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Emerging roles of ferroptosis in modulating the immune landscape of glial tumours

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The brain offers a unique environment for cancer, with limited access to nutrients and highly regulated immune surveillance. Here we explore the role of ferroptosis, a form of metabolically regulated cell death driven by iron-mediated lipid peroxidation, in shaping immune-cell composition and function in glial tumours. We review the complex metabolic crosstalk between cell populations regulating ferroptosis in the glioma milieu. Ferroptosis induces polarization of resident microglia and controls the cytotoxic roles of $CD8^+$ T cells and the immunosuppressive effects of regulatory T cells. We discuss recently uncovered mechanisms of ferroptosis-driven immune evasion and the impact on tumour evolution. Additionally, we analyse mechanisms of synergy in combinations incorporating ferroptosis-inducing agents and immunotherapies, including immune checkpoint blockade and adoptive cell therapies, which aim to induce effective immune responses and durable control in gliomas.

The brain provides a unique metabolic and immune environment for cancer. Limited nutrients and immune surveillance shape tumour evolution and behaviour. Resident microglia and bone-marrow-derived myeloid cells (BMDCs) are the primary immune sentinels in the brain. These immune populations continuously survey the central nervous system (CNS) for disruptions in homeostasis. Peripheral macrophages and dendritic cells (DCs) localize primarily to the blood–brain interface, with limited parenchymal infiltration[1]. Tight endogenous control of microglial activity is critical in preventing damaging autoimmune responses in the CNS. Astrocytic signalling and neuronal activity maintain microglial quiescence[1]. The blood–brain barrier and blood–cerebrospinal fluid (CSF) barrier tightly regulate metabolic and cellular exchange with the periphery to maintain CNS homeostasis. Tumours disrupt this homeostasis and deplete local metabolic stores. This disruption activates deleterious immune feedback loops that sustain tumour growth and drive therapeutic resistance[2]. Metabolism and immune function are tightly intertwined in the CNS, and gliomas hijack this crosstalk to promote tumorigenesis.

Cell fate and function are intimately linked to cellular metabolism. Metabolic plasticity is a key adaptive mechanism under limited nutrient availability, and, under glucose limitation, glial tumours shift towards lipid metabolism[3–5]. In the glioma ecosystem, slow-cycling, chemoradiation-resistant glioma cells and immunosuppressive tumour-associated macrophages and regulatory T cells share metabolic programs and rely on lipid catabolism[6]. Ferroptosis is an iron-dependent, lipid-peroxidation-driven form of cell death that has been explored recently as a therapeutic strategy in glioma[3,5,7]. Given the reliance on lipid catabolism in the tumour microenvironment (TME), ferroptosis may impact the glioma immune landscape by eradicating immunosuppressive cells and altering $CD8^+$ T-cell function[8]. These effects of ferroptosis in the glioma TME are context- and time-dependent.

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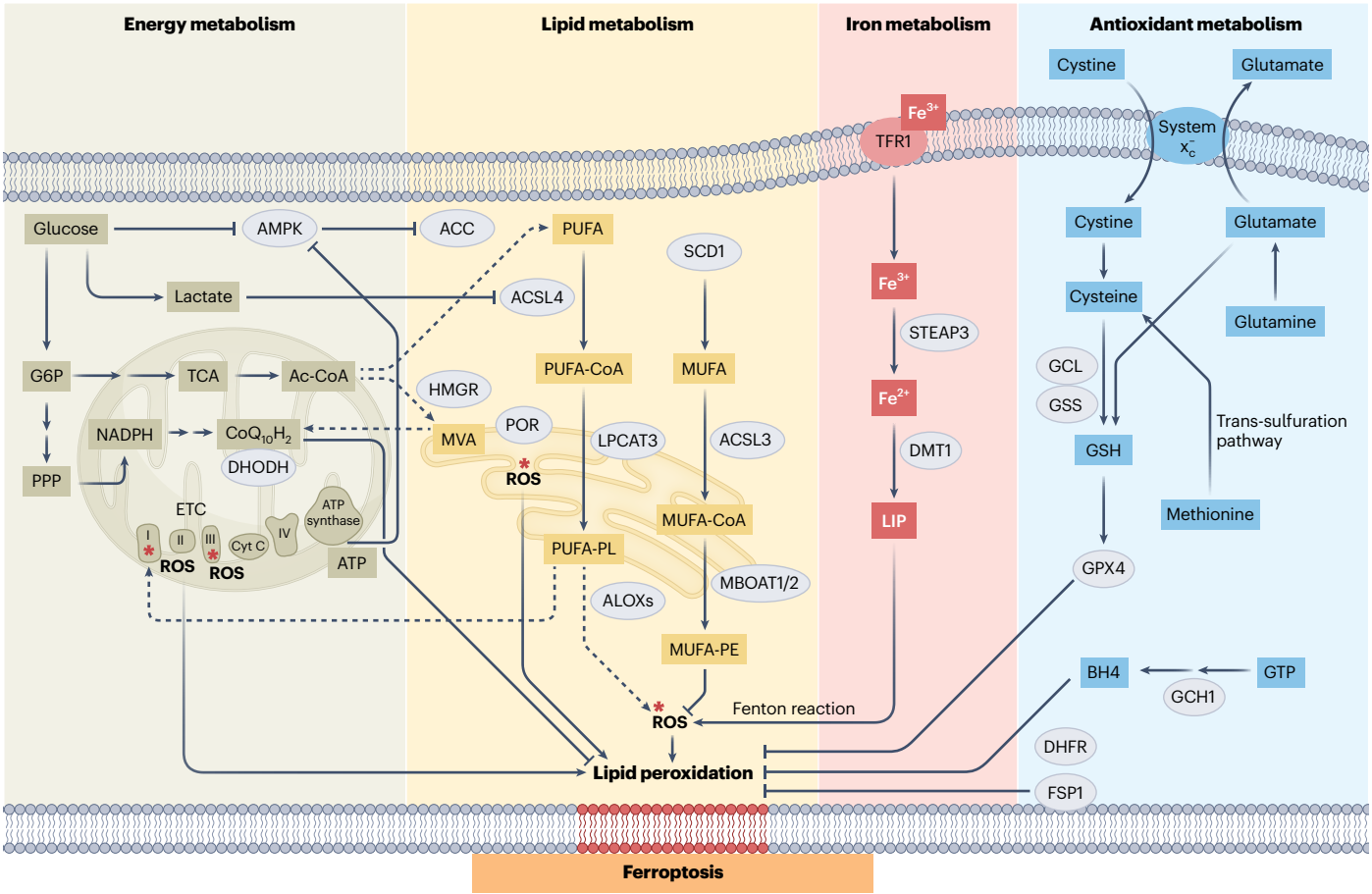

Fig. 1 | A four-node metabolic network regulating ferroptosis. Multiple metabolic pathways in different organelles are involved in ferroptosis. These pathways converge to either promote or block lipid peroxidation. Ferroptotic cell death occurs as a consequence of redox imbalance and the generation of iron-driven lipid hydroperoxides from PUFA phospholipids, with disruption of membrane integrity. The labile iron pool (LIP) is controlled by divalent metal transporter 1 (DMT1) and transferrin receptor 1 (TFR1). There are multiple sources for ROS production, including the electron-transfer chain (ETC) at complex I and III during OXPHOS, the ER via cytochrome P450 oxidoreductase (POR) or the Fenton reaction, and the interaction between hydrogen peroxide and Fe^{2+}. Glucose metabolism is also central in controlling ferroptosis. Glycolysis leads to NADPH generation through the pentose phosphate pathway (PPP), which, in turn, controls lipid peroxidation via the mitochondrial dihydroorotate dehydrogenase (DHODH)/CoQ and plasma membrane FSP1/NADPH/CoQ systems. Furthermore, glycolysis leads to the generation of TCA cycle intermediates and acetyl-CoA, which can then be used for PUFA synthesis. Diacyl PUFAs induce mitochondrial complex I dysfunction and increase ROS production. Acetyl-CoA can also be used in the mevalonate (MVA) pathway for the synthesis of cholesterol and CoQ10, both of which are important in ferroptosis. Lactate generated from glucose catabolism blocks ACSL4 activity and PUFA synthesis, decreasing susceptibility to ferroptosis. Low ATP levels can lead to 5′ AMP-activated protein kinase (AMPK) activation with inhibition of acetyl-CoA carboxylase (ACC) and PUFA synthesis, as well as activation of stearoyl-CoA desaturase-1 (SCD1) and the monounsaturated fatty acid (MUFA) synthesis pathway, thereby decreasing the response to ferroptosis. Different antioxidant systems control redox balance and can be pharmacologically targeted to induce ferroptosis, such as the GSH/GPX4 and the GCH1/BH4 systems. Glutamate is used to import cystine from the extracellular space through the system x_c^-/SLC7A11 antiporter. Both cyst(e)ine and glutamate are used for glutathione (GSH) synthesis by glutamate cysteine ligase (GCL) and glutathione synthetase (GSS). Cysteine can also be synthesized from methionine in the trans-sulfuration pathway. GSH is the key substrate for glutathione peroxidase 4 (GPX4). Finally, tetrahydrobiopterin (BH4), synthesized by the GTP cyclohydrolase 1 (GCH1), a druggable target, is also involved in ferroptosis inhibition and cellular redox balance. ALOX, arachidonic acid lipoxygenases; DHFR, dihydrofolate reductase; FSP1, ferroptosis suppressor protein 1; HMGR, HMG-CoA reductase; MBOAT1/2, membrane-bound O-acyltransferase domain-containing 1 and 2; STEAP3, six transmembrane epithelial antigen of prostate 3. Figure created in BioRender; Banu, M. https://BioRender.com/5hrqkaq (2026).

In this Review we highlight the roles of ferroptosis in shaping the immune landscape in glial tumours. We review immune-sensing mechanisms of glioma cells undergoing ferroptosis, the impact of ferroptosis on innate and adaptive immune cells, and the roles of ferroptosis in driving immune evasion. Finally, we discuss possible therapeutic combinations encompassing ferroptosis inducers and immunotherapies to induce durable control in gliomas.

Tumour–immune cell metabolic crosstalk in the glioma microenvironment and its impact on ferroptosis susceptibility

Despite metabolic plasticity and redundant metabolic pathways, cells in the glioma TME are faced with limited resources. Cells possess built-in failsafe mechanisms capable of sensing malfunctions in genetic and metabolic programs, and lack of metabolic fitness can trigger cell death pathways. Ferroptosis can occur secondary to redox imbalance and iron-dependent oxidative damage to membrane lipids containing polyunsaturated fatty acyl (PUFA) tails[9]. Phosphatidylethanolamines containing arachidonic or adrenic acid, the most common phospholipids encountered in the brain lipidome[10], are key drivers of ferroptosis[11]. During malignant transformation, cells develop a variety of methods to suppress cell death. Ferroptosis evasion mechanisms are important drivers of cancer initiation and progression[12–20], but their role in gliomagenesis has received little attention. The susceptibility of different glioma-cell subpopulations, as well as non-neoplastic cells in the TME, to ferroptosis depends on

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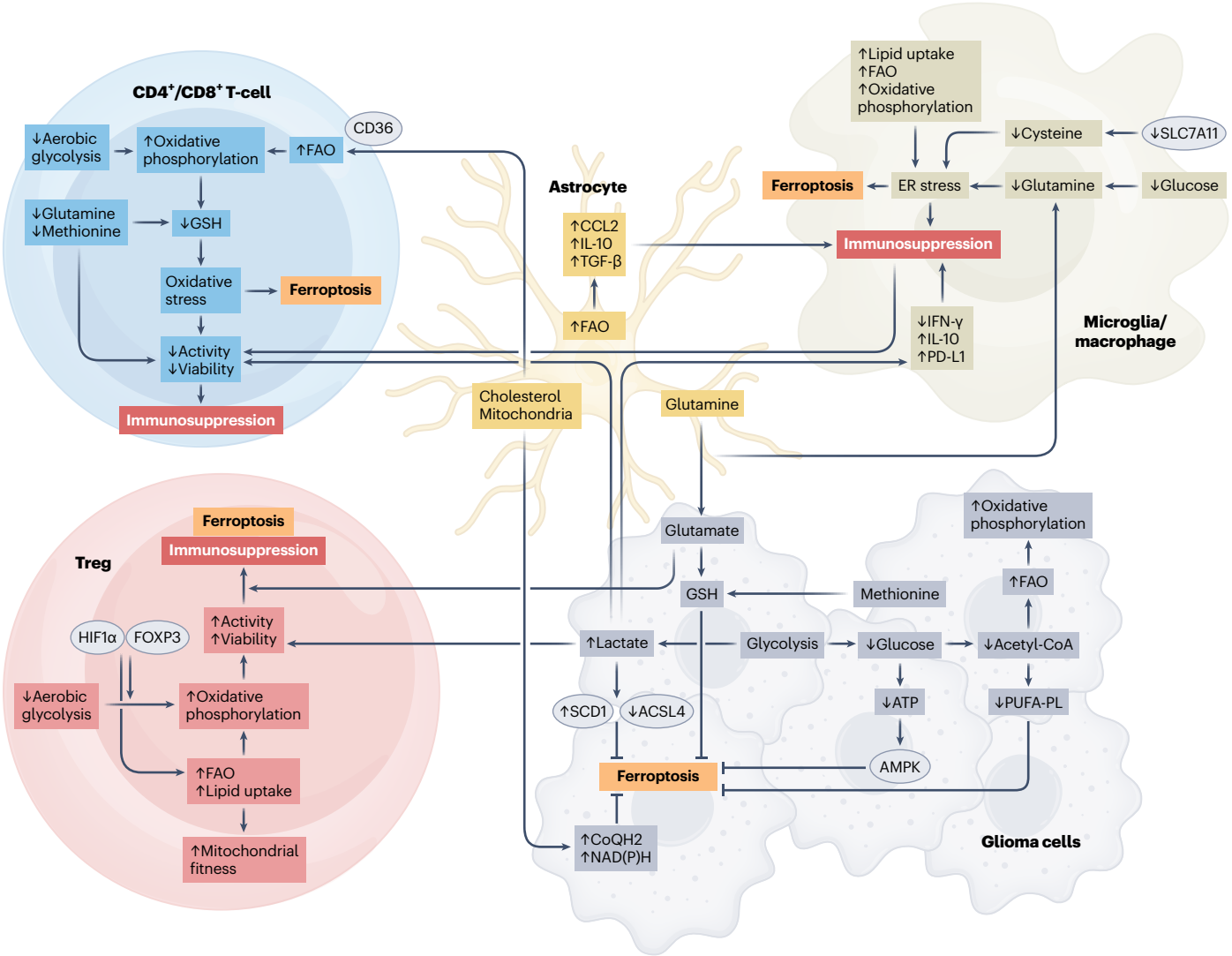

Fig. 2 | Metabolic crosstalk controls ferroptosis susceptibility and immunosuppression in the glioma TME. Metabolite exchange and competition influence immune function and susceptibility to ferroptosis in different cell populations in the glioma TME: glioma cells, effector helper CD4$^+$ and cytotoxic CD8$^+$ T cells, Tregs, myeloid cells (microglia, macrophages) and astrocytes. Aerobic and anaerobic glycolysis in rapidly proliferating tumour cells depletes intratumoral glucose stores and leads to metabolic reprogramming. Lactate, an anaerobic glycolysis by-product, is an important metabolic driver of immunosuppression as it can be used by intratumoral Tregs as substrate, driving their proliferation and suppressive action on effector T cells. It also directly impairs effector T-cell function, and in myeloid cells it results in upregulation of the immune checkpoint inhibitor PD-L1 as well as increased production of the immunosuppressive cytokine IL-10. In glioma cells, lactate leads to ferroptosis resistance through SCD1 activation. Decreased glycolysis in glioma cells also leads to inhibition of PUFA synthesis downstream of AMPK pathway activation. In Tregs, HIF-1α upregulation decreases glycolysis and increases lipid uptake, fatty-acid oxidation (FAO) and OXPHOS, thereby enhancing their metabolic fitness, while potentially increasing their susceptibility to ferroptosis. Lower glucose levels also decrease glutamine levels within the TME, which can affect the function of effector T cells and microglia. Most of the glutamine is exported from tumour-associated astrocytes, which are essential in dispensing nutrients in the brain and thus an important link between ferroptosis and immunosuppression. Astrocyte-derived cholesterol leads to upregulation of CD36 in helper and effector T cells, resulting in increased FAO and oxidative stress, thus inducing ferroptosis. Astrocytes can also transfer mitochondria to quiescent glioma populations; this increases their CoQH2 and NADPH levels and so induces resistance to ferroptosis. Finally, astrocytes also secrete immunosuppressive cytokines, such as CCL2, IL-10 and TGF-β, which induce the recruitment of immunosuppressive macrophages. FOXP3, forkhead box P3. Figure created in BioRender; Banu, M. https://BioRender.com/dn90w3j (2026).

cell-autonomous molecular drivers, such as the expression of SLC7A11, acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), p53 mutations and mouse double minute (MDM2/MDMX)-peroxisome proliferator activator α (PPARα) amplifications, as well as on glioma-microenvironment metabolic and cell–cell crosstalk[9,21–25]. The metabolic network involved in ferroptosis encompasses energy, iron, lipid and glutathione metabolic pathways (Fig. 1). The complex ferroptosis ecosystem has been extensively reviewed elsewhere[22–26], so we focus here on the unique features that pertain to the brain and glioma microenvironment (Fig. 2 and Box 1).

There are four known nodes of ferroptosis defence capable of neutralizing lipid peroxides (GPX4-glutathione (GSH), DHODH-CoQH$_2$, FSP1-CoQH$_2$ and GCH1-BH$_4$)[22,26] (Fig. 1). Several classes of pharmacologic ferroptosis inducer (FIN) targeting each node have been developed. SLC7A11 inhibitors, such as IKE (imidazole ketone erastin) and erastin, block cystine import and rapidly deplete the reduced glutathione pool[27]. Small-molecule covalent inhibitors of glutathione peroxidase 4 (GPX4), such as RSL3, ML210 and ML162, block the cellular GSH-based reactive oxygen species (ROS) detoxification pathway[22,26]. Other FINs, such as FIN56, which acts both at the GPX4 and the ubiquinone (CoQ) level, or FINO$_2$, which interferes with iron

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BOX 1

Metabolic features and ferroptosis vulnerabilities in glial tumours

To sustain rapid growth, glial tumours require large energy reserves and quick access to nutrients for biosynthesis. Gliomas arise in an environment enriched in specific metabolites—glucose, acetate, glutamine, glutamate and cholesterol[144]. Similar to other cancers, gliomas exhibit enhanced glucose uptake followed by glycolysis or oxidative phosphorylation (OXPHOS)[144]. Glucose is readily available in the brain microenvironment. Intriguingly, flux analysis in patients with GBM has demonstrated that acetyl-CoA, a critical metabolic substrate, is derived from alternative, non-glucose carbon sources[37]. Acetate, also abundant in the brain, is an essential energetic substrate in high-grade gliomas oxidized in the tricarboxylic acid (TCA) cycle[37]. In contrast to the human cortex, glial tumours divert glucose carbon from the TCA cycle to produce nucleotides and NAD[144]. Furthermore, gliomas have been shown to prioritize serine uptake to sustain de novo purine synthesis[144]. Glutamine is another abundant substrate in gliomas[50], and its large pool in GBM serves as a critical source of carbon and nitrogen for the production of nucleotides and amino acids[50,54]. Furthermore, unlike most cancers, glial tumours have access to high levels of glutamate, which can be converted into glutamine[144]. Finally, glial tumours rely heavily on locally generated cholesterol for structural membrane integrity[47]. Indeed, the brain is the most cholesterol-rich organ in the human body, where it is predominantly needed for myelin production.

Gliomas demonstrate high metabolic versatility. Similar to other neoplasms, oncogenic alterations have been shown to be intimately linked to metabolic reprograming in glioma. *EGFR* amplifications, the most common gain-of-function mutation in high-grade gliomas, induce fatty-acid synthesis and enhanced cholesterol uptake, modulating the composition of the membrane lipid bilayer[145]. Gain-of-function mutations in *TP53* and *EGFR* have been shown to drive glycolysis in GBM[144,146]. EGFR activation may also directly regulate SLC7A11 activity, cystine metabolism and ROS production[129]. These pathways of metabolic reprogramming are common in other cancers as well, such as lung and colorectal cancer. *CDKN2A* deletion, common in high-grade gliomas, alters lipid metabolism and enhances lipid peroxidation[3]. This is a unique feature of GBM compared to other malignancies. *MYC* is a pan-cancer master regulator of metabolic reprogramming, including GBM, controlling glycolysis, glutaminolysis and nucleotide synthesis[144]. Mutations in the genes encoding the isocitrate dehydrogenase 1 and 2 TCA enzymes (*IDH1/2*), present in over 70% of low-grade glial tumours, as well as acute myeloid leukaemia, cholangiocarcinoma and chondrosarcoma, directly impact metabolic programs. Mutated IDH leads to production of the oncometabolite D-2-hydroxyglutarate, increased dependence on glutaminolysis, increased ROS generation and increased dependence on NADPH-dependent GSH synthesis[58]. Furthermore, *IDH1*-mutant gliomas exhibit increased monounsaturated fatty-acid phospholipids[147]. Diffuse midline gliomas, commonly harbouring a hotspot mutation of lysine 27 to methionine in the genes encoding histone 3 variants (H3K27M), exhibit increased glycolysis, glutaminolysis and TCA-cycle metabolism, with high levels of α-ketoglutarate and high methionine dependence[55,148]. Importantly, IDH1 mutations are mutually exclusive with H3K27 mutations[148], which are unique to glial tumours. Glioma grade and molecular subtype are tightly linked to lipidome. Low-grade oligodendrogliomas exhibit high levels of phosphatidylinositol and phosphatidylserine, whereas high-grade astrocytomas contain elevated levels of PUFAs and phosphatidylcholine[144,149]. GBM relies on triacylglycerol catabolism; mesenchymal GBM exhibits high levels of glycerolipids, and proneural GBM is enriched in glycerophospholipids with PUFA chains[149].

Metabolic reprogramming drives tumour growth, exposing unique dependencies that may be leveraged therapeutically. Genetic mutations may lead to increased sensitivity of specific glioma cell populations to ferroptosis. Mutations in *TP53* and *EGFR* have been shown to confer specific sensitivity to FINs that target the GPX4-SLC7A11 pathway in other cancers[150,151]. *CDKN2A* deletion confers increased susceptibility to GPX4 inhibitors[3]. Quiescent astrocytic-like glioma populations exhibit altered mitochondrial complex I function, with increased lipid peroxidation and depletion of GSH stores, thereby displaying a unique vulnerability to GPX4 inhibitors[5]. Furthermore, mesenchymal glioma cells that are resistant to standard-of-care therapy may exhibit a particular sensitivity to ferroptosis as a consequence of their high intracellular iron levels[152]. The impact of *IDH1* mutations on ferroptosis susceptibility appears to be highly context-dependent. One study demonstrated that *IDH1* mutations in glioma confer resistance to ferroptosis by activating the nuclear factor erythroid 2-related factor 2 (*NRF2*) pathway[153]. Another study reported that high levels of the oncometabolite 2-hydroxyglutarate lead to increased ROS production and degradation of GPX4, thereby sensitizing cells to ferroptosis[154]. Epigenetic, as well as metabolic effects, of *IDH1* mutations in glioma cells and the TME may ultimately impact their response to ferroptosis. Notably, cysteine methionine deprivation sensitizes glioma cells to GPX4 inhibitors, as shown by prolonging survival in mouse models, but this also induces profound alterations in energetic metabolism, as well as amplification of an immunosuppressive TME[7]. Ultimately, mutations in, for instance, *CDKN2* or *IDH1* may serve as biomarkers in future clinical trials to stratify responders to FINs by identifying gliomas with synthetic lethality to ferroptosis.

metabolism, have been less investigated in cancer models. Ferroptosis suppressor protein 1 (FSP1/AIFM2) has recently been discovered to be a GPX4-independent ferroptosis defence system. FSP1, an NAD(P)H-dependent oxidoreductase, generates a reduced non-mitochondrial $CoQH_2$ pool capable of trapping lipid peroxides at the plasma membrane[28]. FSP1 inhibitors appear to be effective in cancer cell lines that are resistant to GPX4 inhibitors[26,29]. The role in ferroptosis suppression of dihydroorotate dehydrogenase (DHODH), an enzyme involved in $CoQH_2$ synthesis, remains controversial[30]. Finally, GTP cyclohydrolase 1 (GCH1), highly expressed in glioblastoma (GBM), generates tetrahydrobiopterin (BH_4), an alternative radical-trapping system capable of blocking ferroptosis[22,26,31]. FSP1 and GCH1 inhibitors have yet to be tested in glioma.

Glucose

Glucose is the main fuel for most T-cell types in the TME, but is in scarce supply. Rapidly proliferating glioma cells consume large amounts of glucose, predominantly relying on glycolysis for energy production[4]. Furthermore, glycolysis also fuels intratumoral neuronal activity, which drives glioma-cell proliferation[32,33]. As a result, this metabolic competition restricts the activity and viability of tumour-infiltrating $CD4^+$ and $CD8^+$ T cells[34]. Immunosuppressive cell populations, such

as regulatory T cells (Tregs), modify their metabolism to avoid competition. $CD4^+$ $FOXP3^+$ Tregs impair immune responses through the competitive consumption of nutrients, the production of immunosuppressive cytokines, the depletion of myeloid cells and the suppression of T-cell responses. FOXP3, a transcription factor expressed in Tregs, directly inhibits glycolysis, activating oxidative phosphorylation (OXPHOS). This effect is most prominent in intratumoral rather than peripheral Tregs[35]. As intratumoral glucose is depleted, impaired glycolysis and energy metabolism in rapidly proliferating glioma cells can induce activation of the AMP-activated protein kinase (AMPK) pathway, with phosphorylation of acetyl-CoA carboxylase and decrease of PUFA-phospholipid biosynthesis, thereby driving resistance to ferroptosis[36]. Glucose availability can also affect interconnected biosynthesis pathways directly linked to ferroptosis. Acetyl-CoA, a critical metabolic substrate in cells, can be obtained either from pyruvate via glycolysis and the Krebs cycle or from acetate via fatty-acid oxidation (FAO) through acetyl-CoA synthetase (ACSS2) upregulation[37]. Acetyl-CoA is required for fatty-acid synthesis as well as cholesterol synthesis via the mevalonate pathway—both critical nodes controlling ferroptosis susceptibility (Fig. 1).

Lactate

Lactate, a by-product of anaerobic and aerobic glycolysis, is abundantly excreted by tumour cells in the milieu of high-grade gliomas, promoting activity of infiltrating Tregs while also suppressing microglial and $CD8^+$ T-cell activity (Fig. 2)[38–40]. In BMDCs, high lactate leads to histone lactylation and increased interleukin-10 (IL-10) secretion, ultimately promoting T-cell dysfunction[41]. Lactate also promotes microglial anti-inflammatory function and induces the expression of programmed death ligand 1 (PD-L1), further fostering intratumoral immunosuppression[38]. Increased lactate in the TME secondary to upregulated lactate dehydrogenase A (LDHA) in tumour cells decreases natural killer (NK)-cell driven immune surveillance by preventing the upregulation of nuclear factor of activated T cells (NFAT) and decreasing interferon-gamma (IFN-γ) production[39]. Conversely, Treg function and viability relies on lactate, funnelled towards the TCA cycle or towards gluconeogenesis as alternative energy sources[40]. Lactate can induce ferroptosis resistance by modulating the production of medium-chain fatty-acid synthesis via upregulation of sterol regulatory element-binding protein 1 (SREBP1), stearoyl-coenzyme A (CoA) desaturase-1 (SCD1) and pyruvate/lactate transporter monocarboxylate transporter 1 (MCT1) with downregulation of ACSL4[42]. Overall, high lactate levels appear to drive an immunosuppressive microenvironment with increased resistance to ferroptosis.

Lipids

The brain, and therefore the glioma TME, are highly enriched in lipid species. Malignant transformation has been linked to lipid metabolism reprogramming, increased lipogenesis, and fatty acyl chain elongation in glioma cells[43]. Tumour-associated macrophage (TAM) polarization towards an immunosuppressive phenotype requires upregulation of lipid uptake, FAO and OXPHOS[43]. Intratumoral Treg function is highly dependent on lipid uptake and fatty-acid metabolism, which promote mitochondrial fitness[44]. Lastly, tumour-associated astrocytes have been shown recently to play a key role in driving immunosuppression in the glioma TME by recruiting pro-tumorigenic macrophages through CCL2, CSF1, transforming growth factor-beta (TGF-β) and IL-10[45]. Astrocyte function in the brain critically relies on lipid catabolism and FAO[46]. Glioma cells are dependent on astrocyte-derived cholesterol, as well as on mitochondrial transfer from astrocytes, to drive tumour progression, demonstrating a dual role for astrocytes in regulating both metabolic and immunological features of the glioma microenvironment[45,47]. Overall, three key cell populations in the glioma microenvironment—TAMs, Tregs and astrocytes—rely on lipid metabolic pathways to induce immunosuppression and tumour progression.

Lipid metabolism also directly impacts susceptibility to ferroptosis. Notably, the neocortex has a high concentration of PUFAs[10]. Accumulation of diacyl-PUFA-phospholipids (PLs) in the TME induces complex I dysfunction in the electron-transport chain, leading to increased production of ROS and initiating mitochondrial lipid peroxidation[48]. In contrast, uptake of specific lipoproteins such as α-tocopherol by cancer cells induces resistance to ferroptosis[49].

GSH and glutamine

GSH is an antioxidant peptide and regulator of cellular redox balance, and is essential to maintain immune cell viability and function. Several amino acids are critical for GSH production, including glutamine/glutamate, methionine, cysteine and glycine. OXPHOS in tumour-infiltrating lymphocytes (TILs) leads to increased production of ROS and consumption of GSH. In the ROS-rich TME, tumour cells and T cells need to quickly replenish GSH. Glutamine is a key metabolite in multiple biosynthesis pathways, including GSH production. Microglia switch to glutamine-based metabolic programs, while glioma cells preferentially rely on glucose as their carbon source[50]. TAMs can achieve glutamine independence through upregulation of glutamine synthetase[51]. Glutamine also plays essential roles in the differentiation and function of TILs[52,53]. Despite the critical roles of glutamine, TILs are not capable of de novo synthesis. Thus, glutamine scarcity in the TME induces rapid TIL exhaustion. Conversely, glutamine is directly synthesized or directly supplied to tumour cells by glioma-associated astrocytes via the ASCT2 glutamine transporter[54]. Instead of being directed towards the Krebs cycle, most glutamine-derived glutamate secreted in the TME by glioma cells via the system x_c^- antiporter, is used by TAMs and T cells[52,53]. Thus, unlike helper and cytotoxic T cells, glioma-associated immune cells develop metabolic plasticity mechanisms to deal with glutamine penury in the TME. Glutamine and glutamate are key substrates in glioma–TME metabolic crosstalk, and directly regulate ferroptosis susceptibility and immune cell function.

Cysteine and methionine

Methionine and cysteine also play critical roles in the viability and function of glioma cells and effector T cells. H3K27-mutant glioma cells (Box 1) are dependent on methionine[55], leading to intratumoral depletion. This, in turn, induces blockade of T-cell cytokine production and immunosuppression through metabolic competition[56]. Cysteine, a critical building block in GSH synthesis, can be synthesized from methionine and glucose through the trans-sulfuration pathway or taken up from the TME through system x_c^- (SLC7A11/SLC3A2), a cystine–glutamate antiporter[57]. In the glucose-deprived glioma TME, the trans-sulfuration pathway is predominantly active in IDH1-mutant glioma cells[58]. Naïve T cells lack the system x_c^- antiporter and import cysteine via the alanine-serine-cysteine (ASC) amino-acid transporter[59]. GSH exported by DCs is the main source of extracellular cysteine in the TME. Tregs block this metabolic crosstalk for the suppression of effector T cells. Conversely, activated T cells overexpress SLC7A11, but cysteine deprivation or SLC7A11 inhibition do not induce T-cell dysfunction[59]. The viability of anti-tumour defender macrophages is critically dependent on SLC7A11 activity, which governs inducible nitric oxide synthase (iNOS)-mediated NO synthesis[60]. Thus, cysteine and methionine are linked to immune cell function and ferroptosis susceptibility by regulating GSH synthesis.

Ferroptosis and tumour cell immunogenicity

Cell death can release specific damage-associated molecular patterns (DAMPs), driving the recruitment of antigen-presenting cells (APCs) and priming adaptive immunity, in what has been termed immunogenic cell death (ICD)[61]. Signals from dying cells can modulate the immune milieu in a variety of ways, including stimulating local inflammatory responses and recruiting resident and peripheral immune cells by inducing phagocytosis and antigen presentation.

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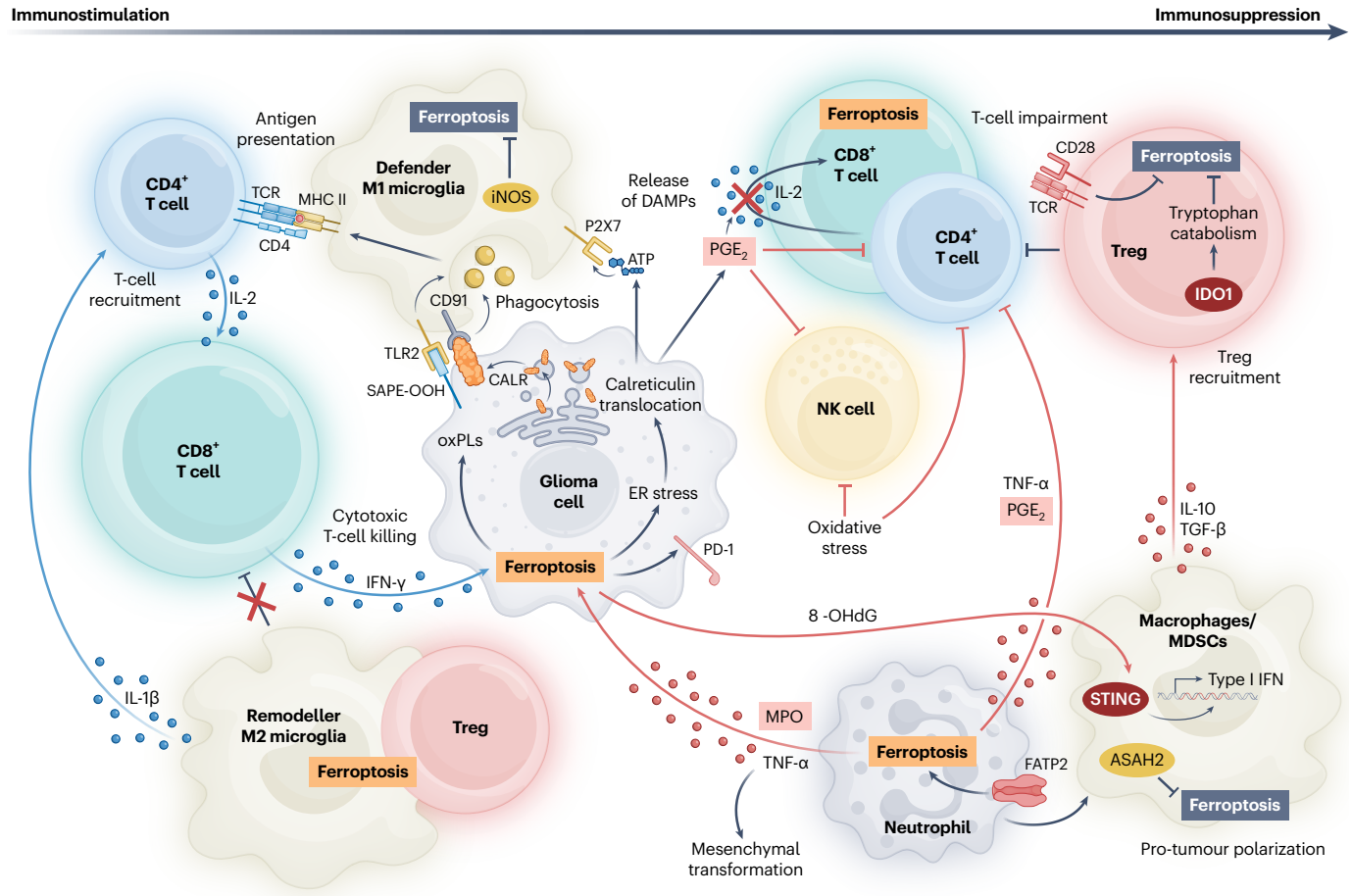

Fig. 3 | Immunostimulatory and immunosuppressive effects of ferroptosis in the glioma TME. The impact of ferroptosis on immune cells depends on its duration and context, and can comprise both immunostimulatory (depicted on the left, blue arrows) and immunosuppressive effects (right, red arrows). Ferroptosis induces ER stress premortem, with calreticulin translocation to the plasma membrane, where it can be bound by microglial CD91, leading to phagocytosis of ferroptotic tumour cells and MHC II-mediated antigen presentation. This, in turn, leads to secretion of IL-2 by $CD4^+$ T cells and subsequent recruitment of $CD8^+$ T cells. Independently, cytotoxic T cells can induce ferroptotic glioma cell death through IFN-γ-driven upregulation of ACSL4. Intratumoral Tregs and pro-tumorigenic M2-like myeloid cell populations can also be removed by ferroptosis. This leads to upregulation of IL-1β with increased T-helper and cytotoxic T-cell anti-tumoral activity. Conversely, proinflammatory M1-like defender myeloid states are resistant to ferroptosis due to their increased iNOS activity. MDSCs and pro-tumour macrophages are also resistant to ferroptosis due to upregulation of their ASAH2 activity and the resulting high levels of neutral ceramidase. Ferroptotic glioma cells can release a variety of DAMPs, which have either immunostimulatory or immunosuppressive effects. PGE_2 is an immunosuppressive DAMP, which impedes NK cell and $CD4^+$ T-cell function and decreases IL-2-driven $CD8^+$ T-cell activation. Furthermore, the presence of ferroptotic tumour cells in the TME leads to oxidative stress and decreased viability of NK cells and $CD8^+$ and $CD4^+$ T cells. Finally, ferroptotic glioma cells also release DNA-damage DAMPs such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), which activate the STING/type I IFN pathways in macrophages, resulting in their polarization into pro-tumour M2 macrophages; these release IL-10 and TGF-β, which increases Treg recruitment. Tregs that overexpress IDO1 and CD28 may be resistant to ferroptosis as a result of different mechanisms. Neutrophils transfer MPO to glioma cells, leading to their ferroptosis and recruitment of immunosuppressive macrophages. Furthermore, PGE_2 and TNF-α released from ferroptotic neutrophils can induce dysfunction in $CD8^+$ and $CD4^+$ T cells, as well as mesenchymal transformation of glioma cells. Most effects depicted have been established in different cancer models and are under active investigation in glial tumours. Figure created in BioRender; Banu, M. https://BioRender.com/r5l4m2m (2026).

This, in turn, promotes anti-tumour immunity by polarizing myeloid cells and stimulating anti-tumour effector lymphocytes[62]. The impact of ferroptosis on immunomodulatory or immunosuppressive signals in glioma merits further investigation (Fig. 3). Although many mechanisms of ICD have been proposed, canonical ICD has been defined by the expression of key DAMPs as tumour cells undergo apoptosis in response to specific stressors, including chemotherapy and radiation[63]. Canonical ICD, including in glioma, has been shown to be mediated, in part, by endoplasmic reticulum (ER) stress, the unfolded protein response (UPR) and the production of ROS[64]. This leads to expression of immunogenic signals, including translocation of the ER chaperone calreticulin (CALR) to the plasma membrane surface, which serves as a pro-phagocytic 'eat-me' signal that binds to CD91/LRP1 on APCs, release of high-mobility group B1 (HMGB1), which binds to toll-like receptor 4 (TLR4) on DCs to activate antigen presentation, and ATP secretion, which serves as a 'find me' signal for DC precursors by binding to the purinergic receptor P2X7[65–68].

Ferroptosis has been shown to induce the UPR and ER stress in the early premortem stages[69], and induces the release of adjuvant-like signals, specifically immunogenic DAMPs and proinflammatory cytokines. Cancer cells undergoing ferroptosis release HMGB1, heatshock proteins or chaperones, as well as cytokines (IFN-γ and IL-2) and proinflammatory metabolites (oxylipins) at specific time points during cell death[70–72]. Studies using murine glioma cell lines have shown that upon ferroptosis induction, CALR, HMGB1 and ATP were maximally released 1–3 h after treatment with FINs[70–72]. DAMPs ensure recruitment of myeloid cells and antigen presentation to T cells, a necessary but insufficient condition for ICD. Indeed, exposure of macrophages

to ferroptotic supernatants induced transcriptional reprograming and cytokine release[72]. Aside from adjuvanticity and antigenicity, induction of adaptive immune responses is a critical aspect of ICD. In vivo efficacy of a novel GPX4 FIN was abrogated by genetic deletion of cytotoxic $CD8^+$ T cells in a pancreatic cancer murine model, whereas depleting $CD4^+$ T cells or neutrophils did not impact tumour control[70]. Intriguingly, SLC7A11 FINs do not appear to induce the recruitment of effector T cells[70]. The study used a novel FIN, N6F11, capable of targeting GPX4 in cancer cells without affecting immune cells, and which may have yet-unknown non-ferroptotic off-target effects[70].

Ferroptotic glioma cells treated with conventional GPX4 inhibitors underwent phagocytosis by DCs in the early premortem stages and led to activation of the adaptive immune system[73,74]. These effects were reversed by the ferroptosis inhibitor ferrostatin-1, but not by necroptosis or apoptosis inhibitors[73]. Furthermore, prophylactic injection of ferroptotic cells appears to induce a vaccination-like protective effect in vivo, demonstrating that ferroptosis may induce $CD8^+$ T-cell-dependent memory, a hallmark of adaptive immunity and ICD[70,73,74]. However, the relatively short exposure to GPX4 inhibitors, the high percentage of residual living cells in the 'vaccine' and the lack of antigen cross-presentation assays raise questions about the validity of these findings. Another study using an inducible GPX4 knockout found that ferroptotic fibrosarcoma cells in fact dampen antigen presentation and DC maturation. Furthermore, prophylactic vaccination with ferroptotic tumour cells in this setting did not elicit protective effects in vivo[71]. This study may indicate that immunogenicity of ferroptosis is highly context-dependent and depends on time course and cancer type. Finally, ferroptosis may inhibit immune evasion through increased expression of CD86 on APCs, increasing T-cell activation[75]. Recent research has shown that the release of ATP drives CD86 expression via the ATP–P2RX7–CD86 axis[76]. Preliminary studies are encouraging but contradictory, and more data are needed to understand ferroptosis-driven ICD in the context of glioma.

Ferroptotic cell death has also been proposed to give rise to the expression of specific lipid mediators that can modulate the TME. Ferroptotic cells produce a wide range of oxidized lipid species, including phospholipids, which serve as phagocytic signals for APCs[72]. For instance, the oxidized phospholipid 1-stearoyl-2-15-HpETE-*sn*-glycero-3-phosphatidylethanolamine (SAPE-OOH) has been identified as a key 'eat-me' signal in response to ferroptotic cell death[77]. After pharmacological GPX4 inhibition with RSL3 or genetic GPX4 knockout, SAPE-OOH was significantly upregulated and was shown to bind to TLR2, inducing phagocytic clearance of ferroptotic cancer cells, both in vitro and in vivo[77]. Of note, TLR2 has been identified as a key receptor on TAMs responsible for the anti-tumour innate immune response[78]. However, ferroptotic cell clearance via phagocytosis was not completely eliminated when TLR2 was absent, suggesting that multiple ligand–receptor pairs exist to promote phagocytosis[77]. Ferroptotic cell death also promotes the production and release of arachidonic acid (AA) derivatives such as 5-, 11- and 15-HETE, which have important roles in stimulating local inflammatory responses[79]. Early ferroptotic cells release ATP, while cells undergoing late-stage ferroptosis (>72 h) generate high levels of lipid peroxides and prostaglandins (PGE_2, PGA_2, PGD_2, PGF_{2a}), which also supports timing as a critical variable in ferroptosis immunogenicity[72].

Ferroptosis and innate immunity

The innate immune system, composed of resident microglia, BMDCs, NK cells and neutrophils, is pivotal in linking ferroptosis and immune responses in the glioma TME. Macrophages exist along a continuum between an M1 (defender), anti-tumoral and proinflammatory state, and an M2 (remodeller), procarcinogenic and immunosuppressive state[2]. Microglia and macrophages can make up almost 12% of the tumour mass within gliomas[80], and they can operate a host of immunosuppressive tactics to advance tumour progression. DAMPs elicited by ferroptosis may polarize myeloid cells via phagocytosis and antigen presentation.

Chronic inflammation in glioma TME aberrantly programs myeloid cell differentiation and maturation, leading to an accumulation of immature myeloid cells such as myeloid-derived suppressive cells (MDSCs), driving local immunosuppression. Ferroptotic tumour cells release CXCL10, which increases MDSC recruitment[81]. MDSCs express high levels of neutral ceramidase or N-acylsphingosine amidohydrolase (ASAH2), enabling ferroptosis resistance[82]. Remodeller macrophages and microglia have been shown to be more sensitive to ferroptosis than their defender counterpart[83]. Defender myeloid cells harbour increased levels of iNOS. iNOS-generated NO can protect against toxic lipid intermediates, thus acting as a substitute for GPX4[83]. Inhibiting GPX4 among TAMs within the brain TME may therefore preferentially target the remodeller/pro-tumour states, without affecting the anti-tumour phenotype[83,84]. Ferroptosis induction may also repolarize pro-tumour macrophages towards an anti-tumour phenotype. However, defender macrophages depend on SLC7A11 for iNOS-dependent NO synthesis and may therefore be predominantly sensitive to system x_c^- FINs[85]. Surprisingly, in a study analysing samples from patients with GBM, high expression of transcriptional ferroptosis markers was associated with increased levels of immune checkpoints on glioma cells, increased infiltration of immunosuppressive macrophages and reduced overall survival[86]. Furthermore, inhibition of ferroptosis in GBM murine models by ferrostatin-1 was synergistic with PD-L1 immune checkpoint blockade (ICB), prolonging survival[86]. Overall, the effects of ferroptosis on myeloid cell populations in the glioma TME appear to be highly context-dependent, with opposite effects noted in acute versus chronic exposure to ferroptosis, as well as GPX4 versus SLC7A11 targeting.

Neutrophils may also respond to ferroptotic glioma cells expressing DAMPs. Neutrophils were found to be spatially and temporally correlated with glioblastoma necrosis, a marker of poor prognosis and tumour aggressiveness[87]. The development of necrosis provides an important cue for the recruitment of peripheral neutrophils. In turn, tumour-associated neutrophils (TANs) further contribute to the development of necrosis in vivo through ferroptosis-driven cytotoxicity to glioma cells by transferring myeloperoxidase (MPO)-containing granules into tumour cells[87]. Furthermore, neutrophils have been found to drive proneural-to-mesenchymal transformation via tumour necrosis factor-alpha (TNF-α) and to increase intratumoral hypoxia in murine glioma models[88]. Necrosis in the glioma TME may therefore supply the conditions necessary for neutrophils to mature and acquire harmful functions, demonstrating an important link between two different types of cell death[87]. Notably, tumour cell death induced by TANs was abrogated by ferroptosis inhibitors, but not those of necroptosis or apoptosis[87]. In other cancers, neutrophils undergoing ferroptosis in the TME due to the upregulation of fatty-acid transport protein 2 (FATP2, also known as Slc27A2) led to the release of oxygenated phosphatidylethanolamine (PE) and phosphatidylcholine (PC) lipid species, as well as PGE_2, which, in turn, induced the suppression of TIL proliferation, thereby promoting tumour growth[89]. Neutrophil-driven ferroptosis during tumour evolution leads to the selection of ferroptosis-resistant clones, capable of evading immune surveillance as part of an immune-editing process that drives resistance to immunotherapy in GBM[90]. Therefore, neutrophils appear to have ferroptosis-dependent deleterious functions in the glioma TME.

Finally, NK cells, important innate immune players in glioma, have been shown to exhibit high levels of lipid peroxidation in the TME, with decreased glycolysis and impaired function. These effects can be mitigated by activation of the NRF2 pathway[91]. Conversely, in other cancers, ferroptotic tumour cells exhibit increased expression of UL16-binding proteins (ULBPs), activating NK cells by binding to the receptor natural killer group 2D (NKG2D) with enhanced IFN-γ secretion and lytic degranulation[92]. Little is known about the effects of ferroptosis on NK cells in the glioma TME.

Ferroptosis and Tregs

Tregs are highly abundant in the TME of multiple immune-cold cancers, including glioma. Immunosuppressive cytokines, such as IL-10 and TGF-β, promote $CD4^+$ T-cell differentiation into Tregs[93]. Treg-mediated immunosuppression has been suggested to occur through several mechanisms, including metabolic competition for glucose via CCR6-CCL20 signalling[94], blocking effector T-cell function, inhibiting cytokine production or disrupting recruitment of TILs[95]. Tregs can also inhibit effector T-cell proliferation via CD25 by lowering the overall pool of IL-2[96]. Therefore, Tregs are an important hurdle for immune therapy in glioma as they hinder the clinical efficacy of immune checkpoint inhibitors and adoptive cell transfer.

Tregs are able to survive in the harsh hypoxic glioma TME at the cost of therapeutic vulnerability to ferroptosis. Recent findings illuminate a role for hypoxia-inducible factor-1α (HIF-1α), the effector of the hypoxic response, as a critical metabolic switch in Tregs[97]. Compared to other T-cell types, Tregs exhibit HIF-1α-dependent upregulation of fatty-acid transporters and predominantly employ FAO and OXPHOS to meet their energetic needs. Nonetheless, intratumoral activated Tregs, but not steady-state Tregs, exhibit low levels of lipid peroxides due to increased GPX4 expression as a consequence of TCR/CD28 co-stimulation[98]. Furthermore, a critical feedback loop between serine and glutathione has been recently identified to control mTOR activity in Tregs, thereby promoting FOXP3 expression[99]. Thus, Tregs are highly dependent on GSH at multiple levels. Lactate, which can hinder effector T-cell function and impede ferroptosis, can be used by Tregs as fuel in the TME[95]. Decreased lactate levels in the TME in conjunction with increased ROS production and decreased GSH levels may promote Treg susceptibility to FINs. Further studies are needed to confirm this mechanistic link. GPX4 inhibition initiates ferroptosis in activated Tregs, leading to increased mitochondrial superoxide production and IL-1β release with an augmented T-helper 17 response[98]. Melanoma-bearing *Foxp3*^{Cre}*Gpx4*$^{fl/fl}$ mice that lack GPX4 in Tregs have decreased tumour burden compared to that of wild-type mice, with elevated levels of infiltrated $CD8^+$ T cells[98]. SLC7A11 inhibition, however, does not affect Treg viability[98]. These findings suggest that inducing GPX4-dependent ferroptosis in Tregs prevents Treg-mediated immunosuppression, in turn promoting $CD8^+$ T-cell infiltration.

Another major druggable metabolic target in Tregs is indolamine 2,3 dioxygenase 1 (IDO), the rate-limiting enzyme in tryptophan catabolism[100]. In IDO-deficient tumours, Treg recruitment and expansion has been shown to be significantly hindered[100]. Recently, tryptophan catabolites were found to decrease susceptibility to ferroptosis and promote tumour progression. Specifically, tryptophan-derived trans-3-indoleacrylic acid (IDA) increases NADH generation[101], while serotonin (5-HT) and 3-hydroxyanthranilic acid (3-HA) act as direct radical-trapping antioxidants[102]. Thus, targeting IDO1 may directly impact both Treg function and response to FINs. Aside from directly affecting Treg viability, ferroptosis may play additional important roles in disrupting Treg function in the tumour TME. CTLA-4 expression is increased in cells undergoing ferroptosis and mediates contact instability between Tregs and DCs[103–105]. Paradoxically, blockade of CTLA-4 appears to result in Treg hyperproliferation[105]. However, the role of CTLA-4 as an inhibitor of immune tolerance in the setting of ferroptosis has yet to be explored in glioma. In glioblastoma resistant to the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, $FOXP3^+$ T cells are highly abundant, suggesting that VEGF blockade promotes Treg-mediated immunosuppression. Moreover, SLC7A11 was found to be upregulated in tumour cells after anti-VEGF therapy, and the increased glutamate in the extracellular space enhanced Treg proliferation and activity in a dose-dependent manner[106]. These findings suggest that anti-VEGFR therapy promotes anti-ferroptotic redox defences in tumour cells and Tregs. Combining ferroptosis induction through SLC7A11 with anti-VEGF therapies may enhance anti-tumour effects by targeting the Treg–tumour metabolic crosstalk.

Ferroptosis and immune evasion

In certain circumstances, ferroptosis may generate an immunosuppressive phenotype. Chronic intratumoral ferroptosis appears to be an important driver of the immunosuppressive TME in gliomas, which alters local metabolic conditions, increases recruitment of macrophages, decreases cytotoxic killing, and upregulates immune checkpoints[86,87] (Fig. 3). Cells undergoing ferroptosis for over 3 h impair DCs from performing antigen cross-presentation and downregulate genes associated with adaptive immunity[73]. Furthermore, DCs carrying ferroptotic cargo are unable to abate tumour growth compared to DCs carrying apoptotic or necroptotic cargo[71]. By-products of increased lipid peroxidation in the TME such as 4-hydroxynonenal (4-HNE) drive intratumoral DC dysfunction by inducing ER stress[107]. Importantly, oxidized lipids such as those produced during ferroptosis appear to also block DC maturation via NRF2-dependent inhibition of nuclear factor-κB signalling[108]. Conversely, early ferroptosis has been shown to induce DC maturation and improve T-cell activity in glioma, and to prohibit tumour growth in an orthotopic drug-resistant mouse model[109]. Thus, the timing and duration of ferroptosis determine the immune-activating or immunosuppressive impact, and must be optimized to realize its potential therapeutic benefit.

Ferroptotic neoplastic cells have been shown to be able to express or release immunosuppressive and pro-tumorigenic signals. HMGB1 has been implicated in dampening the tumour immune response via recruitment of Tregs and suppression of IFN-γ release by effector T cells[110]. Among the AA derivatives released by ferroptotic cells is prostaglandin E2 (PGE_2), which has been shown to promote tumorigenesis[111], radiation resistance and immune evasion[112–114] in glioblastoma. In addition to reducing peroxidized phospholipids, GPX4 suppresses the activation of AA-metabolizing enzymes[11]. Tumour-cell-derived PGE_2 drives NK-cell dysfunction by impairing migration, proliferation, cytotoxicity and IFN-γ production, as well as by blocking crosstalk with DC cells, thereby suppressing IL-12 production and inducing IL-6 release[114,115]. Furthermore, PGE_2 has been shown to inhibit Th1 polarization of $CD4^+$ T cells by limiting IL-2 responsiveness, thereby diminishing $CD8^+$ cytotoxic T-cell activity and promoting the development of regulatory T cells[114,116]. Thus, the presence of PGE_2 in the TME as a result of ferroptosis may be an important barrier to coordinating an effective anti-tumour response.

Immunosuppressive effects of ferroptosis on myeloid cells have been reported in different cancer models. GPX4 knockout in macrophages led to increased peroxides in the TME with promotion of tumour progression secondary to increased DNA mutations[117]. In a different model, inducing ferroptosis by GPX4 deletion promoted tumour growth by increasing levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), an oxidative damage DNA metabolite. This led to activation of the stimulator of interferon gene pathway (STING) with increased macrophage infiltration and pro-tumour polarization[118]. However, all these effects need to be further investigated in glioma models.

Cholesterol-rich microenvironments, such as the glioma TME, induce upregulation of the CD36 fatty-acid translocase in $CD8^+$ T cells, with consequent upregulation of fatty-acid uptake, increased lipid peroxidation and ferroptosis, ultimately leading to reduced cytotoxic cytokine production and tumour progression[119]. Additionally, ferroptotic tumour cells release CXCL10, which induces the upregulation of PD-L1 on $CD8^+$ T cells, further promoting immunosuppression[81]. GPX4-overexpressing $CD8^+$ T cells restore an appropriate production of cytokines with enhanced cytotoxic activity and tumour control in vivo[120,121]. Only activated intratumoral $CD8^+$ T cells exhibit high levels of lipid peroxidation and sensitivity to FINs, while naïve $CD8^+$ T cells in lymph nodes were found to be relatively insensitive to GPX4 inhibition[120]. Follicular helper $CD4^+$ T cells, as well as B cells, important modulators of $CD8^+$ T-cell function and antibody production, have also been shown to be highly dependent on GPX4 activity[120,122]. IFN-γ produced by activated T cells leads to upregulation of ACSL4 and the induction

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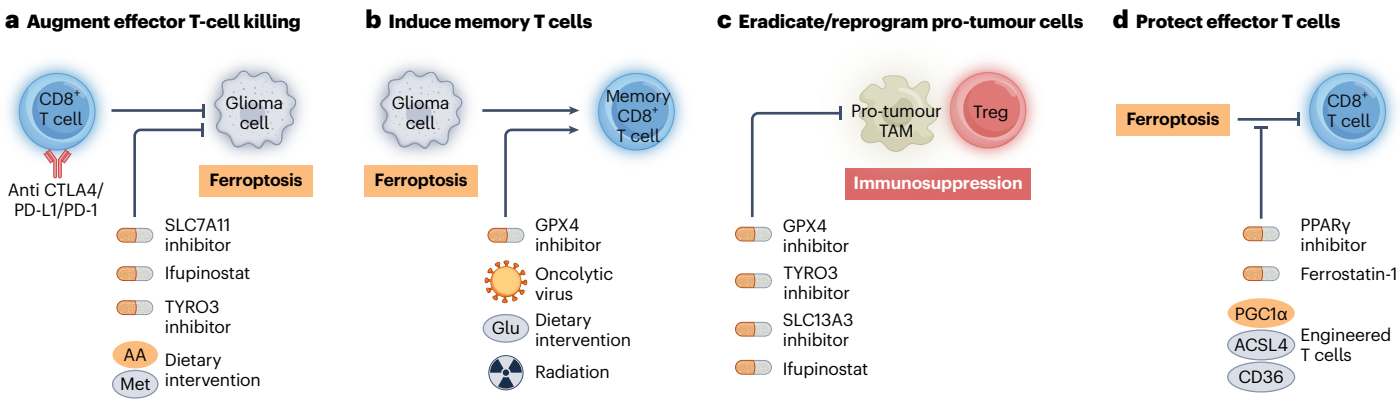

Fig. 4 | Combining immunotherapy with ferroptosis agents. Ferroptosis can boost the response to immunotherapy in glial tumours through different mechanisms. Duration of ferroptosis, choice of ferroptosis agents and timing of treatments may impact the efficacy and synergy of therapeutic combinations. **a**, Ferroptosis augments the killing function of effector $CD8^+$ T cells. CTLA-4 or PD-1/PD-L1 ICB combined with SLC7A11 inhibitors enhance T-cell-driven ferroptosis of tumour cells. Inhibition of TYRO3 increases the response to anti-PD-1 blockade and may synergize with different ferroptosis inducers. Ifupinostat, a dual PI3K/HDAC inhibitor and ferroptosis inducer, also augments the response to anti-PD-1 inhibitors. Dietary interventions, such as supplementation of AA or intermittent methionine (Met) deprivation, have been shown to synergize with ICB and increase ferroptosis in tumour cells. **b**, Glioma cells undergoing ferroptosis may be immunogenic and can activate an adaptive immune response. Ketogenic diets, oncolytic viruses and radiation therapy may synergize with ferroptosis inducers such as GPX4 inhibitors to induce ICD and the generation of memory T cells. **c**, Ferroptosis can also impact immunosuppressive cell populations in the glioma TME, restoring response to ICBs and effector T-cell function. GPX4 inhibitors kill M2 pro-tumour myeloid populations. Ifupinostat or TYRO3 inhibitors reprogram pro-tumour M2 TAMs to a defender M1 state. GPX4 inhibitors may also eradicate immunosuppressive Tregs. Inhibition of the itaconate transporter SLC13A3 increases susceptibility of tumour cells to ferroptosis and ICBs by disrupting crosstalk with immunosuppressive TAMs. **d**, Ferroptosis may impair effector T-cell viability and function. Several strategies could be employed to enhance T-cell metabolic fitness in ferroptotic TMEs: combined treatment with PPARγ agonists, pretreatment with ferrostatin-1, or engineered T cells with constitutively active PGC1α, inactive CD36 or inactive ACSL4. These strategies could enable combinatorial treatments using FINs and adoptive cell transfer. Figure created in BioRender; Banu, M. https://BioRender.com/oqz6w49 (2026).

of ferroptosis in tumour cells, without affecting T-cell viability or function. These findings suggest context- and timing-dependent effects of ferroptosis on effector T cells in the TME[123]. Finally, SLC7A11 inhibition or cystine deprivation have not been implicated in ferroptosis or dysfunction of T cells in vivo[124]. This may be explained by alternative routes of cystine import such as the ASC transporter discussed above.

Immunotherapy strategies with ferroptosis agents

Local convection-enhanced delivery[7], nanoparticle formulations or agents with improved in vivo pharmacokinetics[125] can overcome the limitations of early FINs, such as limited blood–brain barrier passage, opening an avenue for potential Phase 0/1b clinical trials in glioma. Immunotherapies have gained traction as promising therapeutic modalities against metastatic cancers, but clinical trials in glioma have been largely unsuccessful[126–129]. Most immunotherapies function by blocking suppressive signals, in turn promoting the activation of $CD8^+$ T cells. Recent studies have identified important links in other cancer types between ICB and ferroptosis. The levels of canonical ferroptosis markers SLC7a11/SLC3a2, CHAC1, GPX4 or ACSL4 in cancer cells have been proposed as potential biomarkers to predict tumour response to ICBs[26,123,130,131]. Combining SLC7A11 deletion with CTLA-4 inhibition or PD-L1 blockade with cyst(e)inase induced durable anti-tumour responses[124,132]. $CD8^+$ T-cell-driven ferroptosis of tumour cells by IFN-γ-dependent downregulation of system x_c^- is an important mechanism underlying immunotherapy-induced cell death[132,133]. Naïve $CD4^+$ and $CD8^+$ T cells are insensitive to erastin or RSL3[132]. Accordingly, ferroptosis selectively kills cancer cells without affecting the viability of immune cells. In a follow-up study, IFN-γ released from $CD8^+$ T cells in combination with AA was shown to result in tumour-cell ferroptosis through expression of ACSL4[134]. Further studies revealed that administration of AA enhances the efficacy of PD-L1 blockade and anti-cancer immunity, with increased intratumoral IFN-γ + $CD8^+$ T cells[134]. Some cancers, including glial tumours, evade ICB-induced ferroptosis by importing the TCA metabolite itaconate from TAMs, which, in turn, activates the NRF2/SCL7A11 antioxidant mechanism[135]. Pharmacological blockade of the itaconate transporter SLC13A3 in tumour cells restores ferroptosis sensitivity and response to ICBs[135]. However, the synergy of ICB and ferroptosis in glial tumours remains to be investigated. The effectiveness of ICBs in gliomas may be restored by inducing ferroptosis, thereby eradicating immunosuppressive cells in the TME, such as astrocyte-like glioma cells and TAMs, both of which are vulnerable to ferroptotic cell death. Ultimately, the choice of FIN type and immunotherapy, as well as treatment sequence, are crucial aspects in achieving therapeutic synergy, obtaining durable responses and preventing the development of resistance mechanisms in glioma (Fig. 4).

Nutritional interventions, such as restrictive diets, are also able to significantly disrupt the immunosuppressive metabolic crosstalk in the glioma TME, priming tumour cells to ferroptosis and immune attack; however, the effects can be highly context-dependent[2]. Methionine consumption promotes immune evasion by inducing epigenetic dysregulation and malfunction in TILs. As such, methionine supplementation can boost intratumoral immunity in different cancers[56]. Furthermore, our studies on the effects of cysteine and methionine deprivation in glioma models demonstrated increased responsiveness to GPX4 inhibitors, but with worsening local immunosuppression[7]. Importantly, recent studies in renal cell, hepatocellular and colorectal cancer cell lines demonstrated that intermittent methionine deprivation leads to ferroptosis and increased susceptibility to ICBs, with increased cell survival[56,131]. Ketogenic diets can further reduce the amount of glucose in the glioma TME, leading to metabolic reprogramming of intratumoral $CD4^+$ and $CD8^+$ T cells with increased fitness and improved function, including increased levels of IFN-γ[136]. Furthermore, ketogenic diets may lead to a metabolic switch in glioma cells, thereby increasing susceptibility to ferroptosis. Indeed, caloric restriction or

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BOX 2

Ferroptosis and adoptive cell therapies

Leveraging ferroptosis to prime the glioma TME prior to adoptive cell transfer is an appealing strategy. Substantial challenges remain in the application of chimeric antigen receptor (CAR) T cells or NK cells in high-grade gliomas, despite encouraging preliminary reports from recent Phase I trials. One such limitation is the high abundance of immunosuppressive cells, specifically Tregs or immunosuppressive TAMs, which can adversely affect CAR T-cell efficacy via IDO1 and PD-L1[155,156]. The function and memory of infused CAR T cells depend on their persistence and expansion in the TME, both of which are limited in gliomas due to lack of metabolic fitness in the hostile, nutrient-limited TME. Metabolic stress is one of the main drivers of T-cell exhaustion, including in CAR T cells. Furthermore, the epigenetic remodelling of CAR T cells that drives NK-like transition and dysfunction has also been linked to metabolism. One strategy is to engineer CAR T cells with metabolic programs adapted to conditions in the glioma TME, including ferroptosis[157]. For instance, incorporating CD28 and 4-1BB domains leads to increased glucose uptake and glycolysis, as well as enhanced fatty-acid metabolism and mitochondrial activity. Overexpressing phosphoenolpyruvate carboxykinase 1 (PCK1) increases phosphoenolpyruvate (PEP) synthesis and enhances NADPH production through the pentose phosphate pathway[158]. Modulating mitochondrial plasticity in CAR T cells, such as by the engineered expression of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC1α) and upregulation of NRF2 can significantly enhance their metabolic fitness and function, especially under oxidative ferroptotic stress[157]. Furthermore, Notch-stimulated CAR T cells exhibit increased mitochondrial mass and fatty-acid synthesis[159]. Finally, designing CAR-T cells deficient in CD36 or ACSL4 may also be an effective avenue to combine FINs and adoptive cell transfer. CD36- and ACSL4-deficient $CD8^+$ T cells were shown to remain viable in ferroptotic microenvironments without a compromise in function[119]. Adoptive cell transfer of ferrostatin-1-treated $CD8^+$ T cells also demonstrated increased intratumoral cytotoxic ability but with transient ferroptosis protection[119]. Overall, these strategies increase T-cell fitness in the hostile glioma TME, while also enhancing their resistance to ferroptosis, thereby opening the possibility of using engineered T cells in conjunction with FINs. Conversely, engineering CAR T cells to express arginine synthesis enzymes may enhance their function, while also increasing their susceptibility to ferroptosis[160]. Arginine is a nonessential amino acid critical for T-cell metabolic fitness and has been recently shown to promote ferroptosis through polyamine conversion[161]. Intriguingly, arginine depletion in the TME interfered with SLC7A11 inhibitors but not with GPX4 FINs. Therefore, specially engineered CAR T cells would be required prior to their deployment in a ferroptotic TME. Additionally, rewiring the TME via ferroptosis may be a synergistic strategy to prevent metabolic stress, immune suppression and ultimately malfunction during adoptive cell transfer. In this regard, combining CAR T-cell therapy with FINs appears to be a rational approach. FINs may preferentially drive ferroptosis in Tregs or M2 pro-tumour TAMs, thereby improving CAR T-cell memory and cytotoxic functions. Similarly, designing ferroptosis-resistant innate immune cells for adoptive cell transfer, such as iNOS-expressing or NRF2-active CAR NK cells, may lead to more potent FIN-immunotherapy combinations. iNOS has been shown to increase resistance to ferroptosis in M1 macrophages in the tumour TME[83], while activation of NRF2 transcriptional targets protects NK cells from ferroptosis[91]. Thus, using ferroptosis to rewire the immunosuppressive glioma microenvironment for adoptive cell transfer may be an effective strategy that would require strategic engineering of CAR T or CAR NK cells to enhance their metabolic fitness within a ferroptotic TME.

intermittent fasting have been shown to activate lipolysis and FAO in other cancer types, such as pancreatic and breast cancer, while also increasing the recruitment of peripheral $CD8^+$ T cells[137], an appealing strategy in glioma. Nonetheless, such diets can lead to rapid ATP depletion in tumour cells with subsequent activation of mTOR and AMPK signalling pathways, which can lead to ferroptosis resistance[26]. The type and duration of diets, tumour-specific genetic and epigenetic alterations and patient-specific factors, such as gut microbiome, may significantly affect the effects on the glioma TME[138] and ultimately its responses to immune therapies and FINs.

Notably, most of the cancers in which a significant synergy between ICBs and FINs has been observed were already relatively responsive to immunotherapy alone[134]. Therefore, immune-cold tumours, such as glioma and pancreatic cancer, may benefit from inducing ferroptosis-driven TME reprogramming, and drug combinations that target immune and ferroptosis pathways in tandem may thus be a highly effective strategy. However, most of these combinations have yet to be investigated in the complex glioma microenvironment. It was recently reported that TYRO3 serves as an inducer of anti-PD-1/PD-L1 resistance through inhibition of tumour-cell ferroptosis by reducing the M1/M2 TAM ratio and by hindering cytotoxic T-cell activity[139]. Accordingly, inhibition of TYRO3 induced intratumoral ferroptosis[139]. Therefore, combining TYRO3 inhibitors with FINs might be a feasible therapeutic option that could enhance the response to ICBs in immune-cold tumours. Similarly, a combination of ferroptosis and oncolytic viruses increased the immune-mediated anti-tumour response in several cancer models by increasing IFN-γ production and effector memory T cells[140]. Recent results from early-phase clinical trials of oncolytic viruses to treat gliomas are encouraging[141], and a combinatorial approach using ferroptosis inducers may thus further enhance efficacy and help overcome some of the challenges that still exist, such as immune evasion and local immune suppression. Ifupinostat or BEBT-908, a dual PI3K/HDAC inhibitor and ferroptosis inducer, is another agent that may be effectively combined with immunotherapy in glial tumours. Ifupinostat leads to a proinflammatory TME with upregulation of MHC I and induction of STAT1-driven IFN-γ signalling, thereby increasing the response to anti-PD-1 agents in colon and lung cancer[142].

A separate combinatorial strategy could include drugs capable of protecting effector T cells from ferroptosis without affecting killing of tumour cells or immunosuppressive immune cells. For instance, it may be possible to use peroxisome proliferator-activated receptor (PPAR) agonists to protect $CD8^+$ T cells from ferroptosis, while also increasing the synergy of anti-PD-1 blockade and FINs[143]. PPARγ signalling has been shown to increase the metabolic fitness of cytotoxic T cells in high-ROS environments by enhancing mitochondrial OXPHOS, and to increase the effectiveness of PD-1 blockade in colon cancer models[143]. In Box 2 we propose strategies for engineering ferroptosis-compatible T and NK cells. Combining FINs with adoptive cell transfer may lead to lasting therapeutic responses in glial tumours.

Conclusions and perspectives

Despite the effectiveness of immunotherapy in a variety of cancer types, TME composition and the immune-evading strategies of gliomas pose a substantial challenge. Metabolic crosstalk between tumour cells and non-neoplastic cells in the TME (TAMs, astrocytes, TILs) is an important driver of its immunosuppression. Ferroptosis has emerged as a promising strategy to overcome these major therapeutic challenges in various cancers, including in glioma[71,81,83,85,98,130–132]. Here, we have discussed various context- and timing-dependent roles of ferroptosis in modulating the glioma TME. Based on this, we highlight ferroptosis as a potential form of ICD[73] capable of activating the innate immune system with enhanced antigen presentation and with key roles in modulating $CD8^+$ T-cell killing of cancer cells. However, ferroptosis can also have deleterious effects in the glioma TME, including its central role in neutrophil-driven tumour necrosis and immune suppression via the recruitment of BMDCs, or the potential damaging effects on tumour-infiltrating $CD8^+$ or $CD4^+$ T and NK cells. Nevertheless, much remains unknown about the role of ferroptosis in modulating the glioma TME, as the effects of ferroptosis have mostly been studied in other cancer types. Ferroptosis may be an effective strategy to target glioma cells that are resistant to standard-of-care chemoradiation, as well as immunosuppressive cell populations, specifically Tregs and pro-tumour remodeller TAMs. Furthermore, combinatorial therapeutic approaches including FINs and ICB or adoptive cell transfer may help improve the efficacy of cancer immunotherapy.

Several key questions remain. What is the optimal timing and sequence of FINs relative to immune therapies? Which delivery strategies will achieve effective and selective CNS penetration? How can ferroptosis be preferentially induced in glial tumour cells while sparing anti-tumour immune populations? How does ferroptosis within the glioma TME influence adoptive cell-transfer approaches? Finally, which biomarkers can identify patients most likely to respond and define the optimal window during tumour evolution for initiating ferroptosis-based therapies? To address these important questions, additional mechanistic and preclinical translational studies incorporating murine and organoid glioma models are necessary. Furthermore, carefully designed window-of-opportunity clinical trials will be critical for the first-in-human FIN glioma studies so as to optimize pharmacokinetic parameters, maximize on-target effects and ensure synergy with immune therapies.

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Author contributions

M.A.B., M.G.A., T.V.N., C.S. and O.A. researched data for the Review. M.A.B., M.G.A., T.V.N., C.S., D.M.O.H., J.N.B., B.Y.S.K., A.D., P.C., M.L. and B.R.S. contributed substantially to discussion of the content. M.A.B., M.G.A., T.V.N., C.S. and B.R.S. wrote the paper. M.A.B., B.R.S., M.L. and P.C. reviewed and/or edited the manuscript before submission.

Competing interests

B.R.S. is an inventor on patents and patent applications involving ferroptosis, has co-founded and serves as consultant to ProJenX, Inc. and Exarta Therapeutics, holds equity in Sonata Therapeutics, and serves as a consultant to Weatherwax Biotechnologies Corporation and Akin Gump Strauss Hauer & Feld LLP. J.N.B. and P.C. are the founders of Convecta Therapeutics, a company developing convection enhanced delivery drug formulations. J.N.B. is also a consultant for Theracle, Inc., which designs catheters for drug delivery to the brain. M.L. has obtained funding from Arbor Pharmaceuticals, Accuray, BMS and Novartis, and serves as consultant for BMS, Merck, SQZ Biotechnologies, Tocagen and VBI. M.L. is a shareholder in Egret Therapeutics. The remaining authors declare no competing interests.

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