan Y, Teng H, Hang Q, Kondiparthi L, Lei G, Horbath A, et al. SLC7A11 expression level dictates differential responses to oxidative stress in cancer cells. Nat Commun. 2023;14(1):3673. [DOI][PubMed][PMC]
43. Sato H, Tamba M, Ishii T, Bannai S. Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. J Biol Chem. 1999;274(17):11455-11458. [DOI][PubMed]
44. Polewski MD, Reveron-Thornton RF, Cherryholmes GA, Marinov GK, Aboody KS. SLC7A11 overexpression in glioblastoma is associated with increased cancer stem cell-like properties. Stem Cells Dev. 2017;26(17):1236-1246. [DOI][PubMed][PMC]
45. Polewski MD, Reveron-Thornton RF, Cherryholmes GA, Marinov GK, Cassady K, Aboody KS. Increased expression of system xc- in glioblastoma confers an altered metabolic state and temozolomide resistance. Mol Cancer Res. 2016;14(12):1229-1242. [DOI][PubMed][PMC]
46. Tarangelo A, Magtanong L, Bieging-Rolett KT, Li Y, Ye J, Attardi LD, et al. p53 suppresses metabolic stress-induced ferroptosis in cancer cells. Cell Rep. 2018;22(3):569-575. [DOI][PubMed][PMC]
47. Boukalova S, Hubackova S, Milosevic M, Ezrova Z, Neuzil J, Rohlena J. Dihydroorotate dehydrogenase in oxidative phosphorylation and cancer. Biochim Biophys Acta Mol Basis Dis. 2020;1866(6):165759. [DOI][PubMed]
48. Barnes T, Parry P, Hart I, Jones C, Minet M, Patterson D. Regional mapping of the gene encoding dihydroorotate dehydrogenase, an enzyme involved in UMP synthesis, electron transport, and superoxide generation, to human chromosome region 16q22. Somat Cell Mol Genet. 1993;19(4):405-411. [DOI][PubMed]
49. Schild T, Keshari KR. Revealing de novo pyrimidine synthesis as a key vulnerability in brain tumors. Cancer Cell. 2022;40(12):1457-1458. [DOI][PubMed]
50. Spina R, Mills I, Ahmad F, Chen C, Ames HM, Winkles JA, et al. DHODH inhibition impedes glioma stem cell proliferation, induces DNA damage, and prolongs survival in orthotopic glioblastoma xenografts. Oncogene. 2022;41(50):5361-5372. [DOI][PubMed][PMC]
51. Mao C, Liu X, Zhang Y, Lei G, Yan Y, Lee H, et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. Nature. 2021;593(7860):586-590. [DOI][PubMed][PMC]
52. Mishima E, Nakamura T, Zheng J, Zhang W, Santos Dias Mourão A, Sennhenn P, et al. DHODH inhibitors sensitize to ferroptosis by FSP1 inhibition. Nature. 2023;619(7968):E9-E18. [DOI][PubMed]
53. Miao Z, Xu L, Gu W, Ren Y, Li R, Zhang S, et al. A targetable PRR11-DHODH axis drives ferroptosis- and temozolomide-resistance in glioblastoma. Redox Biol. 2024;73:103220. [DOI][PubMed][PMC]
54. Li K, Chen B, Xu A, Shen J, Li K, Hao K, et al. TRIM7 modulates NCOA4-mediated ferritinophagy and ferroptosis in glioblastoma cells. Redox Biol. 2022;56:102451. [DOI][PubMed][PMC]
55. Huan X, Li J, Chu Z, Zhang H, Cheng L, Lun P, et al. Dysregulation of iron homeostasis mediated by FTH increases ferroptosis sensitivity in TP53-mutant glioblastoma. Neurosci Bull. 2025;41(4):569-582. [DOI][PubMed][PMC]
56. Deshmukh P, Unni S, Krishnappa G, Padmanabhan B. The Keap1-Nrf2 pathway: Promising therapeutic target to counteract ROS-mediated damage in cancers and neurodegenerative diseases. Biophys Rev. 2017;9(1):41-56. [DOI][PubMed][PMC]
57. Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Biochim Biophys Acta Mol Cell Res. 2018;1865(5):721-733. [DOI][PubMed]
58. Yu C, Xiao JH. The Keap1-Nrf2 system: A mediator between oxidative stress and aging. Oxid Med Cell Longev. 2021;2021:6635460. [DOI][PubMed][PMC]
59. Fan Z, Wirth AK, Chen D, Wruck CJ, Rauh M, Buchfelder M, et al. Nrf2-Keap1 pathway promotes cell proliferation and diminishes ferroptosis. Oncogenesis. 2017;6(8):e371. [DOI][PubMed][PMC]
60. Wei Y, Duan S, Gong F, Li Q. The RNA-binding protein fragile-X mental retardation autosomal 1 (FXR1) modulates glioma cells sensitivity to temozolomide by regulating ferroptosis. Biochem Biophys Res Commun. 2022;603:153-159. [DOI][PubMed]
61. Sun S, Gao T, Pang B, Su X, Guo C, Zhang R, et al. RNA binding protein NKAP protects glioblastoma cells from ferroptosis by promoting SLC7A11 mRNA splicing in an m^{6}A-dependent manner. Cell Death Dis. 2022;13(1):73. [DOI][PubMed][PMC]
62. Sun Q, Lu H, Yuan FE, Zhao Q, Wei Y, Wang R, et al. SLC10A3 regulates ferroptosis of glioblastoma through the STAT3/GPX4 pathway. Sci Rep. 2025;15(1):21259. [DOI][PubMed][PMC]
63. Zheng X, Toyama T, Siu S, Kaneko T, Sugiura H, Yamashita S, et al. Selenoprotein P expression in glioblastoma as a regulator of ferroptosis sensitivity: Preservation of GPX4 via the cycling-selenium storage. Sci Rep. 2024;14:682. [DOI][PubMed][PMC]
64. Felsberg J, Hentschel B, Kaulich K, Gramatzki D, Zacher A, Malzkorn B, et al. Epidermal growth factor receptor variant III (EGFRvIII) positivity in *EGFR*-amplified glioblastomas: Prognostic role and comparison between primary and recurrent tumors. Clin Cancer Res. 2017;23(22):6846-6855. [DOI][PubMed]
65. Lv D, Zhong C, Dixit D, Yang K, Wu Q, Godugu B, et al. EGFR promotes ALKBH5 nuclear retention to attenuate N6-methyladenosine and protect against ferroptosis in glioblastoma. Mol Cell. 2023;83(23):4334-4351.e7. [DOI][PubMed][PMC]

66. Benitez JA, Ma J, D'Antonio M, Boyer A, Camargo MF, Zanca C, et al. PTEN regulates glioblastoma oncogenesis through chromatin-associated complexes of DAXX and histone H3.3. Nat Commun. 2017;8:15223. [DOI][PubMed][PMC]
67. Georgescu MM. PTEN tumor suppressor network in PI3K-Akt pathway control. Genes Cancer. 2010;1(12):1170-1177. [DOI][PubMed][PMC]
68. Cahuzac KM, Lubin A, Bosch K, Stokes N, Shoenfeld SM, Zhou R, et al. AKT activation because of PTEN loss upregulates xCT via GSK3β/NRF2, leading to inhibition of ferroptosis in PTEN-mutant tumor cells. Cell Rep. 2023;42(5):112536. [DOI][PubMed][PMC]
69. Cai J, Ye Z, Hu Y, Ye L, Gao L, Wang Y, et al. Fatostatin induces ferroptosis through inhibition of the AKT/mTORC1/GPX4 signaling pathway in glioblastoma. Cell Death Dis. 2023;14:211. [DOI][PubMed][PMC]
70. Pirozzi CJ, Hai Y. The implications of IDH mutations for cancer development and therapy. Nat Rev Clin Oncol. 2021;18(10):645-661. [DOI][PubMed]
71. Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, et al. IDH mutation in glioma: Molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020;122(11):1580-1589. [DOI][PubMed][PMC]
72. Badur MG, Muthusamy T, Parker SJ, Ma S, McBrayer SK, Cordes T, et al. Oncogenic R132 IDH1 mutations limit NADPH for de novo lipogenesis through $(D)_2$-hydroxyglutarate production in fibrosarcoma cells. Cell Rep. 2018;25(6):1680. [DOI][PubMed][PMC]
73. Wang TX, Liang JY, Zhang C, Xiong Y, Guan KL, Yuan HX. The oncometabolite 2-hydroxyglutarate produced by mutant IDH1 sensitizes cells to ferroptosis. Cell Death Dis. 2019;10(10):755. [DOI][PubMed][PMC]
74. Liu Y, Chou FJ, Lang F, Zhang M, Song H, Zhang W, et al. Protein kinase B (PKB/AKT) protects IDH-mutated glioma from ferroptosis via Nrf2. Clin Cancer Res. 2023;29(7):1305-1316. [DOI][PubMed][PMC]
75. Sahu U, Mullarkey MP, Murphy SA, Anderson JC, Putluri V, Kamal AHM, et al. IDH status dictates oHSV mediated metabolic reprogramming affecting anti-tumor immunity. Nat Commun. 2025;16(1):3874. [DOI][PubMed][PMC]
76. Bhaduri A, di Lullo E, Jung D, Müller S, Crouch EE, Espinosa CS, et al. Outer radial glia-like cancer stem cells contribute to heterogeneity of glioblastoma. Cell Stem Cell. 2020;26(1):48-63.e6. [DOI][PubMed][PMC]
77. Yabo YA, Niclou SP, Golebiewska A. Cancer cell heterogeneity and plasticity: A paradigm shift in glioblastoma. Neuro Oncol. 2022;24(5):669-682. [DOI][PubMed][PMC]
78. Pine AR, Cirigliano SM, Nicholson JG, Hu Y, Linkous A, Miyaguchi K, et al. Tumor microenvironment is critical for the maintenance of cellular states found in primary glioblastomas. Cancer Discov. 2020;10(7):964-979. [DOI][PubMed][PMC]
79. Vo VTA, Kim S, Hua TNM, Oh J, Jeong Y. Iron commensalism of mesenchymal glioblastoma promotes ferroptosis susceptibility upon dopamine treatment. Commun Biol. 2022;5(1):593. [DOI][PubMed][PMC]
80. Banu MA, Dovas A, Argenziano MG, Zhao W, Sperring CP, Cuervo Grajal H, et al. A cell state-specific metabolic vulnerability to GPX4-dependent ferroptosis in glioblastoma. EMBO J. 2024;43(20):4492-4521. [DOI][PubMed][PMC]
81. Mbah NE, Myers AL, Sajjakulnukit P, Chung C, Thompson JK, Hong HS, et al. Therapeutic targeting of differentiation-state dependent metabolic vulnerabilities in diffuse midline glioma. Nat Commun. 2024;15(1):8983. [DOI][PubMed][PMC]
82. Bou-Gharios J, Noël G, Burckel H. Preclinical and clinical advances to overcome hypoxia in glioblastoma multiforme. Cell Death Dis. 2024;15(7):503. [DOI][PubMed][PMC]
83. Bayona C, Ranđelović T, Ochoa I. Tumor microenvironment in glioblastoma: The central role of the hypoxic-necrotic core. Cancer Lett. 2026;639:218216. [DOI][PubMed]
84. Feldman L. Hypoxia within the glioblastoma tumor microenvironment: A master saboteur of novel treatments. Front Immunol. 2024;15:1384249. [DOI][PubMed][PMC]
85. Sun S, Guo C, Gao T, Ma D, Su X, Pang Q, et al. Hypoxia enhances glioma resistance to sulfasalazine-induced ferroptosis by upregulating SLC7A11 via PI3K/AKT/HIF-1α axis. Oxid Med Cell Longev. 2022;2022:7862430. [DOI][PubMed][PMC]
86. Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med. 2019;381(11):1001-1010. [DOI][PubMed]
87. Su X, Xie Y, Zhang J, Li M, Zhang Q, Jin G, et al. HIF-α activation by the prolyl hydroxylase inhibitor roxadustat suppresses chemoresistant glioblastoma growth by inducing ferroptosis. Cell Death Dis. 2022;13(10):861. [DOI][PubMed][PMC]
88. Hambardzumyan D, Gutmann DH, Kettenmann H. The role of microglia and macrophages in glioma maintenance and progression. Nat Neurosci. 2016;19(1):20-27. [DOI][PubMed][PMC]
89. Chen Z, Feng X, Herting CJ, Garcia VA, Nie K, Pong WW, et al. Cellular and molecular identity of tumor-associated macrophages in glioblastoma. Cancer Res. 2017;77(9):2266-2278. [DOI][PubMed][PMC]
90. Xu X, Zhang Y, Liao C, Zhou H, Wu Y, Zhang W. Impact of ferroptosis-related risk genes on macrophage M1/M2 polarization and prognosis in glioblastoma. Front Cell Neurosci. 2023;17:1294029. [DOI][PubMed][PMC]
91. Hosseinalizadeh H, Mahmoodpour M, Samadani AA, Roudkenar MH. The immunosuppressive role of indoleamine 2, 3-dioxygenase in glioblastoma: Mechanism of action and immunotherapeutic strategies. Med Oncol. 2022;39(9):130. [DOI][PubMed][PMC]
92. Tian Q, Dan G, Wang X, Zhu J, Chen C, Tang D, et al. IDO1 inhibits ferroptosis by regulating FTO-mediated M6A methylation and SLC7A11 mRNA stability during glioblastoma progression. Cell Death Discov. 2025;11(1):22. [DOI][PubMed][PMC]
93. Jung KH, LoRusso P, Burris H, Gordon M, Bang YJ, Hellmann MD, et al. Phase I study of the indoleamine 2, 3-dioxygenase 1 (IDO1) inhibitor navoximod (GDC-0919) administered with PD-L1 inhibitor (atezolizumab) in advanced solid tumors. Clin Cancer Res. 2019;25(11):3220-3228. [DOI][PubMed][PMC]
94. Naing A, Eder JP, Piha-Paul SA, Gimmi C, Hussey E, Zhang S, et al. Preclinical investigations and a first-in-human phase I trial of M4112,

the first dual inhibitor of indoleamine 2,3-dioxygenase 1 and tryptophan 2, 3-dioxygenase 2, in patients with advanced solid tumors. J Immunother Cancer. 2020;8(2):e000870. [DOI][PubMed][PMC]
95. Gao M, Yu W, Xi Z, Zhang Z, Fan X, Wang X. Recent update on the discovery of indoleamine-2, 3-dioxygenase 1 inhibitors targeting cancer immunotherapy. Eur J Med Chem. 2025;298:118017. [DOI][PubMed]
96. Sahu AP, Palsa K, Shenoy G, Slagle-Webb B, Connor JR. Tumor-associated macrophages promote ferroptosis resistance in glioblastoma by stimulating iron-loaded extracellular vesicle release. J Neurooncol. 2026;177(2):99. [DOI][PubMed][PMC]
97. Schwantes A, Shadid Y, Guerrero Ruiz VM, Aliraj B, Wickert A, Palmer MA, et al. Ferroptosis enhances T lymphocyte infiltration into glioblastoma spheroids. Antioxidants (Basel). 2025;14(11):1373. [DOI][PubMed][PMC]
98. Ye LF, Chaudhary KR, Zandkarimi F, Harken AD, Kinslow CJ, Upadhyayula PS, et al. Radiation-induced lipid peroxidation triggers ferroptosis and synergizes with ferroptosis inducers. ACS Chem Biol. 2020;15(2):469-484. [DOI][PubMed][PMC]
99. Song Q, Peng S, Sun Z, Heng X, Zhu X. Temozolomide drives ferroptosis via a DMT1-dependent pathway in glioblastoma cells. Yonsei Med J. 2021;62(9):843-849. [DOI][PubMed][PMC]
100. Yang H, Zhao W, Huang Y, Wu Y, Zou Y, Wang T, et al. Novel imidazotetrazine derivatives overcome temozolomide resistance in glioblastoma by inducing ferroptosis and apoptosis. Cell Death Discov. 2026;12:14. [DOI][PubMed][PMC]
101. Jezierzański M, Nafalska N, Stopyra M, Furgoł T, Miciak M, Kabut J, et al. Temozolomide (TMZ) in the treatment of glioblastoma multiforme—a literature review and clinical outcomes. Curr Oncol. 2024;31(7):3994-4002. [DOI][PubMed][PMC]
102. Wang J, Guo D, Jiang S, Wu W, Gao X. Targeting ferroptosis in cancer: From mechanistic insights to therapeutic approaches. Mol Biomed. 2026;7(1):20. [DOI][PubMed][PMC]
103. Caforio M, Iacovelli S, Locatelli F, Folgiero V. Inducing ferroptosis to improve cancer therapy: A promising tool for enhancing immunotherapy. J Exp Clin Cancer Res. 2025;45(1):10. [DOI][PubMed][PMC]
104. Sun S, Shen J, Jiang J, Wang F, Min J. Targeting ferroptosis opens new avenues for the development of novel therapeutics. Sig Transduct Target Ther. 2023;8(1):372. [DOI][PubMed][PMC]
105. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell. 2012;149(5):1060-1072. [DOI][PubMed][PMC]
106. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, et al. Regulation of ferroptotic cancer cell death by GPX4. Cell. 2014;156(1-2):317-331. [DOI][PubMed][PMC]
107. Yu H, Guo P, Xie X, Wang Y, Chen G. Ferroptosis, a new form of cell death, and its relationships with tumourous diseases. J Cell Mol Med. 2017;21(4):648-657. [DOI][PubMed][PMC]
108. Robe PA, Martin DH, Nguyen-Khac MT, Artesi M, Deprez M, Albert A, et al. Early termination of ISRCTN45828668, a phase 1/2 prospective, randomized study of sulfasalazine for the treatment of progressing malignant gliomas in adults. BMC Cancer. 2009;9:372. [DOI][PubMed][PMC]
109. Wang L, Chen X, Yan C. Ferroptosis: An emerging therapeutic opportunity for cancer. Genes Dis. 2022;9(2):334-346. [DOI][PubMed][PMC]
110. Hassannia B, Wiernicki B, Ingold I, Qu F, Van Herck S, Tyurina YY, et al. Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma. J Clin Invest. 2018;128(8):3341-3355. [DOI][PubMed][PMC]
111. Shimada K, Skouta R, Kaplan A, Yang WS, Hayano M, Dixon SJ, et al. Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis. Nat Chem Biol. 2016;12(7):497-503. [DOI][PubMed][PMC]
112. Zhang X, Guo Y, Li H, Han L. FIN56, a novel ferroptosis inducer, triggers lysosomal membrane permeabilization in a TFEB-dependent manner in glioblastoma. J Cancer. 2021;12(22):6610-6619. [DOI][PubMed][PMC]
113. Hambright WS, Fonseca RS, Chen L, Na R, Ran Q. Ablation of ferroptosis regulator glutathione peroxidase 4 in forebrain neurons promotes cognitive impairment and neurodegeneration. Redox Biol. 2017;12:8-17. [DOI][PubMed][PMC]
114. Friedmann Angeli JP, Schneider M, Proneth B, Tyurina YY, Tyurin VA, Hammond VJ, et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. Nat Cell Biol. 2014;16(12):1180-1191. [DOI][PubMed][PMC]
115. Carlson BA, Tobe R, Yefremova E, Tsuji PA, Hoffmann VJ, Schweizer U, et al. Glutathione peroxidase 4 and vitamin E cooperatively prevent hepatocellular degeneration. Redox Biol. 2016;9:22-31. [DOI][PubMed][PMC]
116. Louandre C, Ezzoukhry Z, Godin C, Barbare JC, Mazière JC, Chauffert B, et al. Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib. Int J Cancer. 2013;133(7):1732-1742. [DOI][PubMed]
117. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390. [DOI][PubMed]
118. Zheng J, Sato M, Mishima E, Sato H, Proneth B, Conrad M. Sorafenib fails to trigger ferroptosis across a wide range of cancer cell lines. Cell Death Dis. 2021;12(7):698. [DOI][PubMed][PMC]
119. Mortensen MS, Ruiz J, Watts JL. Polyunsaturated fatty acids drive lipid peroxidation during ferroptosis. Cells. 2023;12(5):804. [DOI][PubMed][PMC]
120. Dixon SJ, Winter GE, Musavi LS, Lee ED, Snijder B, Rebsamen M, et al. Human haploid cell genetics reveals roles for lipid metabolism genes in nonapoptotic cell death. ACS Chem Biol. 2015;10(7):1604-1609. [DOI][PubMed][PMC]
121. Cao J, Chen X, Chen L, Lu Y, Wu Y, Deng A, et al. DHODH-mediated mitochondrial redox homeostasis: A novel ferroptosis regulator and promising therapeutic target. Redox Biol. 2025;85:103788. [DOI][PubMed][PMC]
122. Teng D, Swanson KD, Wang R, Zhuang A, Wu H, Niu Z, et al. DHODH modulates immune evasion of cancer cells via CDP-Choline

dependent regulation of phospholipid metabolism and ferroptosis. Nat Commun. 2025;16(1):3867. [DOI][PubMed][PMC]
123. Olsen TK, Dyberg C, Embaie BT, Alchahin A, Milosevic J, Ding J, et al. DHODH is an independent prognostic marker and potent therapeutic target in neuroblastoma. JCI Insight. 2022;7(17):e153836. [DOI][PubMed][PMC]
124. Cao Z, Liu X, Zhang W, Zhang K, Pan L, Zhu M, et al. Biomimetic macrophage membrane-camouflaged nanoparticles induce ferroptosis by promoting mitochondrial damage in glioblastoma. ACS Nano. 2023;17(23):23746-23760. [DOI][PubMed][PMC]
125. Li LC, Okino ST, Zhao H, Pookot D, Place RF, Urakami S, et al. Small dsRNAs induce transcriptional activation in human cells. Proc Natl Acad Sci U S A. 2006;103(46):17337-17342. [DOI][PubMed][PMC]
126. Meng X, Jiang Q, Chang N, Wang X, Liu C, Xiong J, et al. Small activating RNA binds to the genomic target site in a seed-region-dependent manner. Nucleic Acids Res. 2016;44(5):2274-2282. [DOI][PubMed][PMC]
127. Li B, Chen X, Qiu W, Zhao R, Duan J, Zhang S, et al. Synchronous disintegration of ferroptosis defense axis via engineered exosome-conjugated magnetic nanoparticles for glioblastoma therapy. Adv Sci (Weinh). 2022;9(17):e2105451. [DOI][PubMed][PMC]
128. Liu B, Ji Q, Cheng Y, Liu M, Zhang B, Mei Q, et al. Biomimetic GBM-targeted drug delivery system boosting ferroptosis for immunotherapy of orthotopic drug-resistant GBM. J Nanobiotechnology. 2022;20(1):161. [DOI][PubMed][PMC]
129. Ge Z, Wang Z, Zhao E, Guo Y, Zhang L, Tian F, et al. Stress granules restrain ferroptosis by sequestering ferritin. Nat Cell Biol. 2026;28(6):1204-1218. [DOI][PubMed]
130. Chen C, Zhu X, Song Z, Xing Y, Jin W, Li F, et al. Dual-targeted bacterial outer membrane vesicles enhance glioblastoma immunotherapy by regulating tumor microenvironment and inducing IFN-γ-mediated ferroptosis. J Nanobiotechnology. 2025;24(1):44. [DOI][PubMed][PMC]
131. Wang X, Shi W, Li M, Xin Y, Jiang X. RSL3 sensitizes glioma cells to ionizing radiation by suppressing TGM2-dependent DNA damage repair and epithelial-mesenchymal transition. Redox Biol. 2024;78:103438. [DOI][PubMed][PMC]
132. Zhu X, Zhou Y, Ou Y, Cheng Z, Han D, Chu Z, et al. Characterization of ferroptosis signature to evaluate the predict prognosis and immunotherapy in glioblastoma. Aging. 2021;13(13):17655-17672. [DOI][PubMed][PMC]
133. Luo Y, Bai XY, Zhang L, Hu QQ, Zhang N, Cheng JZ, et al. Ferroptosis in cancer therapy: Mechanisms, small molecule inducers, and novel approaches. Drug Des Devel Ther. 2024;18:2485-2529. [DOI][PubMed][PMC]
134. Jiang T, Ma W, Dong W, Zhou H, Mao X. Ferroptosis-associated transcriptional factors in neurological diseases: Molecular mechanisms and therapeutic prospects. Exp Mol Med. 2025;57(12):2763-2781. [DOI][PubMed][PMC]
135. Huang Q, Zhang H, Chen S, Wang Y, Zhou J. Ferroptosis in central nervous system injuries: Molecular mechanisms, diagnostic approaches, and therapeutic strategies. Front Cell Neurosci. 2025;19:1593963. [DOI][PubMed][PMC]
136. Wei Z, Yu H, Zhao H, Wei M, Xing H, Pei J, et al. Broadening horizons: Ferroptosis as a new target for traumatic brain injury. Burns Trauma. 2024;12:tkad051. [DOI][PubMed][PMC]
137. Liu Q, Song T, Chen B, Zhang J, Li W. Ferroptosis of brain microvascular endothelial cells contributes to hypoxia-induced blood-brain barrier injury. FASEB J. 2023;37(5):e22874. [DOI][PubMed]
138. Chen L, Hambright WS, Na R, Ran Q. Ablation of the ferroptosis inhibitor glutathione peroxidase 4 in neurons results in rapid motor neuron degeneration and paralysis. J Biol Chem. 2015;290(47):28097-28106. [DOI][PubMed][PMC]
139. Mahoney-Sanchez L, Bouchaoui H, Boussaad I, Jonneaux A, Timmerman K, Berdeaux O, et al. Alpha synuclein determines ferroptosis sensitivity in dopaminergic neurons via modulation of ether-phospholipid membrane composition. Cell Rep. 2022;40(8):111231. [DOI][PubMed]
140. Vásquez V, Krieg M, Lockhead D, Goodman MB. Phospholipids that contain polyunsaturated fatty acids enhance neuronal cell mechanics and touch sensation. Cell Rep. 2014;6(1):70-80. [DOI][PubMed][PMC]
141. Morita S, Kondo T, Tokuda H, Kaneda Y, Izumo T, Nakao Y, et al. Polyunsaturated fatty acids in lipid membranes regulate human neuronal function and amyloid-β production. iScience. 2025;28(6):112557. [DOI][PubMed][PMC]
142. Mosele F, Peltier A, Ozaki Y, Detappe A, Soria JC, André F. The next generation of antibody-drug conjugates. Nat Med. 2026;32(8):2774-2785. [DOI][PubMed]
143. Fu Z, Li S, Han S, Shi C, Zhang Y. Antibody drug conjugate: The "biological missile" for targeted cancer therapy. Sig Transduct Target Ther. 2022;7:93. [DOI][PubMed][PMC]
144. Fan R, Chen C, Mu M, Chuan D, Liu H, Hou H, et al. Engineering MMP-2 activated nanoparticles carrying B7-H3 bispecific antibodies for ferroptosis-enhanced glioblastoma immunotherapy. ACS Nano. 2023;17(10):9126-9139. [DOI][PubMed]
145. Zhang Y, Chi X, Feng R, Xian N, Huang N, Sun S, et al. Intracranial delivery of B7-H3-targeting CAR-T cells for recurrent glioblastoma: A phase 1 trial. Nat Med. 2026;32(9):3268-3275. [DOI][PubMed]
146. Martins TA, Kaymak D, Tatari N, Gerster F, Hogan S, Ritz MF, et al. Enhancing anti-EGFRvIII CAR T cell therapy against glioblastoma with a paracrine SIRPγ-derived CD47 blocker. Nat Commun. 2024;15(1):9718. [DOI][PubMed][PMC]
147. Hamblett KJ, Kozlosky CJ, Siu S, Chang WS, Liu H, Foltz IN, et al. AMG 595, an anti-EGFRvIII antibody-drug conjugate, induces potent antitumor activity against EGFRvIII-expressing glioblastoma. Mol Cancer Ther. 2015;14(7):1614-1624. [DOI][PubMed]
148. Rosenthal M, Curry R, Reardon DA, Rasmussen E, Upreti VV, Damore MA, et al. Safety, tolerability, and pharmacokinetics of anti-EGFRvIII antibody-drug conjugate AMG 595 in patients with recurrent malignant glioma expressing EGFRvIII. Cancer Chemother Pharmacol. 2019;84(2):327-336. [DOI][PubMed]
149. van den Bent M, Gan HK, Lassman AB, Kumthekar P, Merrell R, Butowski N, et al. Efficacy of depatuxizumab mafodotin (ABT-414) monotherapy in patients with EGFR-amplified, recurrent glioblastoma: Results from a multi-center, international study. Cancer

Chemother Pharmacol. 2017;80(6):1209-1217. [DOI][PubMed][PMC]
150. Lassman AB, van den Bent MJ, Gan HK, Reardon DA, Kumthekar P, Butowski N, et al. Safety and efficacy of depatuxizumab mafodotin + temozolomide in patients with EGFR-amplified, recurrent glioblastoma: Results from an international phase I multicenter trial. Neuro Oncol. 2019;21(1):106-114. [DOI][PubMed][PMC]
151. Clement PMJ, Dirven L, Eoli M, Sepulveda-Sanchez JM, Walenkamp AME, Frenel JS, et al. Impact of depatuxizumab mafodotin on health-related quality of life and neurological functioning in the phase II EORTC 1410/INTELLANCE 2 trial for EGFR-amplified recurrent glioblastoma. Eur J Cancer. 2021;147:1-12. [DOI][PubMed]
152. Nguyen KA, Conilh L, Falson P, Dumontet C, Boumendjel A. The first ADC bearing the ferroptosis inducer RSL3 as a payload with conservation of the fragile electrophilic warhead. Eur J Med Chem. 2022;244:114863. [DOI][PubMed]
153. Zhang Y, Cui X, Du J, Cui G, Ling Y, Tang C. Development of the FGFR4-ADC bearing the ferroptosis inducer sulfasalazine for hepatocellular carcinoma. iScience. 2025;28(11):113718. [DOI][PubMed][PMC]
154. Zhang Y, Du J, Cui X, Ling Y, Tang C. Development of a bispecific CDH17-GUCY2C ADC bearing the ferroptosis inducer RSL3 for the treatment of colorectal cancer. Cell Death Discov. 2025;11(1):347. [DOI][PubMed][PMC]
155. Leak L, Dixon SJ. Surveying the landscape of emerging and understudied cell death mechanisms. Biochim Biophys Acta Mol Cell Res. 2023;1870(3):119432. [DOI][PubMed][PMC]
156. Leak L, Wang Z, Joseph AJ, Johnson B, Chan AA, Decosto CM, et al. Tegavivint triggers TECR-dependent nonapoptotic cancer cell death. Nat Chem Biol. 2025;21(12):1873-1884. [DOI][PubMed][PMC]

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