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Ferroptosis in glioblastoma: Molecular determinants, immune crosstalk, and therapeutic opportunities

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ABSTRACT

Glioblastoma(GBM) is characterized by rapid recurrence and resistance to radiochemotherapy, highlighting the need for therapeutic vulnerabilities that extend beyond genetic subtypes. Ferroptosis, an iron-dependent form of lipid peroxidation-driven cell death, has emerged as a promising but complex vulnerability in GBM. In this review, we summarize how ferroptotic sensitivity is shaped by core iron–lipid–antioxidant machinery and by GBM-specific regulatory layers, including mitophagy, m6A-dependent GPX4 regulation, lipid metabolic remodeling, and DNA damage-associated stress responses. We further discuss how ferroptosis interacts with the GBM immune microenvironment, where it may either promote antitumor immunity or be exploited to induce immune-cell dysfunction. Finally, we evaluate therapeutic strategies that combine ferroptosis modulation with radiotherapy, temozolomide chemotherapy, immunotherapy, and nanomedicine-based delivery. We propose that ferroptosis-targeted strategies in GBM should be guided by tumor context, immune-cell preservation, and biomarker-based patient stratification.

1. Introduction

Glioblastoma (GBM) represents the most aggressive and lethal form of primary malignant brain tumors in adults. Despite maximal safe surgical resection followed by standard radiochemotherapy with temozolomide (TMZ), the median overall survival of patients with GBM remains approximately 14–16 months, and long-term survival is exceedingly rare (Hampe et al., 2024; Larsson et al., 2020; Schnöller et al., 2022; Stupp et al., 2017; Tan et al., 2020; Wen et al., 2020). Nearly all patients experience tumor recurrence, underscoring the profound therapeutic resistance and adaptive capacity of this malignancy. Several intrinsic features contribute to the poor clinical outcomes of GBM. First, GBM exhibits pronounced intratumoral and intertumoral heterogeneity, characterized by diverse genetic alterations, epigenetic states, and cellular hierarchies, which collectively enable rapid selection of therapy-resistant subclones (Brisson et al., 2023; Chen et al., 2025a; Gállego Pérez-Larraya and Ducray, 2014; Kay et al., 2024; Omuro, 2013; Wu et al., 2015). Second, GBM cells display remarkable metabolic plasticity, allowing them to adapt to fluctuating nutrient availability, hypoxia, and oxidative stress within the tumor microenvironment (TME) (Butler et al., 2020; Chen et al., 2022; Coniglio, 2023; Hoogstrate et al., 2023; Ma et al., 2021; Wu et al., 2023a). Third, GBM establishes a profoundly immunosuppressive microenvironment, marked by dysfunctional antigen presentation, enrichment of immunosuppressive myeloid populations, and limited responsiveness to immune checkpoint blockade. These factors converge to blunt the efficacy of conventional therapies, including chemotherapy, radiotherapy, and emerging immunotherapeutic strategies. Given these challenges, there is an urgent need to identify alternative vulnerabilities in GBM that transcend genetic heterogeneity and can be therapeutically exploited across molecular subtypes.

Ferroptosis provides a mechanistic framework through which iron handling, membrane lipid composition, and antioxidant buffering can be linked to GBM progression and therapeutic resistance (Minami et al., 2023; Cao et al., 2023). Because these processes are extensively reshaped in GBM, ferroptosis represents both a potential vulnerability and an adaptive survival program (Wang et al., 2024a; Cai et al., 2023a). Importantly, these processes intersect with oncogenic signaling and metabolic programs that are frequently altered in cancer. GBM exhibits a paradoxical relationship with ferroptosis. On one hand, GBM cells are intrinsically prone to ferroptotic stress due to their elevated reactive oxygen species (ROS) levels, high dependence on PUFA-rich lipid pools,

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and increased iron demand to sustain rapid proliferation and metabolic activity (Huang et al., 2023; Su et al., 2019; Wang et al., 2023a; Zhang et al., 2024). On the other hand, GBM actively develops robust anti-ferroptotic mechanisms, such as upregulation of antioxidant pathways, rewiring of lipid metabolism, and activation of stress-adaptive signaling, enabling tumor cells to tolerate chronic oxidative pressure and survive therapeutic insults. This duality positions ferroptosis as both a latent vulnerability and a tightly regulated escape mechanism in GBM biology.

Previous reviews have provided valuable summaries of the canonical mechanisms of ferroptosis, its roles across different cancer types, and its potential therapeutic relevance in GBM (Li et al., 2024; Miao et al., 2024). However, many of these discussions remain either broadly cancer-focused or centered on general ferroptosis biology, with relatively limited integration of GBM-specific features such as intratumoral heterogeneity, blood–brain barrier constraints, immune-cell ferroptosis, radiochemotherapy resistance, orthotopic model evidence, and biomarker-guided therapeutic stratification (Zeng et al., 2025; Li et al., 2025; Mitre et al., 2022). In particular, the dual role of ferroptosis in GBM—as both a tumor-cell vulnerability and a potential driver of immune-cell dysfunction—has not been systematically synthesized in relation to translational feasibility. These gaps support the need for a focused review that specifically examines ferroptosis in the biological and therapeutic context of GBM.

Unlike previous reviews that mainly summarize the canonical biochemical machinery of ferroptosis, this review focuses on how GBM-specific cellular states and microenvironmental pressures reshape ferroptotic thresholds. The objective of this review is to clarify how ferroptosis functions as a context-dependent vulnerability in GBM by integrating evidence from tumor-intrinsic regulation, immune microenvironmental interactions, treatment resistance, and biomarker-guided therapeutic strategies. We organize the discussion around three key questions: which molecular regulators determine ferroptosis sensitivity in GBM cells, how ferroptosis influences tumor–immune interactions, and how ferroptosis modulation can be integrated into therapeutic strategies against radio- and chemotherapy resistance.

This narrative review was based on a literature search of PubMed, Web of Science, and Google Scholar from database inception to June 2026. The search was conducted using combinations of the following terms: “glioblastoma,” “GBM,” “glioma,” “ferroptosis,” “lipid peroxidation,” “iron metabolism,” “GPX4,” “SLC7A11,” “NRF2,” “temozolomide resistance,” “radiotherapy resistance,” “tumor immune microenvironment,” “blood–brain barrier,” and “nanomedicine.” Priority was given to English-language original experimental studies, translational studies, and recent reviews directly related to GBM ferroptosis, immune crosstalk, therapeutic resistance, biomarkers, and ferroptosis-based treatment strategies. Seminal studies defining ferroptosis biology and clinically relevant GBM management were also included where appropriate. Articles were selected according to their relevance to the scope of this review, mechanistic depth, recency, and translational significance. Studies focused only on non-CNS tumors or lacking clear relevance to ferroptosis or GBM were excluded. Because this article is a narrative rather than a systematic review, no formal meta-analysis or risk-of-bias assessment was performed.

2. Core machinery of ferroptosis in GBM

Ferroptosis is executed through three core biochemical modules: iron-dependent redox activity, peroxidation of PUFA-containing membrane phospholipids, and antioxidant defense systems that detoxify lipid hydroperoxides. This section briefly outlines these core components as the mechanistic foundation for understanding how upstream GBM-specific regulators reshape ferroptotic thresholds in later sections.

2.1. Iron metabolism and redox homeostasis

Iron is a central driver of ferroptosis due to its ability to catalyze redox reactions and promote the generation of reactive oxygen species. Intracellular iron exists primarily in two pools: a labile iron pool that actively participates in redox chemistry and a storage pool sequestered in ferritin complexes. Dysregulation of iron uptake, storage, and release can profoundly alter cellular redox homeostasis (Caverzan and Ibarra, 2024; Hayashima and Katoh, 2022; Hayashima et al., 2021; Sahu et al., 2025; Vo et al., 2022). GBM cells exhibit a pronounced iron-dependent phenotype, characterized by increased iron uptake and utilization to sustain DNA synthesis, mitochondrial respiration, and metabolic enzyme activity. Elevated expression of iron transporters and altered ferritin dynamics expand the labile iron pool, thereby enhancing susceptibility to iron-catalyzed oxidative reactions. Through the Fenton reaction, ferrous iron (Fe^{2+}) reacts with hydrogen peroxide to generate highly reactive hydroxyl radicals, which initiate lipid peroxidation and propagate oxidative membrane damage (Minami et al., 2023; Liu et al., 2025a; Mungur et al., 2025; Zhou et al., 2025a). Thus, iron metabolism defines the pro-oxidant input of ferroptosis by controlling the size and reactivity of the labile iron pool.

2.2. Lipid peroxidation and PUFA metabolism

The execution of ferroptosis critically depends on the peroxidation of membrane phospholipids enriched in polyunsaturated fatty acids (PUFAs). Due to their bis-allylic hydrogen atoms, PUFAs are particularly prone to radical-mediated oxidation, making them the primary substrates for lethal lipid peroxidation. In GBM, lipid metabolism is extensively reprogrammed to support rapid growth and adaptation to hostile microenvironmental conditions. Enzymes involved in PUFA activation and incorporation into membrane phospholipids, such as acyl-CoA synthetase long-chain family member 4 (ACSL4), play a pivotal role in determining ferroptosis sensitivity by regulating the availability of oxidizable lipid substrates (Hacioglu and Kar, 2023; Bao et al., 2021; Yee et al., 2020; Zhang et al., 2023a). Elevated PUFA incorporation increases the density of peroxidation-prone phospholipids, thereby lowering the threshold for ferroptotic damage. Therefore, the abundance and composition of PUFA-containing phospholipids determine the substrate pool available for ferroptotic lipid peroxidation.

2.3. Antioxidant defense systems

Counterbalancing iron-driven lipid peroxidation, GBM cells rely on robust antioxidant defense mechanisms that function as the principal “brake” on ferroptosis. Among these, the System Xc^- (SLC7A11)–glutathione (GSH)–glutathione peroxidase 4 (GPX4) axis represents the central protective module (Wang et al., 2024a; Li et al., 2021; Tian et al., 2025; Wang et al., 2025a, 2024a; Zhou et al., 2025b). System Xc^- imports extracellular cystine in exchange for intracellular glutamate, enabling cysteine availability for GSH biosynthesis. GSH serves as an essential cofactor for GPX4, the only known enzyme capable of directly reducing phospholipid hydroperoxides to non-toxic lipid alcohols within biological membranes. Loss of GPX4 activity or depletion of GSH results in uncontrolled lipid peroxidation and rapid induction of ferroptosis (Cai et al., 2023a; Banu et al., 2024; Sun et al., 2025a; Yi et al., 2020). In addition to this core axis, GBM cells frequently activate NRF2-driven transcriptional programs that coordinate a broad antioxidant response, including genes involved in cysteine metabolism, NADPH regeneration, iron sequestration, and detoxification of reactive intermediates. NRF2 signaling thus reinforces ferroptosis resistance by globally enhancing redox buffering capacity and stabilizing cellular antioxidant networks (Cirotti et al., 2024; de Souza et al., 2022; Su et al., 2023; Tuncer and Hacioglu, 2024; Xing et al., 2025; Zheng et al., 2022). These antioxidant systems constitute the major protective arm of ferroptosis, whereas their upstream regulation in GBM is discussed in the following section.

Collectively, iron availability, PUFA-phospholipid abundance, and antioxidant detoxification define the biochemical threshold for ferroptosis. The following section focuses on GBM-specific regulators that modify this threshold under metabolic and therapeutic stress. Section 2 defines the biochemical execution machinery of ferroptosis, whereas Section 3 focuses on upstream GBM-specific regulators that tune this machinery under metabolic, immune, and therapeutic stress.

3. Molecular determinants regulating ferroptosis sensitivity in GBM

Having defined the core biochemical machinery of ferroptosis, this section focuses on GBM-specific regulatory axes that modify ferroptotic thresholds. These mechanisms do not replace the iron–lipid–GPX4 framework; rather, they tune ferroptosis sensitivity by controlling mitochondrial quality, GPX4 expression, lipid substrate availability, and stress-adaptive responses.

3.1. Mitochondrial homeostasis and mitophagy

Mitochondrial quality control represents one GBM-specific layer that modifies the redox threshold for ferroptosis. Mitophagy, the selective autophagic removal of damaged mitochondria, plays a pivotal role in maintaining mitochondrial quality and redox balance. Recent evidence highlights a SIRT3–mitophagy axis as a key modulator of ferroptosis sensitivity in GBM (Li et al., 2024). SIRT3, a mitochondrial deacetylase involved in oxidative metabolism and stress adaptation, functions as a gatekeeper of mitochondrial homeostasis. Inhibition or depletion of SIRT3 enhances mitophagy, leading to the clearance of dysfunctional mitochondria and reshaping intracellular redox dynamics. Importantly, augmented mitophagy following SIRT3 suppression is accompanied by downregulation of SLC7A11, resulting in impaired cystine uptake, reduced glutathione synthesis, and compromised GPX4 activity (Lv et al., 2025). This coordinated remodeling lowers antioxidant capacity and sensitizes GBM cells to ferroptotic stress. These findings underscore a mechanistic link between mitochondrial quality control and the System Xc^-–GSH–GPX4 axis(Fig. 1).

Conceptually, mitophagy in GBM functions as a context-dependent regulator of ferroptosis. While basal mitophagy can protect tumor cells by limiting excessive ROS accumulation, excessive or dysregulated mitophagy may paradoxically promote ferroptosis by destabilizing redox buffering systems. This dual role highlights the importance of mitochondrial dynamics in fine-tuning ferroptotic vulnerability.

3.2. Epigenetic and epitranscriptomic regulation

Epigenetic and epitranscriptomic mechanisms have emerged as critical modulators of cellular stress responses and cell fate decisions. Among these, N6-methyladenosine (m6A) RNA modification plays a central role in regulating mRNA stability, translation efficiency, and stress adaptability under oxidative conditions. In GBM, a recent primary study identified a C5aR1–ERK1/2–METTL3–GPX4 axis as a potential epitranscriptomic mechanism of ferroptosis resistance (Meng et al., 2024). Although C5aR1 is classically recognized as a plasma membrane G protein-coupled receptor, immunofluorescence staining in U87 and U251 GBM cells showed C5aR1 signals not only at the cell membrane but also in the cytoplasm. The same study also detected intracellular C5a signals by immunofluorescence, suggesting a possible intracellular C5a–C5aR1 signaling loop; however, the source, processing, and functional requirement of intracellular C5a remain incompletely defined. Mechanistically, C5aR1 knockdown reduced ERK1/2 activation, decreased METTL3 abundance, impaired METTL3-dependent m6A modification of GPX4 mRNA, and lowered GPX4 expression, thereby increasing lipid peroxidation and ferroptotic susceptibility. Importantly, while C5aR1 upregulation and prognostic association were observed in glioma tissues, the complete intracellular C5aR1–ERK1/2–METTL3–GPX4 cascade has been functionally validated mainly in GBM cell lines and intracranial xenograft models. Therefore, further studies using human GBM specimens are required to confirm whether this intracellular complement-related pathway operates in patient tumors. This finding reveals that ferroptosis resistance can be enforced not only through metabolic rewiring but also through precise epitranscriptomic control. Collectively, these observations elevate GPX4 from a mere metabolic enzyme to a convergence point of signaling and epigenetic regulation, positioning epitranscriptomic plasticity as a critical determinant of ferroptosis sensitivity in GBM (Fig. 2). These findings should be interpreted as a mechanistically supported but still emerging model, because direct evidence for

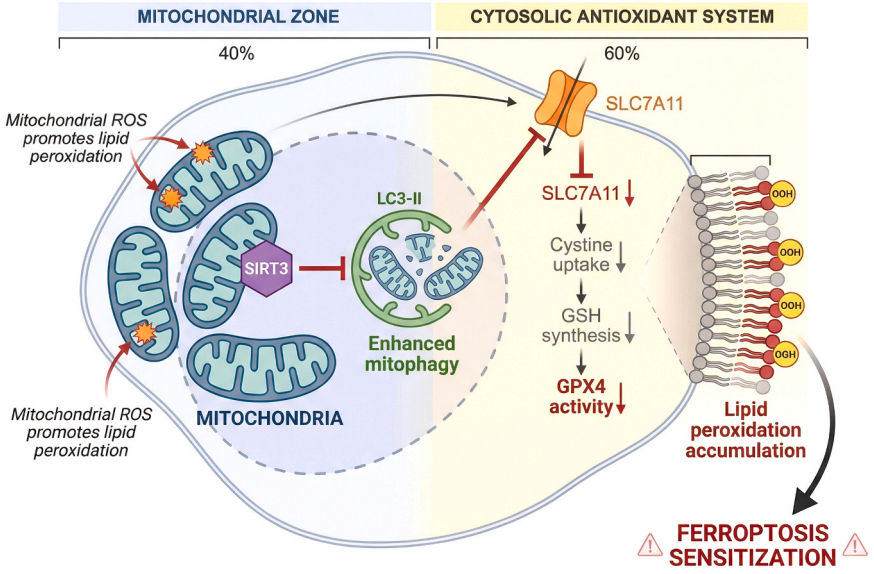

Fig. 1. SIRT3–mitophagy axis regulates ferroptosis sensitivity in glioblastoma. Mitochondrial ROS promotes lipid peroxidation and ferroptotic stress in glioblastoma cells. Inhibition of SIRT3 enhances mitophagy, leading to reduced SLC7A11 expression, impaired cystine uptake, glutathione depletion, and compromised GPX4 activity. This coordinated redox remodeling lowers antioxidant capacity and sensitizes glioblastoma cells to ferroptosis, highlighting mitophagy as a context-dependent regulator of ferroptotic vulnerability.

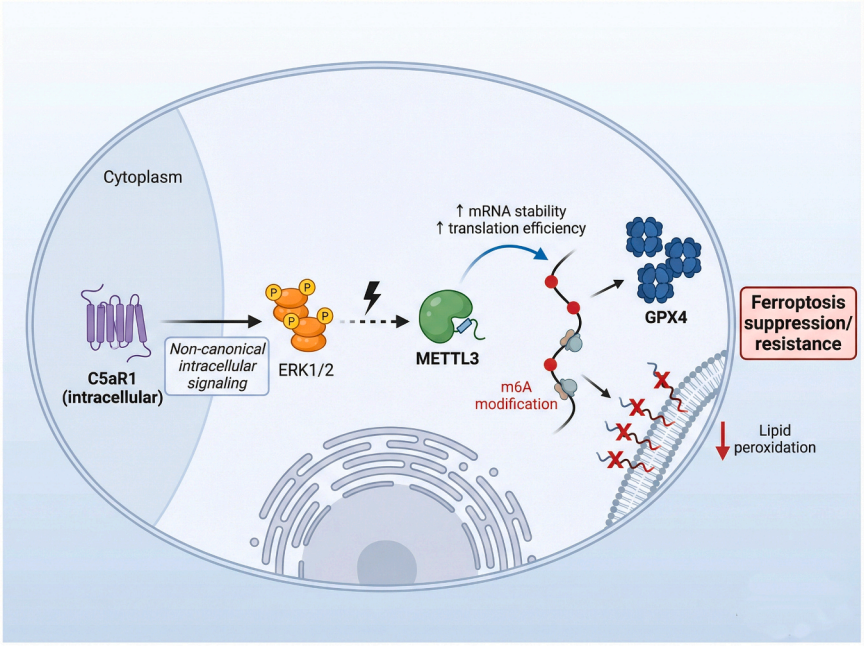

Fig. 2. Epitranscriptomic regulation of ferroptosis resistance via the C5aR1–ERK–METTL3–GPX4 axis in glioblastoma. Intracellular C5aR1 activates ERK1/2 signaling independent of canonical immune pathways, leading to METTL3-mediated m6A modification of GPX4 mRNA. Enhanced m6A methylation stabilizes GPX4 transcripts and increases protein expression, thereby suppressing lipid peroxidation and reinforcing ferroptosis resistance under oxidative stress conditions.

intracellular ligand–receptor activation and full pathway validation in human GBM tissues remains limited.

3.3. Lipid metabolic reprogramming

Whereas Section 2 defines PUFA-containing phospholipids as substrates for ferroptotic damage, recent GBM studies indicate that upstream genetic alterations can actively remodel this substrate pool. Recent studies have identified TRAF3 loss as a driver of ferroptosis resistance through dysregulated lipid metabolism (Zeng et al., 2025). TRAF3 deficiency alters lipid homeostasis in a manner that reduces the accumulation of oxidizable PUFA-containing phospholipids, thereby lowering lipid peroxidation burden and protecting GBM cells from ferroptotic death. This metabolic shift effectively raises the ferroptosis

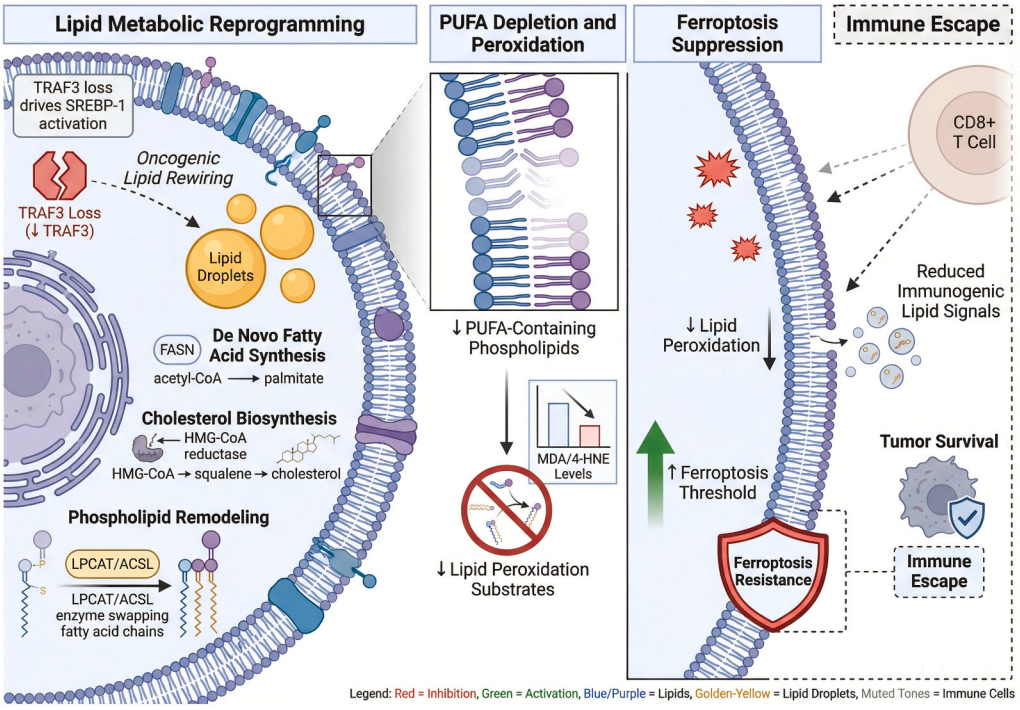

Fig. 3. TRAF3 loss-driven lipid metabolic reprogramming suppresses ferroptosis and immune elimination in glioblastoma. TRAF3 loss induces extensive lipid metabolic rewiring, reducing PUFA-containing phospholipids and lipid peroxidation substrates, thereby raising the ferroptosis threshold and conferring resistance to ferroptosis. This metabolic shift also decreases immunogenic lipid signals, promoting immune escape and facilitating tumor survival and progression.

threshold without directly targeting canonical antioxidant pathways. Notably, TRAF3-dependent lipid metabolic alterations extend beyond intrinsic tumor cell survival. Reduced lipid peroxidation also diminishes immunogenic lipid signals and attenuates immune-mediated tumor elimination (Chin et al., 2025; Han et al., 2022; Liu et al., 2022a). Thus, lipid metabolic reprogramming simultaneously promotes ferroptosis resistance and facilitates immune escape. These findings highlight lipid metabolism as a functional intersection between ferroptosis regulation and tumor–immune interactions, underscoring its dual role in shaping both cell-intrinsic survival and the immunological landscape of GBM (Fig. 3).

3.4. DNA damage response and stress adaptation

The DNA damage response (DDR) constitutes another critical layer of ferroptosis regulation in GBM, particularly in the context of therapeutic stress. Chemotherapeutic agents such as temozolomide induce DNA lesions that activate DDR pathways, which in turn intersect with redox and metabolic programs (Wang et al., 2025a; Zhao et al., 2023). Ferroptosis-associated genes involved in genome stability and lipid metabolism, including FANCD2 and SQLE, have been implicated in GBM progression and treatment resistance. FANCD2, a core component of the Fanconi anemia repair pathway, confers protection against ferroptosis by limiting lipid peroxidation and sustaining redox homeostasis. Elevated FANCD2 expression correlates with enhanced TMZ resistance and altered immune infiltration patterns (Song et al., 2022a). Similarly, dysregulation of SQLE influences lipid composition and ferroptotic susceptibility, linking cholesterol metabolism to chemoresistance and invasive behavior(Fig. 4) (Yao et al., 2022). These observations suggest that DDR activation and metabolic adaptation converge to establish a stress-tolerant ferroptosis threshold, enabling GBM cells to withstand cytotoxic therapies while maintaining malignant potential. Ferroptosis resistance thus emerges as an integral component of therapy-induced adaptation rather than a passive byproduct of treatment.

Together, mitochondrial quality control, epitranscriptomic regulation, lipid metabolic remodeling, and DNA damage–associated stress responses form an interconnected regulatory network that governs ferroptosis sensitivity in GBM. Rather than abolishing ferroptosis outright, GBM cells actively recalibrate this death pathway to balance survival and adaptability, positioning ferroptosis regulation as a central molecular foundation of therapeutic resistance.

4. Immune crosstalk: ferroptosis in the GBM microenvironment

Ferroptosis in GBM extends beyond a tumor cell–intrinsic death mechanism and exerts profound effects on the tumor immune microenvironment. Accumulating evidence indicates that ferroptotic signaling shapes immune activation, immune suppression, and therapeutic responsiveness in a context-dependent manner. Conversely, immune-derived cues and tumor-driven immune modulation feed back to influence ferroptosis sensitivity. This bidirectional interplay positions ferroptosis as a critical regulator of tumor–immune crosstalk in GBM.

4.1. Ferroptosis of tumor cells and anti-tumor immunity

Ferroptotic death of tumor cells is accompanied by the release of diverse damage-associated molecular patterns (DAMPs), oxidized lipids, and stress signals that can modulate immune responses (Neitzel et al., 2025). In principle, ferroptosis has the potential to enhance antitumor immunity by promoting immunogenic cell death–like features, including the exposure of oxidized phospholipids and the release of inflammatory mediators that activate innate immune sensors. However, the immunological consequences of tumor cell ferroptosis in GBM are highly context dependent. While moderate ferroptotic stress may

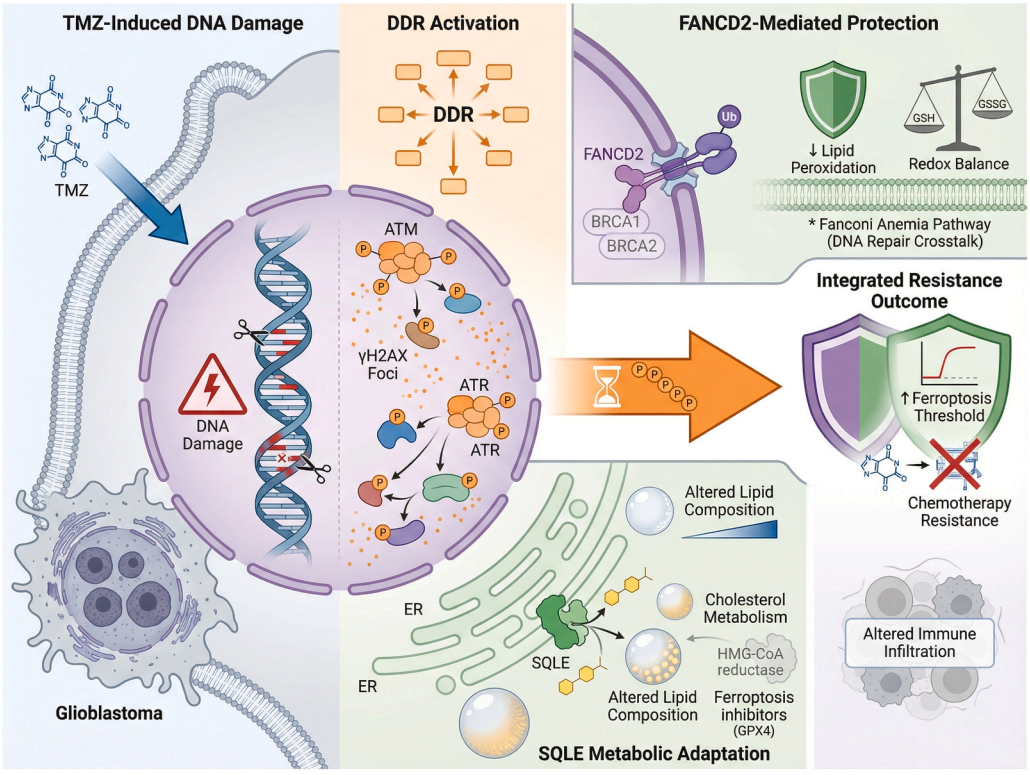

Fig. 4. DNA damage response–driven stress adaptation suppresses ferroptosis in glioblastoma. Temozolomide-induced DNA damage activates the DNA damage response (DDR), leading to upregulation of FANCD2 and dysregulation of SQLE-dependent lipid metabolism. FANCD2 limits lipid peroxidation and preserves redox homeostasis, while altered SQLE activity reshapes lipid composition, collectively elevating the ferroptosis threshold and promoting chemotherapy resistance and tumor persistence.

stimulate immune cell recruitment and activation, excessive lipid peroxidation products can exert immunosuppressive effects, impairing immune cell viability and function. Moreover, the immunogenicity of ferroptosis is shaped by the redox state of the microenvironment and the capacity of surrounding immune cells to detoxify lipid peroxides (Chen et al., 2025a; Rajabi et al., 2025; Wang et al., 2021; Williams et al., 2024). Thus, ferroptosis in GBM tumor cells does not uniformly translate into effective antitumor immunity. Instead, it generates a spectrum of immune outcomes ranging from immune activation to immune dysfunction, depending on the magnitude, spatial distribution, and temporal dynamics of ferroptotic signaling.

4.2. *Tumor-induced ferroptosis of immune cells*

Beyond influencing immune responses indirectly, GBM cells can actively exploit ferroptosis as a mechanism of immune suppression. A striking example is the induction of ferroptosis in tumor-infiltrating immune cells, particularly dendritic cells (DCs), by GBM-derived exosomes (Liu et al., 2022b). Recent studies demonstrate that GBM-derived exosomes promote lipid accumulation in DCs, leading to excessive lipid peroxidation and ferroptotic cell death. Mechanistically, this process is driven by dysregulated lipid metabolism within DCs and is critically dependent on the NRF2/GPX4 antioxidant axis (Yang et al., 2024a). Although NRF2 activation initially serves as a protective response, sustained lipid overload overwhelms antioxidant defenses, rendering DCs susceptible to ferroptosis. Functionally, ferroptosis of DCs results in impaired antigen processing and presentation, reduced T cell priming, and weakened adaptive immune responses (Deng et al., 2021; Schwantes et al., 2025). Consequently, GBM-induced ferroptosis of immune cells establishes a potent immune evasion strategy, allowing tumor cells to suppress antitumor immunity without directly inhibiting immune signaling pathways. This phenomenon represents a paradigm shift in ferroptosis research, revealing that ferroptosis is not exclusively a tumor-suppressive mechanism but can be co-opted by tumors to disable immune surveillance. The selective vulnerability of immune cells to lipid peroxidation underscores the need to consider cell type–specific ferroptosis responses when designing therapeutic interventions (Fig. 5). This observation also raises an important therapeutic concern: systemic or non-selective ferroptosis induction may not uniformly enhance antitumor immunity and could instead worsen immune suppression if dendritic cells, T cells, or other immune populations undergo lipid peroxidation-driven dysfunction. Therefore, ferroptosis-based therapy in GBM should not be conceptualized as global ferroptosis amplification. A more rational strategy is to induce ferroptosis preferentially in tumor cells while preserving immune-cell viability and antigen-presenting function. This may be achieved through tumor-targeted delivery systems, local or stimulus-responsive drug release, exploitation of tumor-specific iron and lipid metabolic dependencies, and combination regimens that reduce tumor ferroptosis resistance without exposing immune cells to excessive oxidative lipid damage.

4.3. *Ferroptosis-related immune remodeling*

Ferroptosis also contributes to broader immune remodeling of the GBM microenvironment by influencing immune cell composition, polarization, and functional states. One notable example is the enrichment of immunosuppressive myeloid populations, particularly M2-like tumor-associated macrophages, in ferroptosis-resistant tumors (Xu et al., 2023). The GDF15–NRF2 signaling axis has been implicated in coordinating ferroptosis resistance with immune suppression. GDF15 not only inhibits ferroptosis in GBM cells by stabilizing NRF2-dependent antioxidant programs but also promotes an immunosuppressive microenvironment characterized by M2 macrophage accumulation. This dual

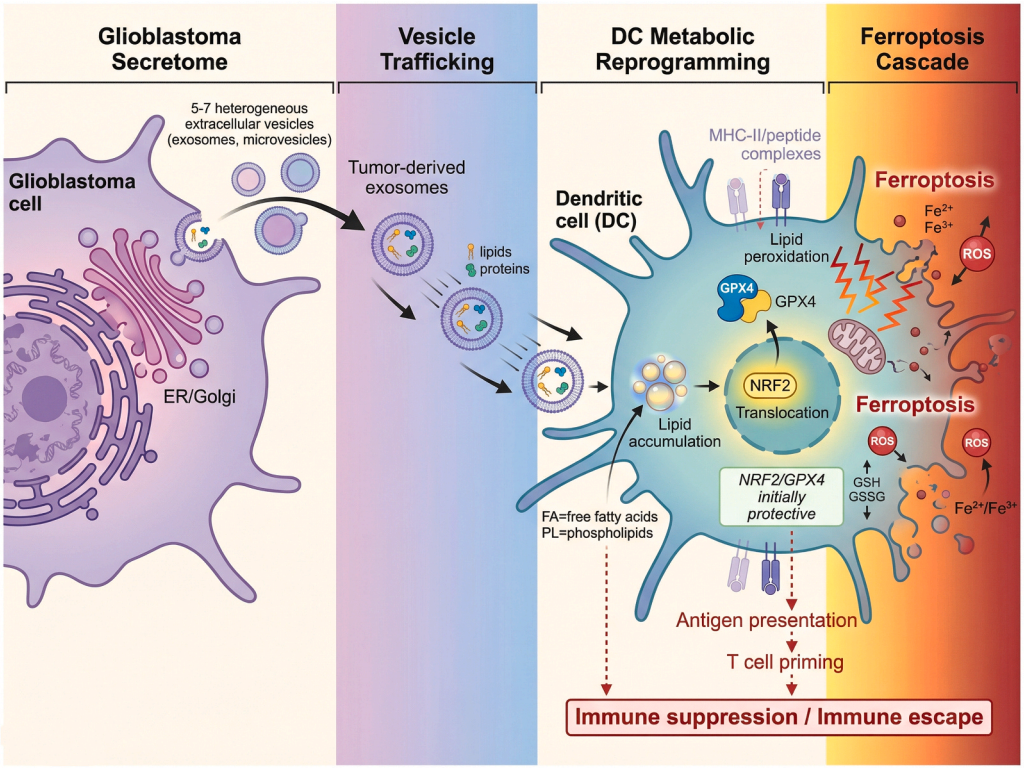

Fig. 5. Glioblastoma-derived exosomes induce ferroptosis in dendritic cells to promote immune escape. Glioblastoma cells release exosomes that drive lipid accumulation in tumor-infiltrating dendritic cells. Sustained lipid overload overwhelms NRF2/GPX4-dependent antioxidant defenses, leading to excessive lipid peroxidation and ferroptotic death of dendritic cells. Loss of functional dendritic cells impairs antigen presentation and T cell priming, thereby suppressing antitumor immunity and facilitating immune evasion.

effect links ferroptosis resistance to diminished immune-mediated tumor control. In addition, expression patterns of ferroptosis-resistance genes correlate with immune infiltration profiles in GBM, suggesting that ferroptotic regulation shapes immune architecture at the transcriptomic level (Ma and Mei, 2023). Tumors with elevated anti-ferroptotic signatures tend to exhibit reduced cytotoxic immune infiltration and enhanced suppressive immune features. Collectively, these findings support a conceptual framework in which ferroptosis functions as a tumor microenvironment–shaping factor, rather than a simple endpoint of cell death. By modulating lipid peroxidation, redox signaling, and immune cell viability, ferroptosis actively influences immune equilibrium and therapeutic responsiveness in GBM(Fig. 6).

5. Ferroptosis and therapeutic resistance in GBM

Therapeutic resistance remains the principal barrier to durable clinical benefit in GBM (Miao et al., 2024). Increasing evidence suggests that resistance to both radiotherapy and chemotherapy is tightly coupled to the ability of GBM cells to suppress ferroptotic cell death. Rather than functioning as an isolated survival mechanism, ferroptosis resistance integrates oxidative stress buffering, metabolic adaptation, and immune modulation, collectively enabling tumor persistence under therapeutic pressure.

5.1. Ferroptosis and radiotherapy resistance

Radiotherapy constitutes a cornerstone of GBM treatment and exerts its cytotoxic effects primarily through the induction of DNA damage and excessive reactive oxygen species (ROS) (Chen et al., 2025a; Liu et al., 2023). In principle, radiotherapy-induced oxidative stress should favor lipid peroxidation and ferroptotic cell death. However, GBM cells frequently acquire adaptive mechanisms that blunt ferroptosis, thereby undermining radiotherapeutic efficacy. A key regulator of this process is the GDF15–NRF2 axis. GDF15 is markedly upregulated in radioresistant GBM and functions as a stress-responsive cytokine that enhances cellular antioxidant capacity (Feng et al., 2025). Mechanistically, GDF15 stabilizes NRF2 signaling by limiting its ubiquitin-mediated degradation, resulting in sustained activation of NRF2-dependent transcriptional programs. These programs encompass genes involved in glutathione metabolism, iron sequestration, and lipid peroxide detoxification, collectively reinforcing ferroptosis resistance. As a consequence, radiotherapy-induced ROS are effectively neutralized before reaching the threshold required to trigger lipid peroxidation–driven ferroptosis (Dong et al., 2026; Sun et al., 2025b). This redox buffering not only preserves tumor cell viability but also reshapes the tumor microenvironment by promoting immunosuppressive features, further diminishing treatment response. Thus, inhibition of ferroptosis emerges as a central mechanism underlying radiotherapy failure in GBM(Fig. 7). These findings suggest that radiotherapy resistance is not merely a consequence of enhanced DNA repair but also reflects a redox-adaptive state in which ferroptotic vulnerability is actively suppressed. Targeting ferroptosis resistance pathways may therefore reopen a therapeutic window for radiosensitization.

5.2. Ferroptosis and chemotherapy resistance

Temozolomide (TMZ) remains the standard chemotherapeutic agent for GBM, yet intrinsic and acquired resistance to TMZ is nearly universal. While TMZ is classically viewed as a DNA-alkylating agent, accumulating evidence indicates that its cytotoxic efficacy is closely linked to oxidative stress and ferroptotic susceptibility. TMZ treatment induces metabolic and redox perturbations that can create a transient ferroptosis-prone window, characterized by elevated lipid peroxidation and compromised antioxidant defenses (Liu et al., 2025b; Moujalled et al., 2022; Shen et al., 2025; Shi et al., 2023; Song et al., 2021; Ye et al., 2025). However, GBM cells frequently neutralize this vulnerability through activation of ferroptosis-resistance genes and adaptive metabolic rewiring.

Several ferroptosis-related regulators have been implicated in TMZ resistance. FANCD2, a key component of the Fanconi anemia DNA repair pathway, suppresses ferroptosis by limiting lipid peroxidation and maintaining redox homeostasis. Elevated FANCD2 expression correlates with enhanced TMZ resistance, increased invasiveness, and altered

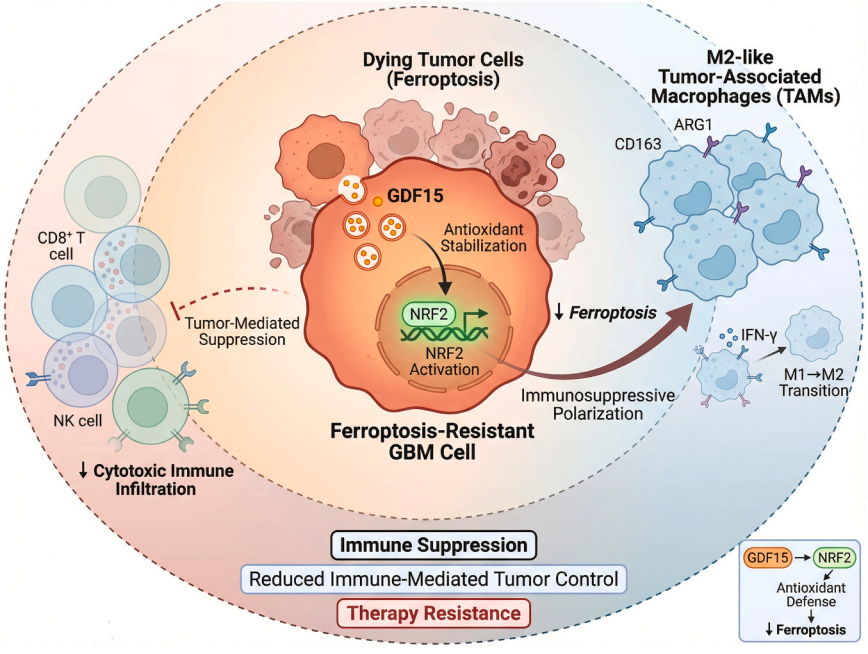

Fig. 6. Ferroptosis resistance drives immune remodeling in the glioblastoma microenvironment. Activation of the GDF15–NRF2 axis suppresses ferroptosis in glioblastoma cells while promoting an immunosuppressive tumor microenvironment. Ferroptosis-resistant tumors exhibit enrichment of M2-like tumor-associated macrophages and reduced cytotoxic immune infiltration, leading to impaired immune-mediated tumor control. These findings highlight ferroptosis as an active regulator of immune architecture rather than a simple cell death outcome.

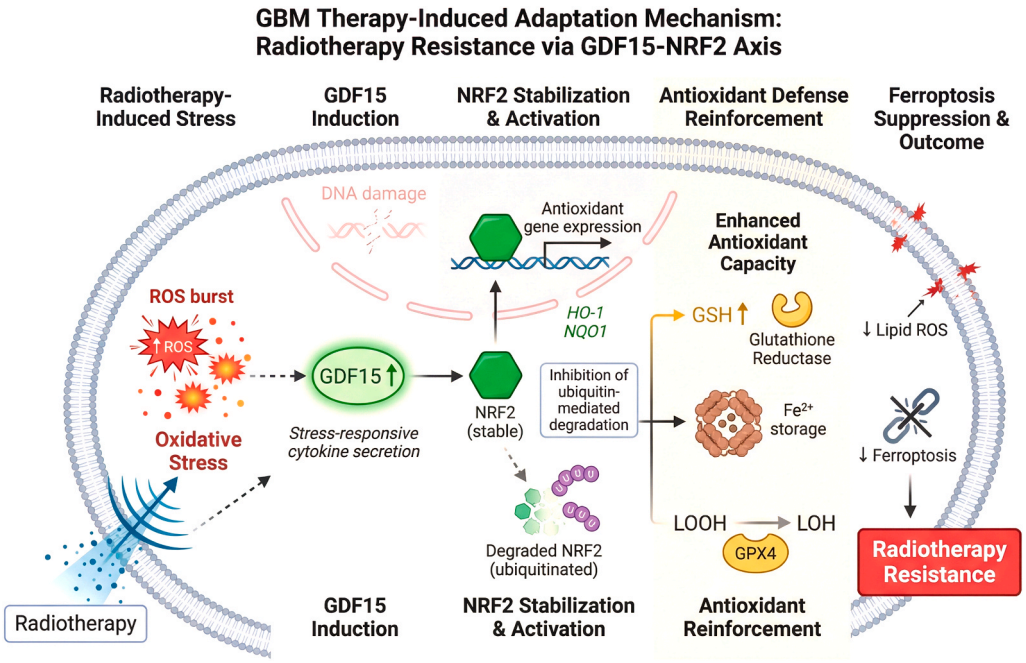

Fig. 7. GDF15–NRF2–mediated redox adaptation suppresses ferroptosis and confers radiotherapy resistance in glioblastoma. Radiotherapy induces excessive ROS that would otherwise promote lipid peroxidation and ferroptosis. In radioresistant glioblastoma, stress-induced GDF15 stabilizes NRF2 signaling, enhancing antioxidant programs including glutathione metabolism, iron sequestration, and lipid peroxide detoxification. This redox buffering neutralizes radiotherapy-induced oxidative stress, suppresses ferroptosis, and ultimately undermines radiotherapeutic efficacy.

immune infiltration. Similarly, dysregulation of SQLE, a rate-limiting enzyme in cholesterol biosynthesis, influences lipid composition and ferroptotic sensitivity, linking sterol metabolism to chemoresistance.

More recently, TEP1 has been identified as a ferroptosis-resistance–associated factor that attenuates lipid peroxidation, promotes tumor progression, and correlates with unfavorable immune phenotypes in

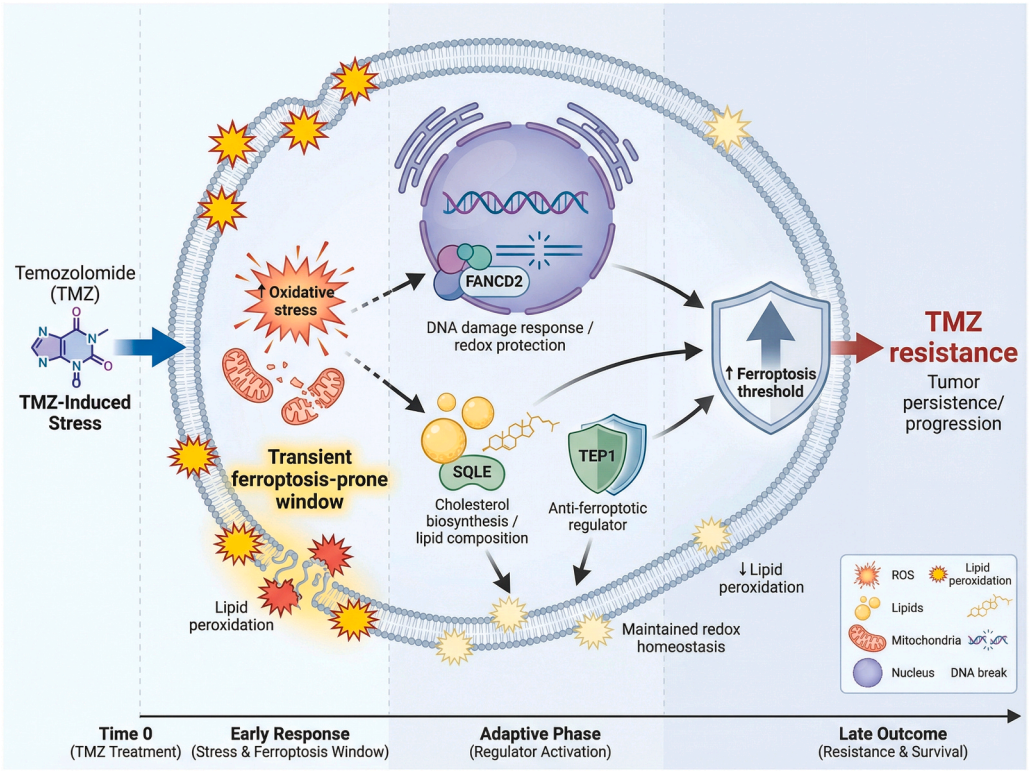

Fig. 8. Adaptive ferroptosis resistance underlies temozolomide chemotherapy resistance in glioblastoma. Temozolomide induces oxidative stress and a transient ferroptosis-prone state characterized by increased lipid peroxidation. Glioblastoma cells counteract this vulnerability by upregulating ferroptosis-resistance regulators, including FANCD2, SQLE, and TEP1, which preserve redox homeostasis, elevate the ferroptosis threshold, and enable tolerance to chemotherapy-induced stress, ultimately promoting tumor persistence and progression.

GBM. Collectively, these observations indicate that TMZ resistance is reinforced by a coordinated elevation of the ferroptosis threshold, allowing tumor cells to tolerate chemotherapy-induced oxidative stress. Importantly, this resistance is not absolute but reflects a dynamic equilibrium that may be therapeutically exploited(Fig. 8).

The GDF15–NRF2 axis and FANCD2/SQLE/TEP1-associated mechanisms are not mutually exclusive but represent partially distinct and convergent ferroptosis-resistance programs (Song et al., 2022a; Yao et al., 2022; Feng et al., 2025). GDF15–NRF2 mainly reflects radiotherapy-associated redox buffering, whereas FANCD2, SQLE, and TEP1 connect DNA damage repair, lipid metabolic remodeling, and ferroptosis-resistance phenotypes to TMZ tolerance (Cirotti et al., 2024; Feng et al., 2025). A single GBM tumor may activate both types of mechanisms simultaneously or sequentially under different therapeutic pressures. Functionally, these pathways converge on elevation of the ferroptosis threshold by enhancing antioxidant defense, reducing lipid peroxide accumulation, altering lipid substrate availability, and promoting stress-adaptive survival (Dixon and Olzmann, 2024; Lee and Roh, 2023). This convergence suggests that effective combination therapy may require biomarker-guided targeting of multiple ferroptosis-resistance layers rather than inhibition of a single pathway.

Taken together, resistance to radiotherapy and chemotherapy in GBM converges on a shared biological principle: the active suppression of ferroptosis. By reinforcing antioxidant networks, remodeling lipid metabolism, and engaging stress-adaptive pathways, GBM cells recalibrate ferroptotic sensitivity to survive therapeutic insults. This convergence provides a compelling rationale for combination strategies that integrate conventional therapies with ferroptosis-targeting interventions. Rather than replacing radiotherapy or TMZ, ferroptosis modulation may lower the adaptive threshold that underlies resistance, thereby restoring or amplifying treatment efficacy. This concept sets the stage for ferroptosis-based combination therapies, which are discussed in detail in the following section.

6. Therapeutic opportunities targeting ferroptosis in GBM

The growing understanding of ferroptosis regulation in GBM has opened new avenues for therapeutic intervention. Rather than serving as a standalone cytotoxic strategy, ferroptosis targeting offers a versatile platform for sensitizing tumors to existing therapies, reshaping the immune microenvironment, and overcoming adaptive resistance. Below, we summarize current and emerging strategies that exploit ferroptosis for translational benefit in GBM.

6.1. Direct ferroptosis induction

Direct induction of ferroptosis aims to overwhelm the intrinsic antioxidant defenses of GBM cells and trigger lethal lipid peroxidation. Among the core nodes of ferroptosis machinery, GPX4, System Xc^-, and iron homeostasis represent the most intensively explored therapeutic targets. Pharmacological inhibition of GPX4 disrupts the enzymatic detoxification of phospholipid hydroperoxides, resulting in rapid accumulation of lipid peroxides and ferroptotic cell death. Given the central role of GPX4 in GBM ferroptosis resistance, its inhibition represents a potent strategy to collapse redox homeostasis, particularly in tumors with elevated oxidative stress. However, systemic GPX4 inhibition raises concerns regarding toxicity in normal tissues, underscoring the need for tumor-selective delivery approaches. Targeting System Xc^- represents an alternative strategy by limiting cystine uptake and depleting intracellular glutathione. In GBM, where SLC7A11 is frequently upregulated as part of an adaptive antioxidant program, System Xc^- inhibition can effectively sensitize tumor cells to ferroptotic stress. Importantly, this approach indirectly impairs GPX4 activity by restricting its essential cofactor, GSH, thereby amplifying lipid peroxidation (Song et al., 2022b; Wang et al., 2023b; Zhao et al., 2025).

In addition, perturbation of iron homeostasis—through increasing the labile iron pool or disrupting iron sequestration—can potentiate ferroptosis by enhancing Fenton chemistry and ROS generation. Although iron-based interventions alone may be insufficient to induce robust ferroptosis, they can substantially lower the ferroptotic threshold when combined with antioxidant pathway inhibition. Collectively, direct ferroptosis induction strategies demonstrate strong antitumor potential but face translational challenges related to selectivity, toxicity, and blood–brain barrier penetration. In GBM, this challenge is particularly important because the blood–brain barrier (BBB) and blood–tumor barrier (BTB) are spatially heterogeneous. Although contrast-enhancing tumor regions may show partial barrier disruption, infiltrative tumor cells at the invasive margin often remain protected by a relatively intact BBB, limiting drug exposure precisely in the cell populations responsible for recurrence.

6.2. Ferroptosis-enhanced immunotherapy

Beyond direct tumor cell killing, ferroptosis modulation offers unique opportunities to enhance antitumor immunity. Increasing evidence suggests that ferroptosis can synergize with immune checkpoint blockade (ICB) by reshaping the tumor immune microenvironment and increasing tumor immunogenicity (Zeng et al., 2025; Liu et al., 2022a; Zhang et al., 2025). Ferroptotic stress in tumor cells may promote immune recognition, but this effect is conditional on preservation of immune-cell viability. In the GBM microenvironment, excessive lipid peroxidation may impair dendritic cells and T cells, thereby converting ferroptosis from an immunogenic process into an immunosuppressive event (Wang et al., 2022; Shao et al., 2024). Thus, ferroptosis-enhanced immunotherapy should be designed to spatially restrict ferroptosis induction to tumor cells and to avoid lipid peroxide spillover into immune compartments. Strategies may include BBB-penetrant tumor-targeted nanoparticles, local hydrogel-based delivery, focused ultrasound-assisted controlled release, receptor- or ligand-guided targeting, and treatment schedules that combine ferroptosis induction with immune checkpoint blockade only after minimizing immune-cell oxidative injury. Importantly, overcoming tumor-intrinsic ferroptosis resistance may prevent the immunosuppressive consequences of lipid peroxidation spillover that otherwise impair immune effector cells. One promising approach to integrate ferroptosis with immunotherapy is the use of nanotechnology-based delivery systems. Nanoparticles engineered to cross the BBB and accumulate in tumor tissue may enable co-delivery of ferroptosis-inducing agents and immunomodulatory payloads, although their translational performance depends on particle size, surface chemistry, ligand specificity, release kinetics, immune compatibility, and reproducible large-scale manufacturing. Notably, MMP-responsive nanoparticles carrying B7-H3–targeted bispecific antibodies have been shown to enhance ferroptosis while simultaneously promoting antitumor immune responses (Fan et al., 2023). This strategy achieves spatial and functional precision, minimizing off-target ferroptosis in immune cells and normal brain tissue. Such ferroptosis-enhanced immunotherapeutic platforms address two major obstacles in GBM treatment: limited immune infiltration and poor drug delivery across the BBB. By integrating ferroptosis induction with immune activation and tumor-selective targeting, these approaches represent a promising translational direction.

6.3. Combination strategies

Given the adaptive nature of ferroptosis resistance in GBM, combination strategies are likely required to achieve durable therapeutic benefit. Rather than replacing standard therapies, ferroptosis modulation is best positioned as a sensitizing strategy that lowers the threshold for treatment-induced tumor cell death. Combining ferroptosis induction with radiotherapy is particularly attractive, as radiation generates ROS and lipid peroxidation pressure that can be amplified by inhibiting antioxidant defenses. Targeting ferroptosis resistance pathways, such as

NRF2-mediated redox buffering, may restore radiosensitivity and counteract adaptive survival mechanisms. Similarly, combining ferroptosis modulation with temozolomide chemotherapy exploits the oxidative and metabolic stress induced by DNA alkylation. By preventing the elevation of ferroptosis thresholds mediated by FANCD2, SQLE, or related stress-adaptive pathways, ferroptosis-targeting agents may reopen TMZ-responsive windows in resistant tumors (Li et al., 2025; Shen et al., 2025; Ye et al., 2025; Chen et al., 2021; Lan et al., 2023; Wu et al., 2023b). Integration of ferroptosis induction with immune checkpoint blockade represents a third major combinatorial strategy. By simultaneously enhancing tumor cell susceptibility to lipid peroxidation and preserving immune effector function, such combinations aim to convert immunologically "cold" GBMs into treatment-responsive tumors.

Overall, these combination approaches highlight ferroptosis as a context-dependent amplifier of existing therapies rather than an isolated therapeutic modality.

7. Biomarkers and patient stratification

The clinical translation of ferroptosis-targeted strategies in GBM critically depends on the identification of robust biomarkers that can stratify patients according to ferroptosis sensitivity. Given the pronounced heterogeneity of GBM, indiscriminate induction of ferroptosis is unlikely to yield uniform benefit and may carry risks of toxicity or immune dysfunction. Biomarker-guided patient selection is therefore essential for the rational deployment of ferroptosis-based therapies.

7.1. Ferroptosis-related gene signatures

Large-scale transcriptomic analyses have facilitated the development of ferroptosis-related gene (FRG) signatures that correlate with prognosis, immune infiltration patterns, and therapeutic response in GBM (Chen et al., 2023; Su et al., 2022; Tian et al., 2022). These signatures typically integrate genes involved in iron metabolism, lipid peroxidation, antioxidant defense, and stress adaptation, thereby capturing the ferroptotic state of tumors at a systems level. FRG-based stratification has revealed that GBM tumors with high ferroptosis-resistance signatures often exhibit poorer survival outcomes, enhanced antioxidant capacity, and an immunosuppressive microenvironment. Conversely, tumors with lower ferroptosis thresholds may display increased sensitivity to oxidative stress and improved responsiveness to therapy. Importantly, these signatures also show associations with immune-related pathways, suggesting that ferroptosis status reflects broader tumor–immune interactions rather than isolated metabolic traits. While such signatures provide valuable prognostic and biological insights, their clinical utility is constrained by reliance on retrospective datasets and correlative analyses. As such, FRG signatures should be viewed as hypothesis-generating tools that require functional validation and prospective testing.

7.2. Candidate ferroptosis-related biomarkers: TEP1, CSPP1, and others

Beyond composite signatures, several individual genes have emerged as potential ferroptosis-related biomarkers with functional relevance in GBM. TEP1 has been identified as a ferroptosis-resistance–associated factor that attenuates lipid peroxidation and promotes GBM cell survival. Elevated TEP1 expression correlates with unfavorable prognosis, reduced ferroptosis sensitivity, and distinct immune infiltration patterns (Chen et al., 2025b). Importantly, functional studies demonstrate that TEP1 suppression enhances susceptibility to ferroptosis inducers, supporting its role as a mechanistically validated biomarker rather than a purely correlative marker. Similarly, CSPP1, initially identified through computational and multi-omics analyses, has been linked to ferroptosis regulation and tumor microenvironment remodeling (Wang et al., 2022). Its expression associates with immune cell infiltration and clinical outcome, positioning CSPP1 as a candidate biomarker at the intersection of ferroptosis and immune regulation. Although functional evidence remains limited compared to TEP1, such markers highlight the expanding landscape of ferroptosis-related determinants with potential diagnostic and prognostic value. Collectively, these biomarkers exemplify different stages along the translational pipeline, from computational association to experimental validation.

7.3. Evidence hierarchy: from association to clinical relevance

A critical challenge in the development of ferroptosis-related biomarkers lies in distinguishing mere statistical associations from true biological causality. To address this issue, ferroptosis biomarkers can be conceptually organized into a hierarchical evidence framework. At the most basic level, database-level associations identify candidate genes through correlations with patient survival, immune infiltration, or ferroptosis-related pathways using bulk or single-cell transcriptomic datasets. A higher level of confidence is achieved through functional validation, whereby experimental manipulation of a biomarker demonstrably alters lipid peroxidation, ferroptosis sensitivity, or redox homeostasis in vitro and/or in vivo. Further advancing translational relevance, therapeutic biomarkers are defined by their ability to predict responses to ferroptosis inducers or ferroptosis-based combination therapies (Wang et al., 2025b; Wu et al., 2025; Yang et al., 2024b; Zhong et al., 2022; Zhu et al., 2021). Ultimately, clinical applicability represents the highest tier, encompassing biomarkers that are reliably measurable in patient specimens and exhibit reproducible predictive value across independent and clinically annotated cohorts. Notably, the majority of currently reported ferroptosis-related biomarkers in GBM remain confined to the first two tiers, highlighting a substantial gap between discovery and clinical implementation. Systematic functional studies and well-designed translational datasets are therefore essential to elevate promising candidates along this hierarchy and enable their integration into precision oncology frameworks.

7.4. Implications for precision ferroptosis-based therapy

Biomarker-guided stratification offers a pathway to precision ferroptosis targeting in GBM. Patients with tumors characterized by high ferroptosis-resistance signatures or elevated expression of anti-ferroptotic factors may benefit from combination strategies that lower the ferroptosis threshold, such as GPX4 or NRF2 pathway inhibition. Conversely, tumors with intrinsically low ferroptosis thresholds may be particularly responsive to ferroptosis-inducing agents or ferroptosis-enhanced radiotherapy and immunotherapy (Gaiaschi et al., 2022). Importantly, biomarkers may also inform treatment sequencing and safety considerations, helping to avoid unintended ferroptosis in immune cells or normal brain tissue. As ferroptosis intersects with immune function and redox homeostasis, biomarker-driven approaches will be indispensable for balancing efficacy and toxicity.

8. Challenges and future perspectives

Despite growing enthusiasm for targeting ferroptosis in GBM, several critical challenges must be addressed before ferroptosis-based strategies can be safely and effectively translated into clinical practice. These challenges highlight the complexity of ferroptosis as a context-dependent biological process rather than a uniformly tumor-suppressive mechanism. One major challenge lies in the cell type–specific nature of ferroptosis. While inducing ferroptosis in tumor cells may confer therapeutic benefit, different cell populations within the GBM microenvironment—including immune cells, endothelial cells, and normal neural cells—exhibit distinct sensitivities to lipid peroxidation and oxidative stress. This heterogeneity raises concerns that indiscriminate ferroptosis induction could result in unintended damage to non-malignant cells, thereby limiting therapeutic windows. Closely related

is the risk of immune cell ferroptosis as an adverse effect. Emerging evidence indicates that GBM can exploit ferroptosis to impair immune surveillance, particularly by inducing lipid peroxidation–driven dysfunction or death in dendritic cells and other immune populations. Therapeutic strategies that globally enhance ferroptotic stress may therefore paradoxically exacerbate immune suppression if immune cells are not adequately protected. Future interventions will need to balance tumor-selective ferroptosis induction with preservation of immune cell viability and function.

Another major barrier to clinical translation is effective and selective drug delivery across the BBB and BTB (Arvanitis et al., 2020; van Tellingen et al., 2015). This issue is especially important in GBM because barrier integrity is spatially heterogeneous: contrast-enhancing tumor cores may exhibit partial BBB disruption, whereas infiltrative tumor cells at the invasive margin are often protected by a relatively intact BBB (Noorani and de la Rosa, 2023; Cai et al., 2023b). As a result, systemic ferroptosis-inducing agents may achieve insufficient exposure in residual tumor compartments that drive recurrence. In addition, many candidate ferroptosis modulators, including GPX4 inhibitors, System Xc− inhibitors, iron-based agents, and lipid peroxidation-amplifying compounds, may be limited by poor aqueous solubility, efflux transporter activity, short circulation time, systemic toxicity, or lack of tumor selectivity (Zhou et al., 2024; Diao et al., 2024). These limitations are particularly relevant because non-malignant neural cells, endothelial cells, and immune cells may also be vulnerable to excessive lipid peroxidation. Nanotechnology-based platforms, ligand-modified carriers, focused ultrasound-assisted BBB opening, intranasal delivery, convection-enhanced delivery, and local implantation strategies may improve intracranial drug delivery, but each approach has specific limitations (Haumann et al., 2020; Zha et al., 2024; Sonabend et al., 2023). For example, nanoparticles must balance BBB penetration, tumor retention, controlled release, immune compatibility, and long-term CNS safety, while invasive local delivery may not adequately cover diffuse tumor infiltration (Zha et al., 2024; Stine and Munson, 2019). Therefore, future ferroptosis-based therapies for GBM should be evaluated not only for tumor-killing potency but also for brain pharmacokinetics, spatial drug distribution, immune-cell preservation, neurotoxicity, manufacturability, and validation in orthotopic or patient-derived models that better recapitulate BBB/BTB heterogeneity.

A related unresolved question is which ferroptosis-inducing agents can effectively cross the BBB. At present, few conventional ferroptosis inducers have convincing evidence of efficient brain penetration as free drugs in GBM. Classical experimental inducers such as erastin and RSL3 are widely used to demonstrate ferroptotic vulnerability in GBM cells, but their BBB permeability, intracranial pharmacokinetics, and clinical feasibility remain poorly established (Li et al., 2021). Sulfasalazine, a System Xc− inhibitor, has been evaluated in glioma models and in a clinical study of recurrent high-grade glioma; however, clinical benefit was limited and tolerability concerns led to caution regarding its further use (Sehm et al., 2016a; Robe et al., 2009). Artemisinin derivatives, including artesunate and dihydroartemisinin, are more attractive because they have evidence of CNS exposure and can induce ferroptosis-like death in GBM cells, but direct validation of their BBB penetration and therapeutic ferroptosis induction in human GBM remains insufficient (Yi et al., 2020; Marijon et al., 2014). Temozolomide readily reaches intracranial tumors and may promote ferroptosis-related vulnerability through xCT/SLC7A11-dependent mechanisms, but it should be viewed as a standard alkylating agent with ferroptosis-modulating effects rather than a dedicated ferroptosis inducer (Sehm et al., 2016b). Therefore, current evidence supports a cautious distinction between BBB-permeable ferroptosis-related agents, ferroptosis inducers with uncertain BBB penetration, and engineered delivery systems designed to transport ferroptosis-inducing payloads across the BBB (Wang et al., 2024b; Liang et al., 2023).

Looking forward, single-cell and spatial multi-omics technologies are poised to transform our understanding of ferroptosis heterogeneity in GBM. Bulk transcriptomic analyses obscure cell type–specific ferroptotic states and spatial gradients of oxidative stress within tumors. High-resolution approaches can reveal how ferroptosis sensitivity varies across malignant subpopulations, immune compartments, and anatomical niches, thereby informing rational combination therapies and biomarker-guided patient stratification. In summary, future progress in ferroptosis-based GBM therapy will require an integrated strategy that combines mechanistic precision, spatial resolution, and translational rigor. Addressing cell type specificity, immune safety, delivery challenges, and intratumoral heterogeneity will be critical for transforming ferroptosis from a compelling biological concept into a clinically actionable therapeutic paradigm.

8.1. *Translational barriers: BBB penetration and in vivo efficacy*

A major translational barrier for ferroptosis-based therapy in GBM is effective and selective drug delivery across the blood–brain barrier (BBB) and blood–tumor barrier (BTB) (Arvanitis et al., 2020; van Tellingen et al., 2015). This issue is particularly important because barrier integrity is spatially heterogeneous in GBM: contrast-enhancing tumor cores may exhibit partial BBB disruption, whereas infiltrative tumor cells at the invasive margin are often protected by a relatively intact BBB (Arvanitis et al., 2020; Sarkaria et al., 2018). As a result, systemic ferroptosis-inducing agents may achieve insufficient exposure in residual tumor compartments that drive recurrence (van Tellingen et al., 2015). Moreover, many candidate ferroptosis modulators, including GPX4 inhibitors, System Xc− inhibitors, iron-based agents, and lipid peroxidation-amplifying compounds, may be limited by poor aqueous solubility, efflux transporter activity, short circulation time, systemic toxicity, or lack of tumor selectivity.

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Although numerous ferroptosis-inducing agents have been validated in GBM cell models, only a smaller subset has been tested in orthotopic or intracranial GBM models with survival as an endpoint. Notably, most of these studies used engineered delivery platforms or combination strategies rather than free conventional ferroptosis inducers. Reported approaches include sorafenib-based ferroptosis induction, biomimetic Fe_3O_4-siPD-L1 delivery, NIR-responsive ferroptosis systems, self-assembled dihydroartemisinin-based nanoplatforms, ferroptosis-enhanced immunotherapy nanoparticles, and hydrogel-liposome systems co-delivering temozolomide and erastin (Vo et al., 2022; Liu et al., 2022b; Zhang et al., 2023b). These studies generally showed tumor-growth inhibition and prolonged survival in orthotopic or intracranial GBM models; however, most remain preclinical, and few have been accompanied by rigorous BBB pharmacokinetics, dose-escalation-defined MTDs, or long-term neurotoxicity evaluation. To clarify the current level of in vivo evidence, we summarized representative ferroptosis-inducing or ferroptosis-enhancing strategies that have been evaluated in orthotopic or intracranial GBM models with survival endpoints. This evidence remains limited and is dominated by engineered delivery systems or combination strategies rather than free conventional ferroptosis inducers (Table 1).

Nanotechnology-based platforms, ligand-modified carriers, focused ultrasound-assisted BBB opening, intranasal delivery, convection-enhanced delivery, and local implantation strategies may improve intracranial delivery of ferroptosis-inducing payloads (Sonabend et al.,

Table 1
Ferroptosis-inducing or ferroptosis-enhancing strategies tested in orthotopic/intracranial GBM models with survival endpoints.

Agent / strategy	Ferroptosis-related mechanism	Orthotopic / intracranial GBM model	Survival endpoint	Main finding	PMID / DOI
Sorafenib ± dopamine	Sorafenib inhibits System Xc−; dopamine enhances iron uptake and lipid peroxidation vulnerability	Orthotopic MES 83 GBM model	Kaplan–Meier overall survival	Sorafenib prolonged survival; sorafenib plus dopamine further increased overall survival and enhanced 4-HNE lipid peroxidation staining	PMID: 35710828
Fe_3O_4-siPD-L1@M-BV2	Fe_3O_4-mediated ferroptosis plus siPD-L1-mediated immune reactivation	Orthotopic drug-resistant GBM model	Survival time	Increased Fe^{2+} and siPD-L1 accumulation in orthotopic GBM tissue, induced ferroptosis, remodeled immune microenvironment, inhibited tumor growth, and prolonged survival	PMID: 35351131
ApoE-TBTP-Au NPs	Au(I)-based NIR-II ferroptosis activation through TrxR–HMOX1-related ferroptosis	Brain-targeted orthotopic GBM model	Survival time	Enabled visualization of BBB penetration and GBM targeting, activated ferroptosis, and extended survival in glioma-bearing mice	PMID: 36869410
L-D-I/NPs	Lactoferrin-targeted self-assembled nanoplatform carrying dihydroartemisinin and indocyanine green; enhances ROS, iron accumulation, and ferroptosis	In situ / orthotopic GBM model	Survival rate / survival time	Crossed the BBB, inhibited in situ glioma progression, and significantly improved survival in experimental mice	PMID: 37460404
S-biAb/ dEGCG@NPs	MMP−2-responsive B7-H3 bispecific antibody nanoplatform; combines ferroptosis activation and immune checkpoint blockade	GBM in vivo model with orthotopic relevance	Survival over 56 days	Enhanced ferroptosis and antitumor immunity; half of treated mice survived beyond 56 days	PMID: 37097811
T + E@LPs-cRGD + GelMA	Local hydrogel-liposome platform co-delivering temozolomide and erastin; promotes ferroptosis and TMZ sensitization	Intracranial / postoperative recurrence-related GBM model	Survival extension	Inhibited intracranial tumor growth and extended survival in murine models	PMID: 37274924
hNRVs carrying RSL3-based payloads	NK cell-derived exosome/liposome hybrid vesicles delivering ferroptosis inducer RSL3 and immune-activating components	Glioma in vivo model	Survival / therapeutic efficacy endpoint	Enhanced antiglioma efficacy by combining ferroptosis induction with immune activation	PMID: 38776411

Abbreviations: BBB, blood–brain barrier; GBM, glioblastoma; GPX4, glutathione peroxidase 4; NIR, near-infrared; ROS, reactive oxygen species; System Xc−, cystine/glutamate antiporter; TMZ, temozolomide.

2023; Wang et al., 2024b; Narsinh et al., 2024). However, each approach has specific limitations. Nanoparticles must balance BBB penetration, tumor retention, controlled release, immune compatibility, and long-term CNS safety, whereas invasive local delivery may not adequately cover diffuse tumor infiltration. In addition, published formal maximum tolerated dose (MTD) data for ferroptosis-inducing agents in orthotopic GBM models remain very limited. Most available studies report selected treatment doses together with short-term safety observations, such as no obvious body-weight loss, acceptable survival, or absence of major histological toxicity, rather than dose-escalation-defined MTDs. Therefore, current preclinical dosing data should be interpreted cautiously as apparently tolerated treatment doses, not as validated MTDs.

These limitations are particularly relevant because non-malignant neural cells, endothelial cells, and immune cells may also be vulnerable to excessive lipid peroxidation. Therefore, future ferroptosis-based therapies for GBM should be evaluated not only for tumor-killing potency but also for BBB/BTB penetration, brain pharmacokinetics, spatial drug distribution, immune-cell preservation, neurotoxicity, manufacturability, and validation in orthotopic or patient-derived models that better recapitulate BBB/BTB heterogeneity.

9. Conclusions

Ferroptosis represents a therapeutically relevant vulnerability in GBM, but its biological consequences depend on cellular context, immune status, and treatment pressure. GBM cells can suppress ferroptosis through coordinated regulation of iron handling, lipid composition, mitochondrial quality control, GPX4-dependent antioxidant defense, and stress-adaptive signaling. At the same time, ferroptosis can influence the immune microenvironment, with potential antitumor effects in tumor cells but harmful consequences when immune cells undergo lipid peroxidation-driven dysfunction. Therefore, future ferroptosis-based strategies should not aim at indiscriminate ferroptosis induction. Instead, they should combine tumor-selective delivery, rational therapeutic combinations, and biomarker-guided patient stratification to improve efficacy while limiting neurotoxicity and immune suppression.

10. Critical view

This review aims to provide a comprehensive and integrative perspective on ferroptosis in GBM by linking molecular regulation, tumor–immune interactions, therapeutic resistance, and translational opportunities within a unified conceptual framework. Unlike many existing reviews that primarily focus on the biochemical mechanisms of ferroptosis or its role in general cancer biology, our review emphasizes the context-specific regulatory landscape of ferroptosis in GBM and highlights its integration with mitochondrial homeostasis, epitranscriptomic regulation, lipid metabolic reprogramming, and DNA damage–associated stress responses. By synthesizing these interconnected regulatory layers, we propose that ferroptosis should be viewed not merely as an isolated form of regulated cell death but as a dynamic cellular state that coordinates metabolic stress adaptation, immune remodeling, and therapy responsiveness in GBM. Another distinctive aspect of this review is the explicit focus on tumor–immune crosstalk mediated by ferroptosis. Emerging evidence suggests that ferroptosis exerts bidirectional effects within the GBM microenvironment: while ferroptotic stress in tumor cells may stimulate antitumor immunity under certain conditions, GBM can also exploit ferroptosis to impair immune surveillance by inducing lipid peroxidation–driven dysfunction in immune cells such as dendritic cells. By integrating these dual roles, this review highlights ferroptosis as an active regulator of immune equilibrium rather than a purely tumor-suppressive mechanism. Furthermore, we emphasize the translational implications of ferroptosis modulation. Instead of advocating indiscriminate ferroptosis induction, we argue that rational and biomarker-guided modulation represents a more viable therapeutic strategy. The review discusses emerging biomarkers, ferroptosis-related gene signatures, and hierarchical evidence frameworks that may enable patient stratification and precision

therapeutic intervention. In this context, ferroptosis targeting is positioned as a sensitizing strategy that can amplify the efficacy of existing therapies—including radiotherapy, temozolomide chemotherapy, and immunotherapy—rather than serving as a standalone treatment modality. In terms of scope, this review covers the molecular determinants regulating ferroptosis sensitivity in GBM, its interactions with the tumor immune microenvironment, its contribution to therapeutic resistance, and the emerging strategies to exploit ferroptosis for clinical benefit. The depth of coverage focuses on mechanistic insights supported by recent experimental and translational studies, while also highlighting conceptual gaps that require further investigation. Future progress in this field will likely depend on integrating high-resolution multi-omics technologies, spatial analysis of ferroptosis heterogeneity, and advanced drug delivery platforms capable of overcoming the blood–brain barrier. Overall, this review proposes that ferroptosis represents a central vulnerability and regulatory hub in GBM biology. By framing ferroptosis as a nexus connecting metabolism, immunity, and therapeutic adaptation, we hope to provide a conceptual foundation that may guide future mechanistic research and facilitate the development of precision ferroptosis-based therapeutic strategies in GBM.

Ethics approval and consent to participate

Not applicable.

Authors' contributions

Jihu Wang and Guifeng Zhang contributed to literature collection, data interpretation, and initial drafting of the manuscript. Zhiming Zheng assisted in conceptual development and critical revision of the manuscript. Zheng Wang conceived the review framework, supervised the project, critically revised the manuscript for important intellectual content, and approved the final version. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language polishing and improvement of readability. The tool was not used to generate original scientific content, analyze data, create figures, or draw conclusions. All content was critically reviewed, revised, and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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