

Research advances in the interplay between ferroptosis and T cells in the tumor microenvironment (Review)

SHIHAN TANG^{1*}, WENBO XU^{1*}, YICHEN LI^{1*}, CHUWEI LIU¹, WEITAO LIU¹, RUIHAN LIANG¹, QIANHUI LIAO¹, HAN SUN¹, ZHUOYAN WANG¹, LINGCHANG SHI¹, QIYING LIU² and HUIPING LIU¹

¹Key Laboratory of Oncology of Traditional Chinese Medicine, Hunan University of Traditional Chinese Medicine, Changsha, Hunan 410208, P.R. China; ²Department of Traditional Chinese Medicine, Changsha Hospital for Maternal and Child Health Care, Changsha, Hunan 410007, P.R. China

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Abstract. Despite advances in tumor immunotherapy, its clinical efficacy remains constrained by challenges such as limited response rates, drug resistance and an immunosuppressive microenvironment; moreover, conventional therapeutic strategies often overlook the key constraints imposed by intrinsic tumor cell death resistance and metabolic reprogramming on antitumor immune responses. Based on the aforementioned practical dilemmas, the present review focused on the reciprocal regulatory crosstalk between ferroptosis and T cell immunity within the tumor microenvironment (TME) and further proposes novel therapeutic strategies that co-target ferroptosis in tumor cells

and T cell immunity. Ferroptosis substantially strengthens T cell-dependent antitumor immunity. In turn, activated T cells dynamically regulate the susceptibility of tumor cells to ferroptosis, forming a positive immune feedback loop. Related combinatorial strategies have shown synergistic potential in preclinical studies, opening promising avenues to overcome existing therapeutic resistance. Nevertheless, multiple barriers impede clinical translation, including tumor heterogeneity, off-target toxicity of ferroptosis inducers and dysregulation of T cell subset balance. To address these issues, future application of nanodelivery systems for TME-specific intervention, combined with differential metabolic remodeling to reshape immunosuppressive networks, is expected to drive the development of next-generation precision immunotherapeutic combinations. Collectively, the present review systematically elucidated the mechanistic interplay between ferroptosis and T cell immunometabolism, providing a theoretical foundation for developing targeted therapies to overcome tumor immune resistance.

Correspondence to: Professor Huiping Liu, Key Laboratory of Oncology of Traditional Chinese Medicine, Hunan University of Traditional Chinese Medicine, 300 Xueshi Road, Yuelu, Changsha, Hunan 410208, P.R. China
E-mail: 1074983953@qq.com

Professor Qiying Liu, Department of Traditional Chinese Medicine, Changsha Hospital for Maternal and Child Health Care, 416 Chengnan East Road, Yuhua, Changsha, Hunan 410007, P.R. China
E-mail: 2843403653@qq.com

*Contributed equally

Abbreviations: TME, tumor microenvironment; ROS, reactive oxygen species; PUFA-PL, polyunsaturated fatty acid phospholipid; GSH, glutathione; GPX4, glutathione peroxidase 4; AMPK, AMP-activated protein kinase; MUFA, monounsaturated fatty acid; TFR1, transferrin receptor 1; Treg, regulatory T cell; Th, helper T cell; FTH1, ferritin heavy chain 1; CTL, cytotoxic T lymphocyte; IRF, interferon regulatory factor; Tfh, T follicular helper cell; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; FAO, fatty acid oxidation; mTORC, mTOR complex; TIM-3, T cell immunoglobulin and mucin domain 3; CAR-T cell, chimeric antigen receptor T cell; LXR, liver X receptor

Key words: ferroptosis, T cells, tumor microenvironment, immune cells, immunotherapy

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1. Introduction

The tumor microenvironment (TME) is a complex ecosystem composed of tumor cells and diverse stromal and immune cells, and metabolic abnormalities are a hallmark of the solid TME (1,2). CD8⁺ cytotoxic T cell-mediated anti-tumor immunity underpins the efficacy of immunotherapy (3). Nevertheless, hypoxia, nutrient deprivation and accumulation of metabolic toxins drive T cell exhaustion, thereby limiting the therapeutic benefits of immunotherapy (4). Identifying

metabolic targets that modulate T cell function remains a challenge in tumor immunology.

Ferroptosis is an iron-dependent form of programmed cell death driven by lipid peroxidation (5). Early studies primarily focused on the direct tumor-killing effect of ferroptosis. Advances in immunometabolism in recent years have uncovered bidirectional crosstalk between ferroptosis and T cell immunity: ferroptosis-mediated immunogenic cell death in tumor cells can activate T cells, while effector molecules secreted by activated T cells in turn modulate the susceptibility of tumor cells to ferroptosis (6). Meanwhile, accumulated oxidized lipids and nutrient competition within the TME can trigger ferroptosis in tumor-infiltrating T cells, further dampening anti-tumor immunity (7,8). Distinct T cell subsets exhibit divergent metabolic profiles and marked differences in ferroptosis sensitivity, which complicates therapeutic intervention (9).

Combination regimens integrating ferroptosis modulation and immunotherapy have demonstrated synergistic anti-tumor effects in numerous preclinical models (10). However, multiple practical hurdles remain, including tumor heterogeneity, off-target injury to immune cells, and the lack of intervention strategies selective for specific T cell subsets. Herein, we systematically review the reciprocal regulatory mechanisms between ferroptosis and T cells in the TME, summarize combined therapeutic strategies targeting both components, analyze existing challenges, and envision future research directions, so as to provide insights into developing novel tumor immunometabolic therapies.

2. Molecular mechanisms and metabolic regulation of ferroptosis

Ferroptosis represents a distinctive type of programmed cell death that differs morphologically and molecularly from other canonical cell death modalities, such as apoptosis, necroptosis and pyroptosis. Morphologically, ferroptotic cells display shrunken mitochondria, condensed mitochondrial membranes and disrupted mitochondrial cristae. As the primary intracellular source of reactive oxygen species (ROS), mitochondria accelerate vigorous lipid peroxidation under a hypermetabolic state, which serves as a central trigger for ferroptosis. Mechanistically, ferroptosis arises from metabolic dysfunction-driven massive build-up of oxidized polyunsaturated fatty acid-containing phospholipids (PUFA-PLs), which ultimately leads to cell death (11).

Core pathways of ferroptosis

Ferroptosis-promoting pathways

Lipid peroxidation. Ferroptosis is fundamentally orchestrated by iron-dependent lipid peroxidation through two distinct cascades: Enzymatic and non-enzymatic pathways. The non-enzymatic cascade stems from disrupted iron homeostasis. Excess cytosolic Fe^{2+} drives the Fenton reaction to produce hydroxyl radicals ($\text{OH}^\cdot$) (12-14), which trigger spontaneous lipid peroxidation (15). By contrast, enzymatic ferroptosis requires PUFAs as obligate oxidation substrates (13). Acyl-CoA synthetase long chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) act as key regulatory factors responsible for PUFA

activation and membrane incorporation (16). Mechanistically, ACSL4-mediated esterification of arachidonic acid (AA) into membrane phospholipids is indispensable for the execution of ferroptosis. Doll *et al* (16) demonstrated this through genetic and pharmacological manipulation of ACSL4 activity in multiple cancer cell lines. Using genome-wide clustered regularly interspaced short palindromic repeats (CRISPR) screening and microarray analysis of ferroptosis-resistant cells, the aforementioned study identified *Acs4* as an essential gene for ferroptosis initiation. Pfa1 cells with *Acs4* knockout were resistant to ferroptosis induced by RSL3 and erastin. Cells with double knockout of *Gpx4* and *Acs4* could even survive in the absence of *Gpx4*, and reintroduction of ACSL4 restored cellular sensitivity to ferroptosis. Lipidomic results revealed that *Acs4* deletion reduced the esterification of AA and adrenic acid onto phosphatidylethanolamine (PE), accompanied by decreased levels of ferroptosis-associated oxidized phospholipid products and undetectable lipid peroxidation in cells. In basal-like breast cancer cells, ACSL4 expression levels correlated with ferroptosis sensitivity: knockout of ACSL4 in tumor cells conferred ferroptosis resistance, while reconstitution of this gene restored the susceptible phenotype. Pharmacological studies demonstrated that thiazolidinedione-mediated inhibition of ACSL4 recapitulated the lipid profile of *Acs4* knockout cells, suppressed lipid peroxidation and ferroptosis, and alleviated ferroptosis-mediated tissue injury in mice. Collectively, these findings confirm that ACSL4 mediates the incorporation of PUFAs such as AA into membrane phospholipids, a process indispensable for ferroptosis execution. ACSL4 specifically catalyzes AA to produce AA-CoA, which is esterified by lysophosphatidylcholine acyltransferase 3 (LPCAT3) to form PE-AA, and AA lipoxygenases (LOXs) which trigger lipid peroxidation (12,13,16). Excessive oxidative accumulation of PUFA-PLs within cell membranes is a prerequisite for ferroptosis (13,15). Magtanong *et al* (17) found that exogenous monounsaturated FAs can compete with PUFAs for membrane integration, thereby reducing ferroptosis sensitivity by altering the pool of lipid substrates available for peroxidation. From a biochemical perspective, lipid peroxidation commences with the removal of bis-allylic hydrogen from PUFA-PLs, generating reactive lipid radical intermediates in the presence of oxygen (18,19). If this process is blocked, excessive accumulation of peroxy radicals compromises plasma membrane integrity and eventually causes cell lysis (20,21).

Furthermore, the core axes governing ferroptosis, particularly the cystine/glutamate antiporter (Xc⁻)-glutathione (GSH)-GSH peroxidase 4 (GPX4) axis and iron metabolism, can directly modulate the susceptibility of infiltrating immune cells to lipid peroxidation, thereby establishing an intrinsic link between tumor cell death and T cell-mediated immunity (22). Within tumor cells, oxidative stress suppresses GSH synthesis and inactivates GPX4, thus aggravating the buildup of toxic lipid peroxides (23). Notably, lipid metabolism participates in ferroptosis while supplying tumor cells with membrane components and energy to support proliferation and metastasis. The membrane components include phospholipids containing PUFAs, such as AA and adrenic acid), among which PE is key. Other phosphoglycerides include phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylserine (PS). On the one hand, these membrane

phospholipids serve as the structural foundation of cell membranes, supporting membrane synthesis and remodeling during tumor cell proliferation and migration. On the other hand, the ω -6 PUFAs bound to them can be incorporated into phospholipids under the catalysis of enzymes such as ACSL4 and LPCAT3, subsequently undergoing lipid peroxidation to directly trigger ferroptosis. In contrast, the incorporation of MUFAs into membrane phospholipids replaces membrane PUFAs and thereby reduces the sensitivity of tumor cells to ferroptosis (24). Furthermore, a variety of signaling and metabolic routes, including Hippo, AMP-activated protein kinase (AMPK), glycolysis and autophagy, also participate in the regulation of ferroptosis (25-27).

From a metabolic perspective, PUFA accumulation serves as a key marker of ferroptosis (28). Once PUFAs in the membrane undergo modification by ACSL4 and LPCAT3, they become susceptible to ROS-mediated attack, leading to the formation of lipid hydroperoxides that disrupt the membrane structure (29-31). Conversely, exogenous MUFA can suppress ferroptosis by substituting for PUFA on cell membranes (32,33). PE plays a key role in this process, participating in PUFA activation and transmembrane transport (13,33). Downstream peroxidative byproducts such as 4-hydroxynonenal and malondialdehyde interfere with normal cellular physiology by forming covalent conjugates with intracellular biomacromolecules (32).

Notably, lipid peroxide accumulation within the TME not only drives ferroptosis in tumor cells but also directly affects the function of tumor-infiltrating T lymphocytes. Specifically, after taking up oxidized lipids via the scavenger receptor CD36, CD8⁺ T cells become particularly susceptible to lipid peroxidation-induced ferroptosis, leading to impaired effector functions (34).

Iron metabolic imbalance. In addition to lipid peroxidation, imbalance of cellular iron homeostasis is also a key condition driving the occurrence of ferroptosis. Strict iron homeostasis maintains essential cellular physiological functions, while disrupted iron balance is closely related iron-dependent regulated cell death, namely ferroptosis. Under physiological conditions, intracellular iron trafficking is precisely orchestrated to sustain dynamic equilibrium. In detail, transferrin-conjugated ferric iron (Fe^{3+}) is internalized through transferrin receptor 1 (TFR1) (35); inside endosomes, STEAP3 metalloredutase and other cellular reductases convert Fe^{3+} into ferrous iron (Fe^{2+}) (36), which is subsequently transported into the cytosol via divalent metal transporter 1 (DMT1) (37,38); cytosolic Fe^{2+} follows two major metabolic routes: A fraction is pumped out of cells by ferroportin (FPN) (39-41), and the rest is sequestered by ferritin subunits [ferritin heavy chain 1 (FTH1)/ferritin light chain] for intracellular storage (36-38). Hepcidin regulates iron efflux by promoting FPN degradation (42). Moreover, nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy releases stored iron back into the labile iron pool (43).

However, in pathological contexts such as malignant tumors, iron homeostasis is disrupted, resulting in cytosolic iron overload that robustly fuels ferroptosis. Tumor cells enhance iron uptake by overexpressing TFR1, STEAP, DMT1, ZIP8 and ZIP14 (44-48). Concurrently, tumors suppress FPN expression to block iron efflux (44), forming a pro-ferroptotic

microenvironment. Excess labile Fe^{2+} triggers ferroptosis via two principal mechanisms. Accumulated Fe^{2+} drives the Fenton reaction to produce abundant ROS, which directly provoke toxic lipid peroxidation (49,50); and Fe^{2+} serves as an essential cofactor for LOXs, accelerating LOX-mediated peroxidation of PUFAs. Furthermore, aberrant expression of iron metabolism-related genes (such as iron-responsive element-binding protein) and factors such as the iron and oxygen microenvironment also profoundly affect the sensitivity to ferroptosis (51,52).

Given the central role of iron metabolism in ferroptosis, numerous studies have focused on intervening in iron metabolic nodes. Intervention strategies targeting ferroptosis (such as the iron chelator deferoxamine) provide new directions for disease treatment (53,54). Hou *et al* (43) demonstrated that autophagy-mediated ferritin degradation (ferritinophagy) releases labile iron to drive ferroptosis and identified NCOA4 as a key regulatory factor in this process. Gao *et al* (55) demonstrated via CRISPR-based genetic screening that TFR1 overexpression in cancer cells was directly associated with enhanced ferroptosis sensitivity.

Taken together, these results highlight the regulatory role of iron metabolism in modulating ferroptosis, laying a rigorous mechanistic framework for designing ferroptosis-targeted therapeutic regimens.

Amino acid metabolism. Beyond lipid and iron metabolism, amino acid metabolism also participates in the regulation of ferroptosis, among which the cystine-GSH metabolic axis plays a central regulatory role, impairment of this axis leads to intracellular GSH depletion and GPX4 inactivation, thereby triggering ferroptosis.

System Xc^- is a heterodimeric antiporter composed of solute carrier family 3 member 2 (SLC3A2) and SLC7A11 subunits. It imports extracellular cystine into cells in exchange for intracellular glutamate efflux. Internalized cystine is subsequently reduced to cysteine, an indispensable precursor for GSH synthesis. As an essential cofactor of GPX4, GSH enables GPX4 to detoxify toxic lipid hydroperoxides, curb uncontrolled lipid peroxidation and maintain plasma membrane integrity. Inhibition of System Xc^- limits cellular cysteine supply, impairs GSH generation and weakens GPX4 catalytic activity. The resultant buildup of lipid peroxides eventually initiates ferroptotic cell death (56,57). Therefore, pharmacological intervention targeting the Xc^- -GSH-GPX4 cascade has become a core strategy to modulate ferroptosis. For example, cisplatin trigger ferroptosis in tumor cells. It is not a direct targeted inhibitor of GPX4. Instead, it mainly induces DNA damage and depletes intracellular GSH, indirectly reducing the substrate supply for GPX4, impairing the capacity of GPX4 to eliminate lipid peroxides, thereby promoting the accumulation of lipid peroxides and driving the initiation of ferroptosis (58).

Apart from cystine, numerous other amino acids participate in the complex ferroptosis regulatory network. As the direct precursor of GSH, cysteine metabolism directly determines cellular antioxidant competence (59). Within the nutrient-deficient TME, remodeled amino acid metabolism further alters tumor susceptibility to ferroptosis. For instance, lysosomal cysteine depletion induces ferroptosis

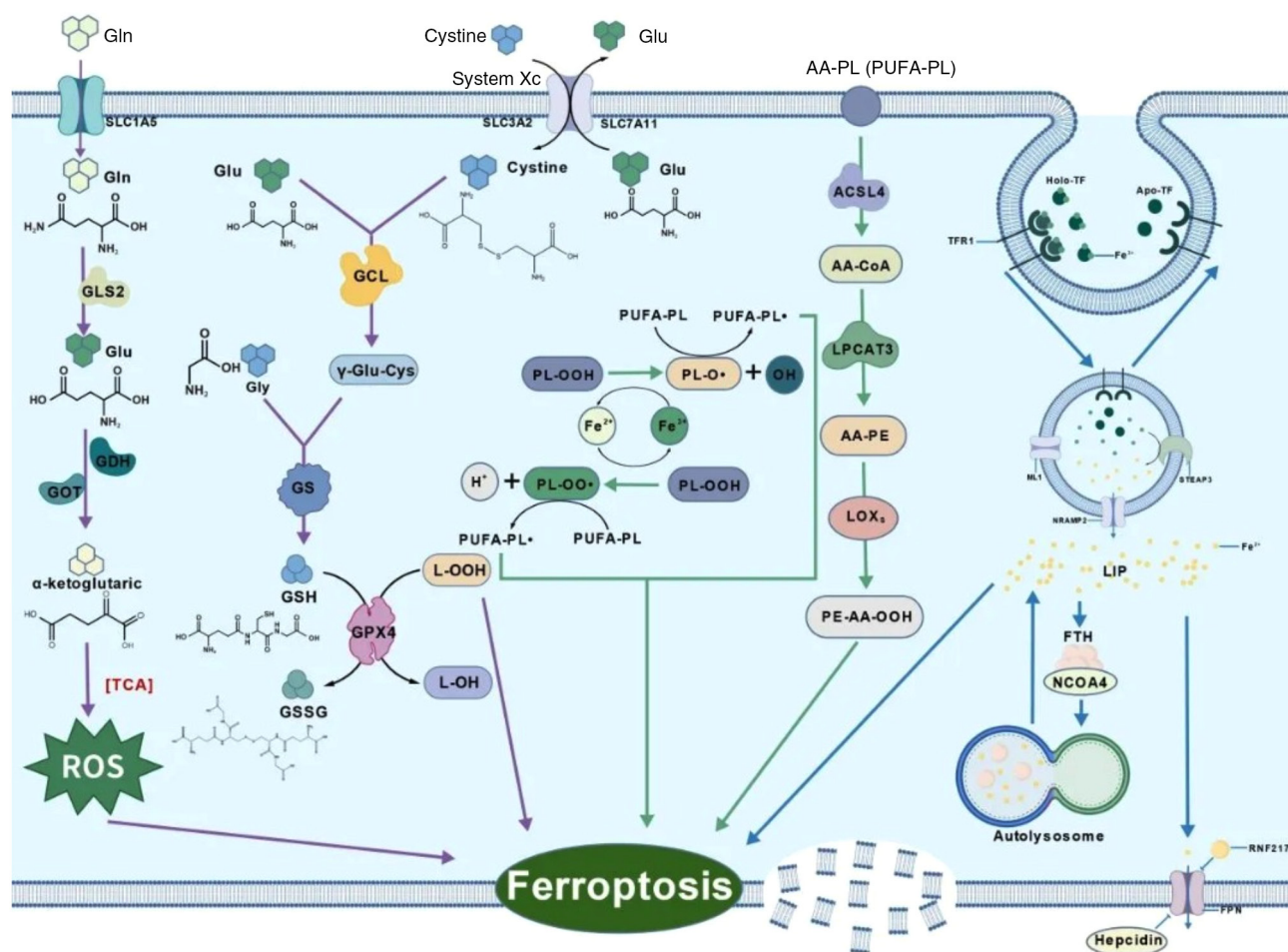


Figure 1. Ferroptosis is governed by three interwoven core metabolic axes: Lipid peroxidation, aberrant iron homeostasis and impaired amino acid metabolism. The present figure illustrates that ACSL4/LPCAT3-mediated PUFA esterification, excessive TFR1-dependent iron uptake and suppression of the Xc⁻-GSH-GPX4 antioxidant defense axis cooperate to execute ferroptosis. Importantly, these pathways do not operate in isolation; instead, they intersect with intrinsic metabolic programs in T cells, laying a foundation for the subsequent discussion of the immunomodulatory function of ferroptosis. ACSL4, acyl-CoA synthetase long chain family member 4; SLC1A5, solute carrier family 1 member 5; SLC3A2, solute carrier family 3 member 2; GSH, glutathione; GPX4, glutathione peroxidase 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; TCA, tricarboxylic acid; TFR1, transferrin receptor 1; PUFA-PL, polyunsaturated fatty acid-containing phospholipids; LOXs, lipoxygenases; STEAP3, STEAP3 metalloredutase; NRAMP2, natural resistance-associated macrophage protein 2; FPN, ferroportin; FTH, ferritin heavy chain; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species; GSSG, oxidized glutathione; GLS2, glutaminase 2; LIP, labile iron pool; NRAMP2, natural resistance-associated macrophage protein 2.

by repressing activating transcription factor 4 and sequentially activating the kynurenine pathway (60). In line with this mechanism, the cysteine-binding agent CysRx increases tumor ferroptotic sensitivity by redistributing intracellular cysteine reservoirs (60). Additionally, some tumor cells lose functional amino acid synthases such as argininosuccinate synthase 1, rendering them reliant on exogenous amino acid uptake; such metabolic reprogramming confers strong ferroptosis resistance (61).

In conclusion, amino acid metabolism orchestrates the initiation and progression of ferroptosis by regulating GSH production, GPX4 activity and downstream signaling cascades. These discoveries not only deepen mechanistic insights into ferroptosis, but also identify promising metabolic targets for treating malignant tumors and other diseases (Fig. 1).

Defense systems

GSH-GPX4 pathway. The GSH-GPX4 pathway serves as the core defense mechanism against ferroptosis in cells, and its function depends on the synergistic action

of GSH and GPX4 to maintain cellular redox homeostasis through precise regulation of lipid peroxidation levels.

This pathway operates via a ‘substrate supply-enzymatic catalysis’ cascade. GSH serves as the key reducing agent and electron donor (15), providing the essential reducing power for GPX4; GPX4, in turn, utilizes its catalytic activity to directly reduce cytotoxic lipid hydroperoxides (L-OOH) to harmless lipid alcohols (L-OH), thereby effectively blocking the chain reaction of lipid peroxidation (62,63). Once this pathway is compromised, for example, by GPX4 inactivation due to GSH depletion (64) or loss of GPX4 function caused by direct inhibitors such as RSL3, excessive accumulation of lipid peroxides occurs, ultimately triggering ferroptosis.

The maintenance of GPX4 activity depends on adequate selenium supply and GSH levels. As a selenoprotein, when selenium intake is insufficient or GSH synthesis is restricted, the catalytic capacity of GPX4 is markedly reduced, compromising the cellular ability to eliminate lipid peroxides and thereby increasing susceptibility to ferroptosis (65).

Furthermore, the GSH-GPX4 pathway also plays a key role in the tumor immune microenvironment. GPX4 is highly expressed in regulatory T cells (Tregs), and its deficiency triggers ferroptosis in Tregs, disrupts the immunosuppressive microenvironment, promotes T helper (Th)17 responses and enhances antitumor immunity (66,67). This indicates that this pathway not only regulates the death process of tumor cells themselves, but also indirectly participates in tumor progression by influencing immune cell functions, thereby providing new targeting concepts for cancer therapy.

In addition to protecting tumor cells, the GSH-GPX4 axis is equally key for maintaining T cell homeostasis. Specific deletion of GPX4 in Tregs leads to excessive accumulation of lipid peroxides and triggers ferroptosis upon the T cell receptor (TCR)/CD28 co-stimulation, thereby compromising their immunosuppressive function and unleashing antitumor immunity (67).

NADPH-ferroptosis suppressor protein 1 (FSP1)/coenzyme Q10 (CoQ10) pathway. The NADPH/FSP1-CoQ10 pathway is a key ferroptosis defense mechanism independent of GPX4, which effectively inhibits lipid peroxidation at the plasma membrane through the antioxidant action of reduced coenzyme Q10 (CoQ10H2).

The core of this pathway lies in FSP1. FSP1 is targeted to the plasma membrane through N-terminal myristoylation, which serves as the structural basis for its function (68,69). Upon localization, FSP1 functions as an NADPH-dependent oxidoreductase that utilizes NADPH to reduce oxidized CoQ10 to its reduced form, CoQ10H2 (ubiquinol) (70). CoQ10H2, as a potent lipophilic antioxidant, can both directly neutralize lipid radicals to halt the propagation of lipid peroxidation and regenerate other antioxidants such as α -tocopherol, thereby synergistically enhancing ferroptosis resistance (70).

Overexpression of FSP1 effectively antagonizes ferroptosis induced by GPX4 inhibitors, suggesting that its action is independent of the GPX4 pathway (71-73). Therefore, simultaneous inhibition of FSP1 and GPX4 can synergistically induce ferroptosis, providing a potential therapeutic strategy for related diseases (73). In tumors, high expression of FSP1 confers ferroptosis resistance by maintaining CoQ10H2 levels (74,75); whereas blocking this pathway with specific inhibitors such as iFSP1 renders tumor cells susceptible to ferroptosis due to uncontrolled lipid peroxidation (73).

In addition, FSP1 primarily mediates CoQ10 reduction at the plasma membrane, which spatially complements the mitochondrial dihydroorotate dehydrogenase-mediated CoQ10 reduction pathway, collectively establishing a multilayered defense system against lipid peroxidation (74).

p62-kelch-like ECH-associated protein 1 (Keap1)-nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Unlike the GSH-GPX4 and FSP1-CoQ10 pathways, which directly execute antioxidant functions, the p62-Keap1-Nrf2 signaling pathway plays a key role at the level of transcriptional regulation in cellular antioxidant stress responses and the regulation of ferroptosis. Under homeostatic conditions, the transcription factor Nrf2 is constitutively degraded via the ubiquitin-proteasome pathway through its binding to Keap1, thereby maintaining low basal levels (76). Upon exposure to oxidative stress, the autophagy adaptor protein p62 competitively binds to Keap1, relieving Keap1-mediated degradation

of Nrf2, which promotes Nrf2 phosphorylation and nuclear translocation, thereby initiating transcription of downstream target genes (76,77).

Upon activation, this pathway suppresses ferroptosis through multilayered synergistic regulation: In terms of iron metabolism, Nrf2 upregulates the expression of FTH1 and FPN, promoting iron storage and efflux to maintain cellular iron homeostasis (78); in terms of antioxidant defense, Nrf2 enhances the expression of glutamate-cysteine ligase, GSH synthase and the cystine transporter SLC7A11 to promote GSH synthesis and activates antioxidant enzymes such as heme oxygenase-1 (HO-1), collectively facilitating the clearance of ROS (79,80).

The pathological importance of this pathway varies across tissue contexts. Activation of this pathway has been demonstrated to protect cardiomyocytes from doxorubicin (DOX)-induced ferroptosis (81). In tumors, however, sustained Nrf2 activation resulting from KEAP1 deficiency enhances cancer cell resistance to ferroptosis, suggesting that targeting this pathway may represent a therapeutic strategy to induce ferroptosis in tumors (82). Furthermore, by downregulating SLC7A11 expression and suppressing System Xc⁻ function, p53 enhances cellular sensitivity to ferroptosis, further illustrating the crosstalk among different signaling pathways in the regulation of ferroptosis (Fig. 2).

Effects of the TME metabolic competition on ferroptosis. The aforementioned defense systems against ferroptosis primarily elucidate the antioxidant regulatory network from the perspective of cell-intrinsic mechanisms, whereas metabolic competition within the TME profoundly influences the ferroptosis sensitivity of cancer cells from the external aspect. The TME is a complex ecosystem composed of tumor cells, immune cells and stromal components (83). The TME is often characterized by nutrient and oxygen deprivation caused by rapid tumor growth, which creates a metabolically starved niche (84), such nutritional deficiency drives extensive metabolic reprogramming and further influences key ferroptosis-related pathways. For example, nutrient restriction drives bladder cancer cells to secrete glutamine:fructose-6-phosphate amidotransferase 1-enriched small extracellular vesicles. These vesicles activate the hexosamine biosynthetic pathway in vascular endothelial cells to promote angiogenesis, reshaping the local metabolic landscape and indirectly inhibiting ferroptosis. Meanwhile, nutrient scarcity within the TME induces mixed lineage kinase domain like pseudokinase phosphorylation and enhances autophagy and vesicle secretion. This adaptive metabolic response helps tumor cells cope with metabolic stress and modulates lipid peroxidation and iron homeostasis, which are closely associated with ferroptosis (85).

Metabolic competition between glutamine and cysteine. Among the numerous metabolic competitive relationships within the TME, the metabolic competition between glutamine and cysteine constitutes a key link in regulating ferroptosis. Tumor cells take up extracellular cysteine via the Xc⁻ antiporter (SLC3A2/SLC7A11) to maintain GSH synthesis, which sustains GPX4 activity and suppresses harmful lipid peroxidation. Following immunotherapy-induced activation, CD8⁺ T cells secrete IFN- γ to suppress system Xc⁻ activity, which hinders cysteine uptake in tumor cells. This signaling cascade

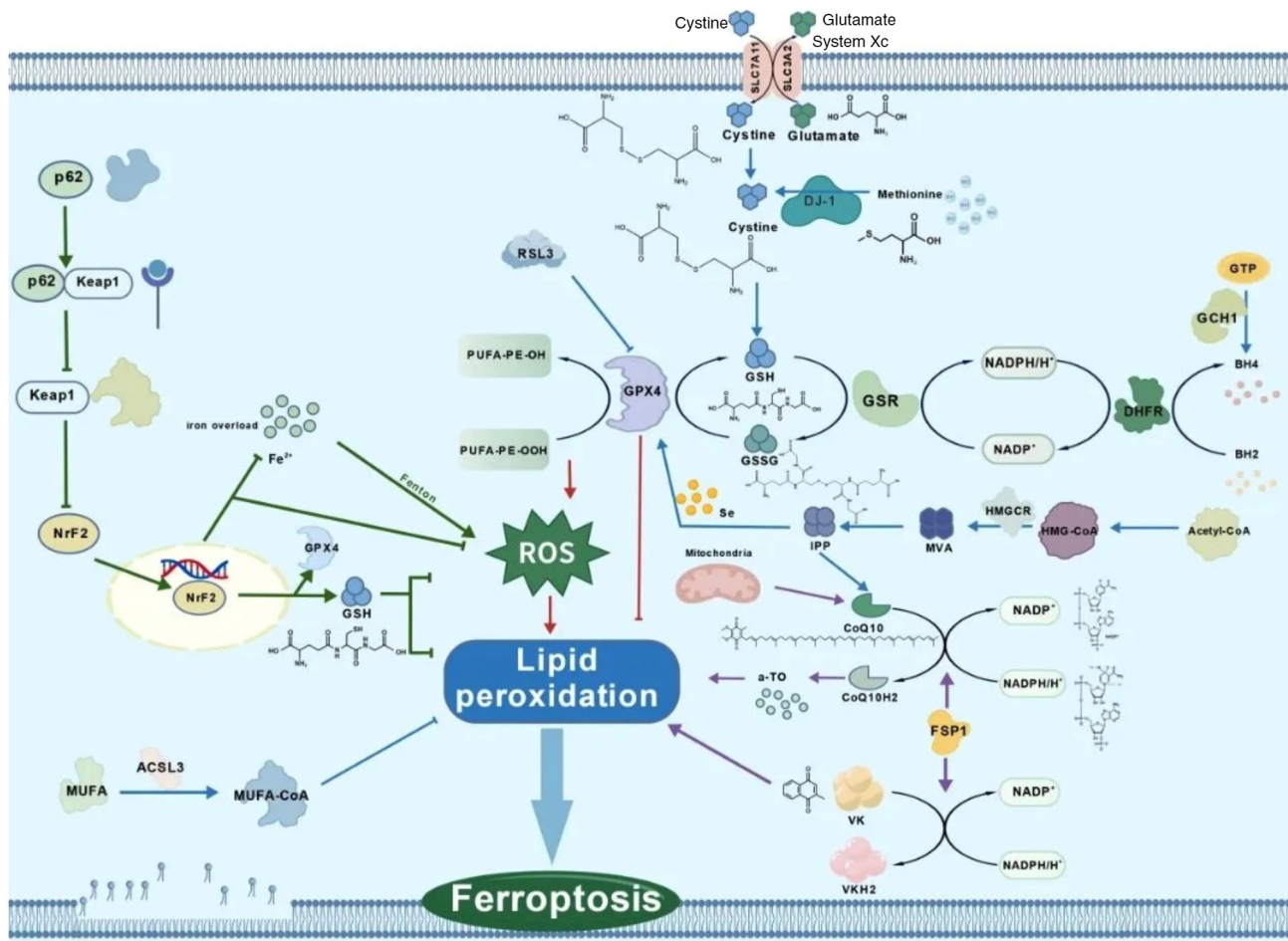


Figure 2. Cells deploy a multilayered defense network against ferroptosis. The p62-Keap1-Nrf2 pathway serves as a master regulator that regulates antioxidant genes at the transcriptional level, whereas the GSH-GPX4 and FSP1-CoQ10 pathways function as parallel effector systems that directly neutralize lipid peroxides at the mitochondrial and plasma membrane levels, respectively. This hierarchical defense architecture not only protects tumor cells but also determines the ferroptosis susceptibility of infiltrating T cells, thereby shaping the immunological landscape of the TME. Keap, kelch-like ECH-associated protein; Nrf2, nuclear factor erythroid 2-related factor 2; ACSL3, acyl-CoA synthetase long chain family member 3; MUFA, monounsaturated fatty acid; GSH, glutathione; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; GSSG, oxidized glutathione; CoQ10, Coenzyme Q10; FSP1, ferroptosis suppressor protein 1; BH4, tetrahydrobiopterin; BH2, dihydrobiopterin; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11.

leads to GSH depletion and lipid peroxide buildup, ultimately sensitizing malignant cells to ferroptosis (86-88).

Glutamine metabolism is closely linked to cysteine utilization: Glutamine catabolism produces glutamate, which serves as an essential substrate for Xc⁻-mediated exchange of extracellular cysteine (89). Accelerated glutamine flux raises intracellular glutamate levels, promotes cysteine uptake and provides precursors for GSH synthesis (90,91), thereby strengthening GPX4-mediated antioxidant defense (92). By contrast, inhibition of glutaminase (GLS1) reduces glutamate production, which both restricts GSH synthesis and impedes cysteine uptake, leading to the accumulation of ROS and lipid peroxides and notably increasing ferroptosis sensitivity (93). In line with this observation, GLS1 knockout in MCF-7 and HCT116 cancer cell lines lowers intracellular GSH concentrations and cysteine uptake, rendering tumor cells more susceptible to erastin-induced ferroptosis, whereas ectopic GLS1 restoration rescues GPX4 expression and mitigates oxidative injury (93). Moreover, ferroptosis inducers such as erastin upregulate the glutamine transporter SLC1A5 to promote glutamate uptake (94). However, excessive glutamate efflux

competitively interferes with cysteine exchange, which further aggravates GSH depletion and accelerates ferroptosis (95).

Regulatory roles of hypoxia and high lactate environments. Hypoxia and high lactate levels, two signature traits of the TME, co-ordinately regulate ferroptosis sensitivity. Hypoxia stabilizes hypoxia-inducible factor (HIF)-1 α to redirect cellular metabolism toward glycolysis, which in turn causes substantial lactate deposition (44). Lactate enhances ferroptosis resistance mainly through two pathways. On the one hand, lactate upregulates stearoyl-CoA desaturase-1 to promote MUFA synthesis (82), while simultaneously inhibiting ACSL4 to reduce PUFA accumulation, thereby blocking lipid peroxidation at the substrate level (61). On the other hand, lactate inhibits AMPK to enhance System Xc⁻ activity, promoting cysteine uptake and GSH synthesis and strengthening GPX4 function (44). Furthermore, hypoxia also stimulates HIF-1 α -mediated carbonic anhydrase IX expression, leading to extracellular acidification and enhanced intracellular iron sequestration. These changes blunt the Fenton reaction and suppress ferroptosis (92).

However, hypoxia and high lactate levels can, under certain conditions, also promote ferroptosis: HIF-2 α , through upregulating hypoxia-inducible lipid droplet-associated protein, promotes the enrichment of PUFAs in the plasma membrane; under acidotic conditions, inhibition of diacylglycerol O-acyltransferase can lead to PUFA release and peroxidation, accelerating ferroptosis (92). However, the aforementioned pro-ferroptotic effects are largely dependent on specific experimental conditions; in the majority of TME contexts, hypoxia and high lactate levels still predominantly enhance ferroptosis resistance, for example, in lung cancer, hypoxia markedly boosts defense capacity through the HIF-1 α /angiopoietin-like 4 axis in a GPX4-dependent manner (61).

3. Functional and metabolic characteristics of T cells in the TME

Cell subpopulations and their metabolic regulation

Cytotoxic T lymphocytes (CTLs). T cells originate from bone marrow hematopoietic stem cells. After undergoing positive and negative selection in the thymus, they mature and differentiate into CD8⁺ or CD4⁺ T cells (96-98). CTLs mainly consist of subsets expressing diverse cytotoxic proteins, including granzyme B, perforin and granulysin (98). Upon activation by antigen-presenting cells, CTLs recognize major histocompatibility complex (MHC) class I-peptide complexes on target cell surfaces via the TCR, thereby eliminating target cells (98-100). However, tumor cells can downregulate MHC class I expression via molecules such as β -1,4-galactosyltransferase 5, thereby escaping immune surveillance (101). Furthermore, MHC matching may also accelerate CD8⁺ T cell exhaustion (102).

CTLs destroy target cells mainly through two pathways. The first is the perforin/granzyme pathway: CTLs secrete perforin to form pores on the target cell membrane, allowing granzymes to enter target cells and induce apoptosis (103-105); the second is the Fas-Fas ligand (FasL) pathway. FasL on the surface of CTLs binds to Fas expressed on target cells, thereby activating caspase-mediated apoptotic signaling (106-108). These two pathways differ in killing efficiency and mechanism and are regulated by cytokines. For instance, IL-4 can upregulate FasL expression in T cells, switching the CTL-mediated cell lysis from the PFN-dependent perforin pathway to FasL-dependent killing (109).

The functional fitness of CTLs within the TME is markedly affected by their intrinsic susceptibility to ferroptosis, which is determined by metabolic status and lipid composition. CTLs accumulating peroxidized PUFAs in cell membranes are more prone to ferroptosis, whereas CTLs with enhanced antioxidant capacity, particularly via the GPX4 pathway, exhibit greater resistance and sustained effector functions (110).

In the TME, multiple cytokines collectively regulate the function of CTLs. IFN- γ exerts dual roles within the TME. On the one hand, it enhances the cytotoxicity of CTLs and promotes antitumor immunity (111-113); on the other hand, it can induce the expression of immunosuppressive molecules (such as B7 homolog 4) or promote C-X-C motif chemokine ligand (CXCL) 11 secretion, thereby impairing T cell function and fostering tumor progression (112,114,115). Moreover, sustained high expression of interferon regulatory factor (IRF) 4 also contributes to CD8⁺ T cell exhaustion (116,117).

IL-4 exerts immunosuppressive effects within the TME. Specifically, IL-4 facilitates tumor growth, impedes CTL differentiation and triggers T cell exhaustion. Furthermore, it may remodel the cytotoxic effector mechanism of T cells by switching the dominant killing pathway from the perforin pathway to the FasL pathway (118-122).

In addition to cytokine-mediated regulation, physical and microenvironmental factors also influence the infiltration and function of CTLs. Interventions such as low-dose radiotherapy can enhance CD8⁺ T cell infiltration and function by modulating the TME, as exemplified by the induction of C-X-C motif chemokine receptor (CXCR) 6⁺ CD8⁺ T cell aggregation and activation (123-125). Nevertheless, tumor stromal stiffening, TGF- β signaling activation and epithelial-mesenchymal transition can restrain CD8⁺ T cell infiltration and facilitate tumor immune escape (126).

Helper T cells [(Th)1, Th9 and follicular helper T cells (Tfh)]. The aforementioned CTL-mediated cytotoxic response represents a key effector arm of antitumor immunity, whereas CD4⁺ T cells regulate tumor immune responses in a more diverse manner through differentiation into distinct helper T cell subsets. This differentiation process is finely regulated by cytokines such as IL-4 and TGF- β , enabling each subset to exert complex roles within the TME.

Th9 cells differentiate under the combined induction of IL-4 and TGF- β and produce the signature cytokine IL-9 (127). This cell subset possesses potent antitumor potential, and secreted IL-9 can recruit dendritic cells and monocytes, thereby eliciting robust CD8⁺ CTL responses to eliminate tumors (128-130). The differentiation and function of Th9 cells are finely regulated by metabolic pathways, including HIF-1 α -mediated glycolysis, sirtuin 1 expression, as well as FA and cholesterol metabolism (131-134).

In synergy with the antitumor effects of Th9 cells, Th1 cells are likewise a key effector subset in antitumor immunity. Their differentiation and function are driven by cytokines such as IL-12, which promotes IFN- γ secretion by Th1 cells, enhances CD8⁺ T cell differentiation and suppresses the function of Tregs (135-137). Th1 cells can directly inhibit tumor cell proliferation and enhance their sensitivity to radiotherapy and chemotherapy (138). Mitochondrial function is key for Th1 responses, and the loss of transmembrane protein 11 protein impairs mitochondrial function, thereby weakening Th1 responses (139).

Tfh cells are a unique subset of CD4⁺ T cells that assist B cell activation and enhance germinal center (GC) responses (140-142). The key transcription factor for their differentiation is BCL-6, and they characteristically express molecules such as CXCR5, programmed cell death protein 1 (PD-1) and inducible T cell co-stimulator (143-145). Tfh cells play a key role in promoting GC formation, B cell activation, antibody class switching and memory B cell generation through the secretion of IL-21 and CXCL13. Of note, angio-immunoblastic T cell lymphoma, which originates from Tfh cells, frequently exhibits high expression of Tfh-associated antigens such as BCL-6 and CXCL-13 (146,147). Moreover, factors such as IL-6 in the TME may participate in its pathological processes. In AITL, this cytokine is primarily secreted by neoplastic Tfh cells, macrophages and dendritic cells, and engages in multi-layered pathological progression

via activating the JAK-STAT3 signaling axis. IL-6 promotes survival and proliferation of neoplastic Tfh cells, sustains BCL-6 expression and consolidates their malignant phenotype. On the other hand, it targets microenvironmental B cells to trigger B cell activation and plasma cell differentiation, leading to polyclonal hypergammaglobulinemia; it also promotes follicular dendritic cell proliferation, induces vascular endothelial growth factor secretion, stimulates high endothelial venule neogenesis and stromal remodeling in lymph nodes, establishing a tumor-supportive microenvironment. Furthermore, IL-6 drives Th17 differentiation and inhibits Treg function, disrupting local immune homeostasis, amplifying autoimmune-like inflammation, exacerbating systemic immune disturbance in AITL and generating a pro-tumor inflammatory positive feedback loop (148). Elevated IRF4 levels can inhibit Tfh differentiation. TCR signal-driven upregulation of IRF4 (interferon regulatory factor 4) reprograms CD4⁺ T cells toward the Teff (effector T cell) lineage. At the molecular level, abundant IRF4 preferentially binds to low-affinity ISRE (interferon-stimulated response element) cis-elements within Prdm1 (encoding Blimp-1 protein), driving Blimp-1 transcription while antagonizing the Bcl6-mediated Tfh transcriptional program; this regulatory effect is independent of IL-2 signaling. Functionally, this results in a substantial decrease in GC-Tfh (germinal center follicular helper T) cell proportion, directly compromising Tfh-dependent germinal center responses, preventing the formation of antigen-specific GC B (germinal center B) cells, and ultimately weakening antigen-specific B cell affinity maturation and humoral immune responses (149).

Tregs. Unlike Th1, Th9 and CTLs, which exert the aforementioned antitumor effects, Tregs are key immunosuppressive cells within the TME, and their function is closely linked to metabolic stability. Tregs exhibit unique metabolic dependencies that render their sensitivity to ferroptosis distinct from that of other T cell subsets. These include heavy reliance on FA oxidation (FAO) and oxidative phosphorylation (OXPHOS) for energy with low glycolytic activity; high dependence on the GPX4/GSH antioxidant system, where GPX4 deletion or inhibition rapidly induces ferroptosis in Tregs while effector T cells are relatively tolerant; and strong dependence on the cystine/glutamate antiporter (xCT) and GSH synthesis pathway, whereby xCT inhibition selectively depletes GSH in Tregs and enhances their susceptibility to ferroptosis. Tregs are highly dependent on FAO and utilize GPX4 as an antioxidant barrier, positioning ferroptosis as an important regulatory node for Treg stability and suppressive function within the TME (67).

At the mechanistic level, GPX4, a key regulatory enzyme of ferroptosis, is key for maintaining the homeostasis and suppressive function of Tregs. GPX4 prevents Tregs from undergoing ferroptosis by eliminating lipid peroxides; when GPX4 is deficient, TCR stimulation triggers the accumulation of lipid peroxidation and ferroptosis, leading to impaired immunosuppressive function of Tregs and production of pro-inflammatory factors (67,148).

The immunosuppressive function of Tregs does not act alone; rather, through interactions with tumor cells, cancer-associated fibroblasts (CAFs) and other components, it collectively shapes an immunosuppressive TME. For instance,

tumor-derived lactate induces pro-angiogenic effects in CAFs, and Tregs synergize with CAFs to upregulate inhibitory molecules such as programmed death-ligand 1 (PD-L1), thereby excluding CTLs (150-153). In addition, specific chemokines (such as CXCL10) and metabolic transcription factors (such as HIF-1 α) can also modulate Treg accumulation and functional balance (154-156).

Lipid metabolism is central to Tregs function in the TME. Tregs rely heavily on FAO for energy (157) and sustain their potent immunosuppressive function by taking up exogenous FAs via CD36 or activating the sterol regulatory element-binding proteins (SREBP)-FA synthase (FASN) pathway for endogenous synthesis, thereby meeting their metabolic demands (158-161). Inhibition of these lipid metabolic pathways [such as via SREBP cleavage-activating protein or FASN knockout or FA-binding protein 5 (FABP5) inhibition] impairs intratumoral Treg accumulation and function, thereby potentiating antitumor immunity (160,162). Notably, lipid synthesis in T cells is also essential for their PD-1 expression. In CD103⁺ Treg cells, lipid synthesis and cholesterol metabolic pathways are highly activated. Lipid metabolic reprogramming modulates intracellular signaling cascades to drive PD-1 transcription. In the TME of glioblastoma treated with radiotherapy plus concurrent immune-checkpoint-blockade (RT + Conc.IT), up-regulated lipid biosynthesis and peroxisome proliferator-activated receptor (PPAR) signaling reshape the T-cell transcriptome and promote the accumulation of PD-1 transcripts at the transcriptional level, consequently elevating PD-1 protein abundance and facilitating the acquisition of the T cell exhaustion phenotype. Accordingly, targeting this pathway enhance the efficacy of PD-1 blockade therapy (163).

Memory T cells: mTOR and AMPK pathways in long-term immunological memory. Unlike the immediate effector functions primarily mediated by the aforementioned T cell subsets, the long-term persistence of memory T cells is key for durable antitumor immunity, and this persistence is associated with their ability to resist ferroptosis. The mTORC2-AKT-glycogen synthase kinase-3 β (GSK3 β) axis sustains GPX4 expression and prevents lipid peroxidation in memory CD4⁺ T cells, positioning ferroptosis as a key determinant of longevity of memory T cells (164).

At the level of metabolic regulation, AMPK serves as a cellular energy sensor and is activated upon metabolic stress, such as glucose deprivation, in T cells (165,166). Activated AMPK is essential for the generation of central memory T cells. In the nutrient-competitive TME, AMPK confers survival and proliferative advantages to effector T cells and memory T cells (167,168). AMPK α 1 activity is required for the *in vivo* survival of CTLs following cessation of immunological stimulation (169,170). Enhancing AMPK signaling (such as via overexpression of AMPK γ 2) can improve T cell fitness under low-glucose conditions (171), however, its role is complex, as it can both enhance the inflammatory function of conventional Th cells and augment the suppressive function of regulatory T cells (172).

The PI3K/AKT/mTOR pathway serves as a central hub that integrates immunological signals and cellular metabolism, influencing the fate of memory T cells (173). mTORC2 signaling promotes the long-term maintenance of memory CD4⁺ T cells by inhibiting ferroptosis (164). Of

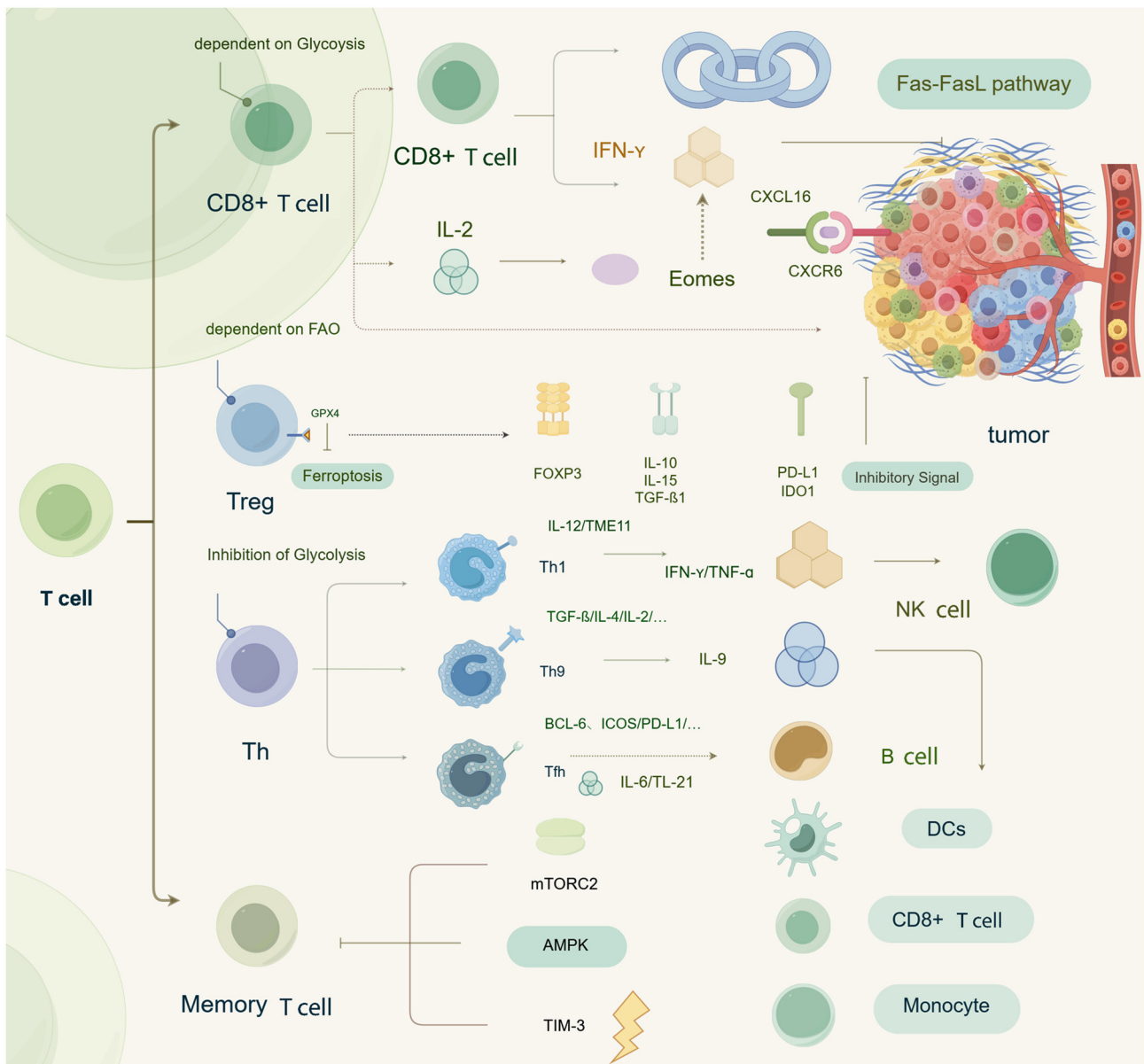


Figure 3. Metabolic landscape of T cell subsets in the TME is heterogeneous. Naive T cells can differentiate into CD8⁺ effector cells, Tregs, Th subsets and memory T cells, with each subset possessing unique metabolic dependencies, ranging from glycolysis-driven effector functions to FAO-supported memory persistence. This figure highlights that these metabolic states directly modulate ferroptosis susceptibility, and GPX4 acts as a core node integrating metabolic signaling and ferroptosis resistance across diverse T cell lineages. CXCL, C-X-C motif chemokine ligand; CXCR, C-X-C motif chemokine receptor; TME, tumor microenvironment; Th, helper T cell; PD-L1 programmed death-ligand 1; mTORC, mTOR complex; TIM-3, T cell immunoglobulin and mucin domain 3; ICOS, inducible T cell costimulatory; NK, natural killer; DC, dendritic cells; FasL, Fas ligand; IDO1, indoleamine-pyrrole 2,3-dioxygenase; FAO, fatty acid oxidation; GPX4, glutathione peroxidase 4; Treg, regulatory T cell; FOXP3, forkhead box P3; AMPK, AMP-activated protein kinase.

note, although rapamycin, an mTOR inhibitor, is regarded as an immunosuppressive agent, and may increase the number of vaccine-induced, antigen-specific T cells with a central memory phenotype and to improve the quality of memory cells in specific models (174,175).

T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) is one of the markers of T cell exhaustion. TIM-3 signaling is essential for effector T cell differentiation (176,177). During antigen stimulation, TIM-3 signaling drives sufficient mTORC1 activation through the activation of RHEB like-1, thereby promoting T cell differentiation toward an effector phenotype rather than a memory phenotype. Blockade of TIM-3 leads to insufficient mTORC1

activation, skewing T cell differentiation toward a memory phenotype (176,178) (Fig. 3).

4. Ferroptosis and T cell interactions in the TME

Effects of ferroptosis on T cell function

CTLs: Proliferation and activation, cytotoxicity and cytokine secretion. Ferroptosis exerts a dual role in regulating CD8⁺ T cells within the TME, representing both an opportunity to enhance antitumor immunity and a challenge that drives T cell functional exhaustion.

On one hand, ferroptosis indirectly activates CD8⁺ T cells by triggering immunogenic cell death in tumor cells. For

example, ferroptosis of tumor cells enhances the capacity of CD8⁺ T cells to produce IFN- γ (179); apolipoprotein L3 (APOL3) enhances tumor cell sensitivity to ferroptosis while simultaneously potentiating CD8⁺ T cell cytotoxicity through metabolic regulation (180); the IL-9/STAT3 signaling pathway protects specific CD8⁺ T cell subsets, such as Tc9 cells, from ferroptosis by upregulating FAO, thereby sustaining their long-term antitumor activity (181).

On the other hand, ferroptosis can directly impair the function of CD8⁺ T cells. Within the TME, Ma *et al.* (34) demonstrated that tumor-infiltrating CD8⁺ T cells upregulate CD36 in response to TME cholesterol, and that CD36-mediated uptake of oxidized lipids directly induces lipid peroxidation and ferroptosis in these cells, thereby impairing their antitumor activity (24). This mechanism has been validated in both human cancer specimens and murine tumor models, wherein CD36 expression is associated with unfavorable patient survival (24). Cholesterol metabolism further upregulates CD36, exacerbating T cell functional exhaustion (34).

To address the aforementioned paradox, a core strategy involves protecting T cell function through metabolic regulation. Supplementation with MUFA reduces cellular lipid peroxidation levels and protects T cells (182); genetic engineering approaches, such as GPX4-armed oncolytic viruses, can downregulate CD36 and alleviate lipid peroxidation, thereby restoring the antitumor function of CD8⁺ T cells both *in vitro* and *in vivo* (183).

In summary, effective immunotherapy requires the coordinated exploitation of ferroptosis to eliminate tumor cells while simultaneously protecting effector T cells from ferroptosis through precision metabolic interventions, thereby maximizing antitumor immune efficacy.

Th1/Th2 balance and cytokine secretion in Th cells. Ferroptosis influences the function of Th cells through multi-layered regulatory mechanisms. Lipid metabolism serves as the core mechanism by which ferroptosis regulates Th cell differentiation. Lipid peroxidation products specifically promote Th1 cell activation and exacerbate immune responses (184). Meanwhile, key enzymes such as ACSL4 directly participate in regulating the Th1/Th2 balance by remodeling the cellular lipid metabolic profile (185).

Building upon the aforementioned metabolic regulation, ferroptosis emerges as a key determinant of the fate of memory T cells. The regulation of Th cells and their related subsets by ferroptosis is context-dependent across different disease settings. For instance, in the context of tumors, LPCAT3-induced ferroptosis suppresses the infiltration of lymphocytes such as Tfh and Tregs, thereby disrupting the homeostatic balance of Th cells (186); in autoimmune diseases, high mobility group AT-hook 1 (HMGAI) inhibits ferroptosis in Tfh cells through the STAT3/GPX4 signaling pathway, thereby paradoxically promoting the survival of pathogenic T cells (187).

Multiple molecules play key roles in regulating ferroptosis in Th cells. For example, CD36-mediated uptake of oxidized lipids drives the ferroptotic process in CD8⁺ T cells. In the TME, cholesterol induces scavenger receptor CD36 upregulation in tumor-infiltrating CD8⁺ T cells. As an FA transporter, CD36 mediates massive uptake of ω -6 PUFAs such as AA) enriched in the TME. The incorporated PUFAs are integrated into membrane phospholipids, leading to accumulation of

intracellular lipid peroxides and triggering ferroptosis, which in turn impairs the capacity of CD8⁺ T cells to secrete cytotoxic cytokines including IFN- γ and TNF- α (34); GPX4, as an antioxidant enzyme, serves as a core factor in maintaining T cell functional homeostasis and conferring resistance to ferroptosis (188).

Overall, ferroptosis regulates the balance between pro-inflammatory Th1 and anti-inflammatory Th2 cells through pathways including lipid metabolism (189); this context-dependent bidirectional regulation provides novel therapeutic targets for immune-related diseases.

Effects on memory T cells: Survival, proliferation, differentiation and tumor response speed upon re-exposure. Ferroptosis influences the survival, proliferation, differentiation and long-term antitumor immunity mediated by memory T cells through the regulation of metabolic status and the immune microenvironment.

At the level of survival, the long-term persistence of memory T cells relies on a stable metabolic state. Deficiency of the key metabolic regulator mitochondrial trans-2-enoyl-CoA reductase (MECR) disrupts mitochondrial function, leading to iron accumulation and increased susceptibility to ferroptosis, thereby impairing the survival and function of effector memory T cells (TEMs) (190).

At the level of microenvironment remodeling, specific ferroptosis-related pathways shape a favorable microenvironment. For example, high expression of the ferroptosis-associated gene CDGSH iron sulfur domain 2 is positively associated with memory T cell infiltration and negatively associated with the presence of immunosuppressive Tregs (191). Tumor subtypes with specific ferroptosis signatures exhibit increased central memory T cell infiltration and are associated with improved patient prognosis. The signature profile of these tumors features low GPX4 expression, high ACSL4 expression, decreased SLC7A11/xCT levels, accumulation of lipid peroxidation products (4-hydroxynonenal/malondialdehyde) and GSH depletion (192).

At the level of therapeutic intervention, targeted interventions enhance immunological memory. Precise triggering of tumor cell ferroptosis by inducers such as iridium (III) complexes effectively promotes the generation of TEMs, establishes durable antitumor immunological memory and prevents tumor recurrence (193).

In summary, modulating ferroptosis sensitivity is a key factor influencing memory T cell function and the kinetics of antitumor responses, offering a novel direction for enhancing the long-term efficacy of immunotherapy.

Effects on Tregs. Ferroptosis markedly influences the stability and function of Tregs through the modulation of key antioxidant enzymes and metabolic pathways, a process that holds implications for both tumor immunity and autoimmunity.

At the level of antioxidant defense, GPX4 is a core factor in maintaining Treg homeostasis. GPX4-deficient Tregs accumulate lipid peroxides and undergo ferroptosis, thereby impairing their immunosuppressive function and potentiating antitumor immune responses (67,194). Conditional deletion of Gpx4 in Tregs drives Th17 cell differentiation and perturbs the immune equilibrium (195).

At the level of metabolic regulation, loss of PDK1 perturbs iron balance in Tregs, elevates ROS generation and triggers

both apoptotic and ferroptotic cell death (196). FABP5 maintains the immunosuppressive function of Tregs by regulating lipid metabolism and its downregulation leads to mitochondrial dysfunction and metabolic impairment (197).

At the level of therapeutic application, ferroptosis inducers can specifically eliminate Treg cells within the TME, thereby reversing immunosuppression and enhancing antitumor immunity. For example, oxaliplatin/ferritin aggregates induce ferroptosis by potentiating the Fenton reaction, notably reversing the immunosuppressive microenvironment in glioma (198).

Ferroptosis-mediated modulation of Tregs represents a promising avenue in cancer immunotherapy. Selective triggering of ferroptosis in Tregs potentiates antitumor immunity and offers a new therapeutic approach for tumor immunotherapy.

Regulatory molecular mechanisms

Iron metabolism-associated molecules. The occurrence of ferroptosis in T cells is precisely regulated by a series of key molecules involved in iron metabolism, with the core mechanism centering on the balance between the production and clearance of lipid peroxidation. This equilibrium directly determines T cell fate and immune function.

GPX4 is the core antioxidant enzyme that defends against ferroptosis by scavenging lipid peroxides. In T cells, loss of GPX4 function directly triggers ferroptosis and impairs immune competence (110). Notably, specific deletion of GPX4 in Tregs can disrupt immune homeostasis while simultaneously enhancing antitumor immunity (67).

SLC7A11, a cystine transporter, serves as the key rate-limiting step in the synthesis of GSH, an essential cofactor for GPX4. Its expression is dynamically regulated by immune signals, for example, IL-13 promotes its degradation to induce ferroptosis (199), whereas IFN- γ released by CD8⁺ T cells promotes ferroptosis in tumor cells by suppressing SLC7A11 expression on these cells.

In addition, transcription factors such as IRF8, Nrf2 and p53 modulate ferroptosis sensitivity in a context-dependent manner, either promoting or suppressing it through the regulation of downstream target genes including HO-1 and p21. For example, IRF8 sustains the sensitivity of tumor cells to ferroptosis by suppressing p53, thereby ensuring effective T cell-mediated killing (200).

Collectively, the precise modulation of T cell ferroptosis through the targeting of iron-metabolic regulators, such as GPX4, SLC7A11 and key transcription factors, represents an emerging and promising approach for boosting antitumor immunity or treating autoimmune disorders.

Lipid peroxidation-related molecules. Another component of the regulatory network, together with iron metabolism-associated molecules, is constituted by lipid peroxidation-related molecules. Lipid metabolic reprogramming is a critical determinant of T cell ferroptosis sensitivity. For example, APOL3 degrades lactate dehydrogenase and reduces lactate concentration, thereby both enhancing CD8⁺ T cell cytotoxicity and promoting ferroptosis in tumor cells (180). Conversely, CD36-mediated uptake of oxidized lipids exacerbates lipid peroxidation in tumor-infiltrating CD8⁺ T cells, directly leading to their functional exhaustion (7).

Several key metabolic pathways safeguard T cells via augmentation of antioxidant capacity. The IL-9/STAT3 axis, by promoting FAO and improving mitochondrial function, markedly diminishes lipid peroxidation in Tc9 cells, enabling them to acquire durable antitumor functionality (181). Meanwhile, the GTP cyclohydrolase 1/tetrahydrobiopterin pathway provides key compensatory protection when GPX4 is inhibited, alleviating lipid peroxidation and maintaining T cell homeostasis (201).

The functional homeostasis of T cells is remodeled under metabolically stressed conditions. In the context of metabolic abnormalities such as obesity, impaired Nrf2 nuclear translocation reduces the expression of antioxidant genes such as HO-1 in Treg cells, resulting in increased oxidative stress and a predisposition to ferroptosis, which ultimately perturbs immune equilibrium and aggravates inflammatory responses (201).

In summary, targeting lipid peroxidation-related molecules to modulate the metabolic status and redox balance of T cells provides novel molecular targets for precisely intervening in T cell function and enhancing immunotherapy.

Involvement of signaling pathways. Lipid peroxidation-related molecules directly regulate the production and clearance of lipid peroxidation, whereas the MAPK signaling pathway constitutes a more complex regulatory network at the level of signal transduction, exerting bidirectional regulation on ferroptosis through its distinct branches and being involved in immune modulation.

Distinct MAPK family members exhibit contrasting effects on ferroptosis. The JNK/p38 axis typically facilitates ferroptosis by upregulating TFR1 expression and promoting ferritinophagy, which results in iron accumulation and ultimately drives ferroptotic cell death (202). For example, in the TME, TNF- α -derived from M1 macrophages induces ferroptosis in pancreatic cancer cells by activating p38 MAPK signaling and upregulating ACSL4 expression (203); in acute lung injury, IL-17A also promotes ferroptosis in alveolar epithelial cells through the Act 1 adaptor protein/tumor necrosis factor receptor-associated factor 6/p38 MAPK pathway (204). Conversely, the ERK signaling axis generally acts to inhibit ferroptosis. For instance, ERK-mediated RENG phosphorylation represses p53 function, leading to upregulated expression of the cystine transporter SLC7A11 and strengthened antioxidant capacity (205). In colorectal cancer, dictamnine exerts its antitumor effects through dual mechanisms: Inducing ferroptosis in cancer cells via ERK phosphorylation inhibition and restraining the polarization of tumor-promoting M2 macrophages (206).

In addition to directly regulating ferroptosis, the MAPK pathway also indirectly influences ferroptosis-related immune responses by modulating immune cell function. For example, stimulator of interferon response cGAMP interactor 1 trafficking induces IL-2 and TGF- β 2 expression through activation of the MAPK-cAMP response element-binding protein (CREB) signaling axis, thereby promoting Treg differentiation (207); conversely, the Cbl proto-oncogene B inhibitor NX-1607 enhances T cell antitumor capacity by activating the MAPK/ERK pathway (208). During systemic immune reactions, as observed in COVID-19, the MAPK pathway and ferroptotic signaling are typically concurrently activated,

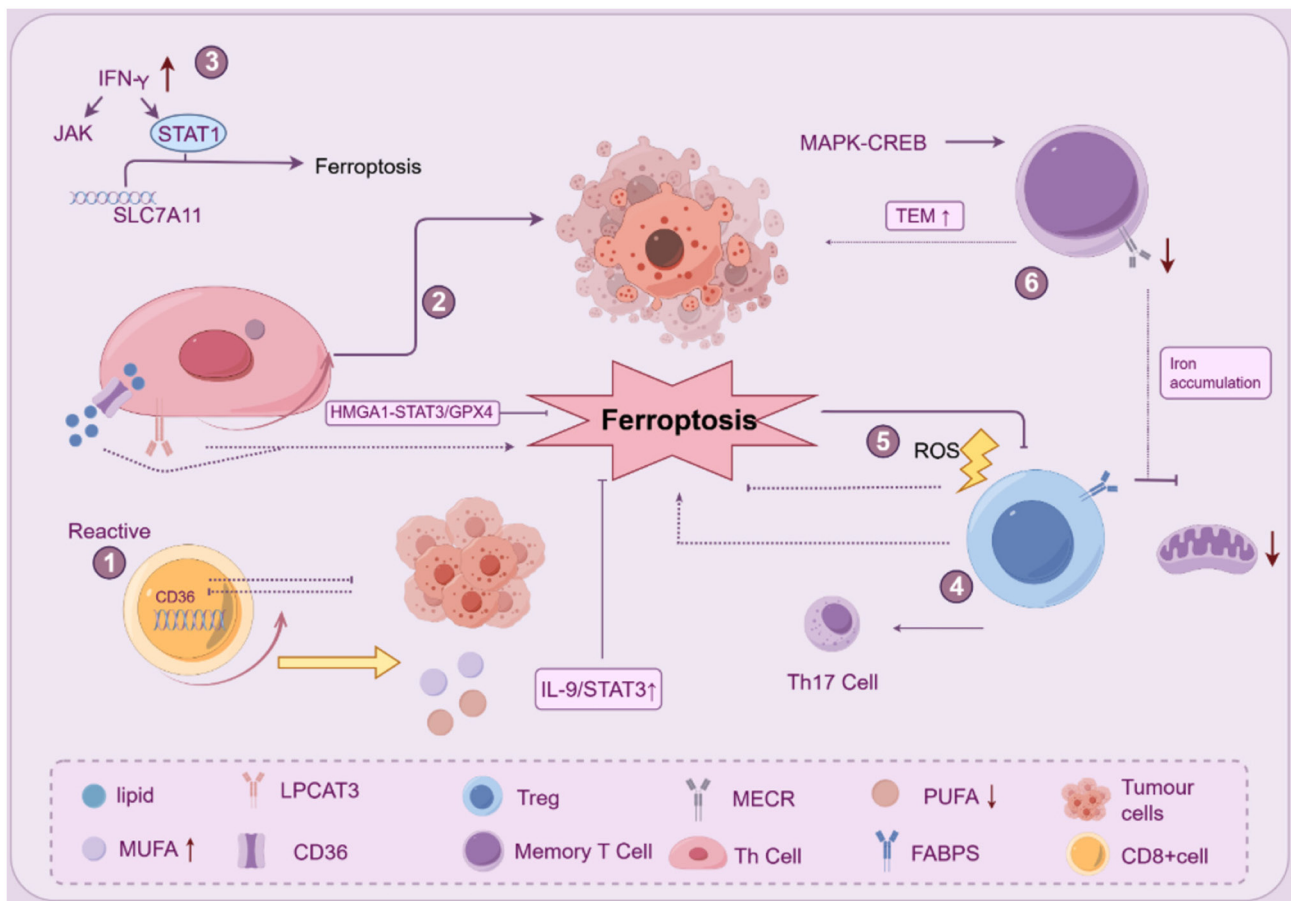


Figure 4. Summary of the bidirectional regulation of T cells by ferroptosis via an intricate signaling network. The diagram depicts the convergence of lipid peroxidation products, iron metabolism regulators and MAPK signaling in the control of T cell proliferation, differentiation and effector activity. Of particular note, the IFN- γ -STAT1 axis acts as a core hub that both initiates tumor cell ferroptosis and establishes a positive feedback circuit to enhance CD8⁺ T cell activation, thus defining ferroptosis as a metabolic-immune checkpoint. SLC7A11, solute carrier family 7 member 11; LPCAT3, lysophosphatidylcholine acyltransferase 3; Treg, regulatory T cell; Th, helper T cell; PUFA-PL, polyunsaturated fatty acid phospholipid; GPX4, glutathione peroxidase 4; AMPK, AMP-activated protein kinase; MUFA, monounsaturated fatty acid; HMG1, high mobility group AT-hook 1; TEM, effector memory T cells; CREB, cAMP response element-binding protein; ROS, reactive oxygen species; MECP, mitochondrial trans-2-enoyl-CoA reductase; FABPS, fatty acid-binding proteins.

along with alterations in T cell subset composition (209), highlighting their involvement in the maintenance of immune equilibrium.

In summary, the MAPK signaling pathway constitutes a finely tuned regulatory network that not only directly determines cellular sensitivity to ferroptosis but also indirectly shapes the ferroptosis-associated immunological landscape through extensive modulation of immune cell functions, thereby providing key signaling targets for the intervention of related disease (87) (Fig. 4).

Regulation of ferroptosis by T cells

CTLs

Secreted factors. Activated CTLs directly induce ferroptosis in tumor cells through the secretion of IFN- γ , which represents a key mechanism of their antitumor cytotoxicity. The mechanistic link between IFN- γ and ferroptosis was established by Wang *et al* (88) who demonstrated that CD8⁺ T-cell-derived IFN- γ downregulates SLC3A2 and SLC7A11 expression, impairs cystine uptake and promotes lipid peroxidation in tumor cells (78). CD8⁺ T cell-derived IFN- γ activates the STAT1 signaling pathway in tumor cells via the IFN- γ receptor. Activated STAT1 upregulates IRF1, which

in turn directly suppresses the transcriptional expression of SLC7A11 and SLC3A2, the two key subunits of the System Xc⁻ (88). This effect restricts cystine uptake by tumor cells, leading to impaired GSH synthesis, compromised antioxidant defense and ultimately resulting in the accumulation of lipid peroxidation and ferroptosis.

Beyond the STAT1-IRF1-SLC7A11 core pathway, IFN- γ can also promote ferroptosis through other pathways. Liao *et al* (87) extended this paradigm by demonstrating that IFN- γ works with AA to induce ACSL4-dependent ferroptosis, and that this pathway is associated with enhanced immune surveillance and checkpoint blockade responses in patients with cancer (87). IFN- γ also promotes ferroptosis through an ACSL4-dependent pathway. IFN- γ stimulates ACSL4 expression, facilitating the esterification of UFAs such as AA into membrane phospholipids, thereby increasing the susceptibility of the cell membrane to lipid peroxidation (87,185). In addition, IFN- κ , a type I INF, contributes to tumor ferroptosis in a cooperative manner via the INF- α/β receptor (IFNAR)/STAT1/ACSL4 signaling axis (182).

On the basis of the aforementioned mechanisms, researchers have begun to explore engineered immunotherapeutic strategies. For example, IFN- κ chimeric antigen

receptor (CAR)-T cells exhibit superior antitumor efficacy (182). Meanwhile, the combination of IFN- γ with iron dextran enhances ferroptosis through ferritinophagy, thereby increasing tumor sensitivity to immunotherapy. Notably, miR-21-3p, as a downstream effector molecule of IFN- γ , can be delivered via a nanosystem to potentiate the efficacy of anti-PD-1 therapy, offering a novel strategy for clinical combination treatment.

Collectively, CTLs induce ferroptosis in tumor cells by directly modulating iron and lipid metabolism via IFN- γ secretion. This mechanistic insight not only expands our knowledge of T cell antitumor activity but also offers novel therapeutic targets and strategies to improve the outcomes of cancer immunotherapy.

Cytotoxicity: Perforin and granzyme, and the TNF pathway. Beyond cytokine-mediated effects, CTLs employ the perforin-granzyme cytotoxic pathway to directly induce ferroptosis in target cells. Granzyme B (GrB), a critical effector protease, exerts its pro-ferroptotic function by directly cleaving GPX4 and degrading FSP1, a ferroptosis suppressor, thus compromising the antioxidant capacity of tumor cells and facilitating ferroptotic cell death (210). Perforin facilitates granzyme entry into target cells by forming transmembrane pores, a mechanism conceptually analogous to that of pore-forming toxins, which have been shown to activate regulated necrosis (72,211). In CAR-NK92MI cell therapy, the perforin/granzyme system has been demonstrated to be a key mechanism underlying ferroptosis-related cell death (212). Granzyme A (GzA) exhibits context-dependent opposing functions. In the setting of intestinal inflammation, GzA drives GPX4 transcription via the cAMP/PKA/CREB axis, which inhibits ferroptosis in intestinal epithelial cells and preserves mucosal barrier integrity (213). This dual functionality underscores the context-specific nature of ferroptosis regulation exerted by different granzyme family members.

CD4⁺ T cells. Unlike CD8⁺ T cells, which actively induce ferroptosis in target cells through effector molecules, CD4⁺ T cell viability and functional competence are closely associated with ferroptosis sensitivity, which is governed by an intricate network of metabolic and molecular regulators and exerts pivotal effects in various immune settings.

The metabolic state of CD4⁺ T cells forms the basis of their resistance to ferroptosis. The mTORC2-AKT-GSK3 β signaling axis sustains the expression of the key antioxidant enzyme GPX4, preventing lipid peroxidation and thereby ensuring the long-term survival of virus-specific memory CD4⁺ T cells (164). Conversely, deficiency in the mitochondrial FA synthesis gene MECR leads to intracellular iron accumulation and impaired oxidative metabolism, markedly increasing the sensitivity of effector and memory CD4⁺ T cells to ferroptosis (190).

In addition to metabolic regulation, dysregulated expression of particular molecules acts either to promote or inhibit ferroptosis. For instance, trafficking protein particle complex subunit 1 deficiency triggers endoplasmic reticulum stress and p53 activation, which in turn drives lipid peroxidation, resulting in ferroptosis of naïve CD4⁺ T cells and the development of autoinflammatory conditions (214). By contrast, mitotic arrest deficient 2 like-2 suppresses ferroptosis and

promotes CD4⁺ T cell survival by activating the mTOR signaling pathway (215).

In specific pathological microenvironments, CD4⁺ T cell subsets participate in disease progression by forming feedback loops. For example, in breast cancer, a unique population of IL1 β +CXCL3⁺CD4⁺ (Fer-CD4) T cells induce ferroptosis in neutrophils through the IL1 β /IL1R1/NF- κ B axis. This process, in turn, promotes the differentiation of Fer-CD4 T cells themselves, establishing a positive feedback loop that drives tumor immune suppression (216).

In summary, ferroptosis in CD4⁺ T cells is subject to multilayered and networked regulation. Understanding and targeting these regulatory nodes provide new potential strategies for intervening in immune-related diseases such as cancer and autoimmune disorders.

T cell-mediated metabolic reprogramming. Regardless of whether CD8⁺ or CD4⁺ T cells are considered, their functional status and ferroptosis sensitivity are profoundly influenced by glucose metabolism, amino acid metabolism and ROS levels. This process constitutes a complex metabolic regulatory network and profoundly shapes the overall landscape of the tumor immune microenvironment. Glucose metabolism is one of the key factors affecting T cell ferroptosis. SLC2A3 (GLUT3), acting as both a glucose transporter and a ferroptosis marker, influences the tumor immune microenvironment by accelerating glycolysis (217), nanoplateforms such as Cu₂O@Au exert dual effects: They catalyze glucose oxidation to produce H₂O₂ and concurrently deplete GSH, thereby efficiently triggering tumor cell ferroptosis while also facilitating dendritic cell maturation and T cell recruitment (218). Copper-alanine nanoparticles loaded with glucose oxidase and cinnamaldehyde) nanoparticles potentiate ferroptosis and antitumor immune responses via cascade Fenton chemistry and enzymatic catalysis, simultaneously consuming GSH and producing large amounts of ROS (219).

Meanwhile, competition for amino acids is equally key, tumor cells, through high expression of SLC7A11, compete with T cells for cystine, leading to impaired GSH synthesis in T cells and increased CD36-mediated lipid uptake, ultimately triggering ferroptosis and functional exhaustion (8). By contrast, Th9 cells depend on peroxisome proliferator-activated receptor (PPAR)- γ -facilitated cystine import to protect against ferroptosis-like cell death (220). In addition, tryptophan catabolism via the kynurenine pathway modulates ferroptosis susceptibility. Tryptophan 2,3-dioxygenase⁺ fibroblasts secrete kynurenine, which upregulates FTH1 expression in metastatic tumor cells and consequently strengthens their ferroptosis resistance (221).

Further upstream, signaling pathways that couple metabolism and nutrient sensing play a key role in ferroptosis control. DEP domain containing 5, GATOR1 subcomplex subunit suppresses mTORC1-driven purine catabolism, thereby protecting CD8⁺ T cells from lipid ROS accumulation and inadvertent ferroptosis (222). Methionine confers protection against ferroptosis through Nrf2 activation, leading to increased expression of GPX4, SLC7A11 and FTH1 (223). Leveraging these mechanistic insights, the bimetallic nanzyme Fe/Cu-HPC@GOx/PEG potentiates antitumor immunity in bladder cancer through the synergistic induction of ferroptosis and cuproptosis (224). In general, targeting the metabolic

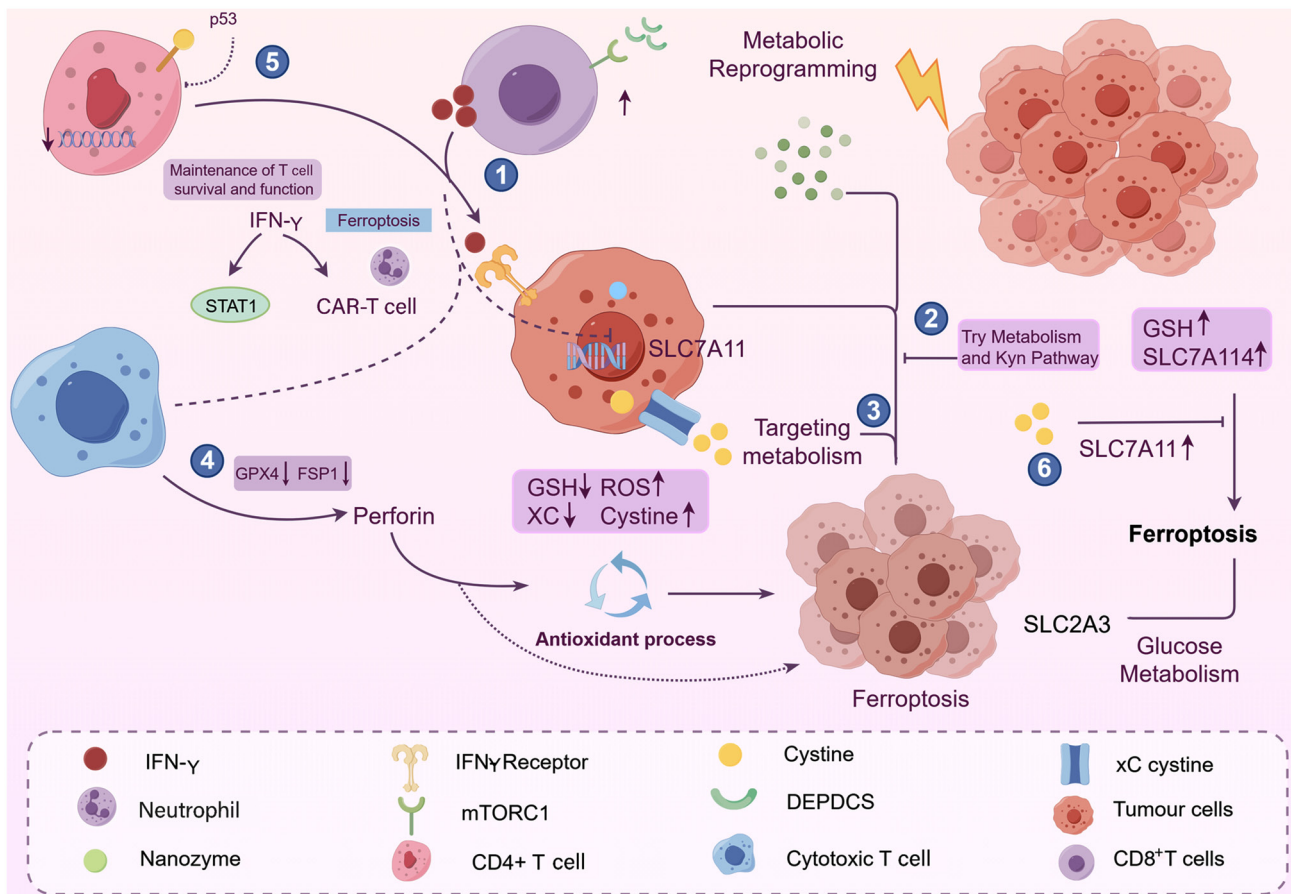


Figure 5. T cells actively remodel the ferroptosis landscape via metabolic reprogramming. On one hand, tumor cells outcompete T cells for cystine through SLC7A11; on the other, CTL-derived IFN- γ downregulates SLC7A11 in tumor cells to trigger ferroptosis. Concurrently, T cells themselves are subject to ferroptotic control through glucose and amino acid metabolism, creating a dynamic equilibrium wherein metabolic competition governs the efficacy of antitumor immunity. The figure consolidates these multifaceted interactions into a cohesive conceptual framework. GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; ROS, reactive oxygen species; GSH, glutathione; SLC7A11, solute carrier family 7 member 11; SLC2A3, solute carrier family 2 member 3; mTORC, mTOR complex; DEPDC5, DEP domain containing 5, GATOR1 subcomplex subunit; CAR-T, chimeric antigen receptor T cell.

reprogramming network of T cells to protect or reshape T cell function while concomitantly inducing ferroptosis in tumor cells represents a key strategy for improving the efficacy of immunotherapy (Fig. 5).

5. Combined therapy targeting ferroptosis and T cells

Existing approaches

Combined application of ferroptosis inducers and immune checkpoint inhibitors (ICIs). PD-L1, encoded by the CD274 gene, is a transmembrane protein that inhibits T cell function by binding to PD-1 on the surface of T cells, thereby mediating tumor immune evasion (225). In various types of cancer, such as melanoma, lung, bladder cancer, breast cancer and prostate cancer, PD-L1 expression is upregulated to evade immune surveillance. ICIs targeting the PD-1/PD-L1 pathway have demonstrated some clinical efficacy (226); however, the limited response rate has prompted researchers to explore combination therapeutic strategies, among which ferroptosis induction has attracted widespread attention as a sensitizing approach.

Numerous studies have demonstrated that ferroptosis induction synergistically potentiates the efficacy of ICIs, with the underlying mechanism entailing regulation at multiple levels (10,227). For example, inhibition of nucleoprotein 1

promotes CD4 and CD8⁺ T cell infiltration and enhances the response to PD-1 blockade (228,229). Heterogeneous nuclear ribonucleoprotein L suppresses ferroptosis by regulating the yin yang 1/PD-L1 axis; its knockdown reduces PD-L1 expression, enhances CD8⁺ T cell-mediated ferroptosis of cancer cells, and synergistically enhances the antitumor effects of anti-PD-1 therapy in castration-resistant prostate cancer (226). Furthermore, inhibition of phosphoglycerate mutase 1 promotes ferroptosis and CD8⁺ T-cell infiltration in hepatocellular carcinoma (HCC) by downregulating lipocalin 2 and PD-L1, producing a synergistic effect with anti-PD-1 therapy (230).

In addition to the aforementioned molecular pathways that directly regulate PD-L1 expression, beyond immune checkpoint blockade, the synergistic potential of ferroptosis extends to adoptive T cell therapies, particularly CAR-T cell therapy, where metabolic regulation of the TME can further enhance therapeutic efficacy. In colorectal cancer models, RSL3-induced ferroptosis increases the frequency of tumor neoantigen-specific IFN- γ ⁺ CD8⁺ T cells, thereby enhancing the efficacy of anti-PD-1 therapy (231). In gastric cancer, simvastatin not only induces ferroptosis but also enhances the therapeutic effect of PD-1 blockade by recruiting CD8⁺ T cells and modulating the TME (232).

It should be emphasized that while ferroptosis induction promotes immune activation, it carries the risk of inducing immunosuppressive feedback, which makes combination blockade strategies particularly essential. For example, GPX4-deficiency-induced ferroptosis can trigger CXCL10-dependent CD8⁺ T cell infiltration but is accompanied by PD-L1 upregulation and high mobility group box 1 (HMGB1)-mediated accumulation of myeloid-derived suppressor cells (MDSCs); combined blockade of PD-1 or HMGB1 can enhance T cell activity and prolong survival (179). Extending this rationale, investigators have leveraged nanomaterials and small-molecule pharmaceuticals to directly modulate the TME: Arsenic trioxide promotes the infiltration of T cells, NK cells and dendritic cells by inducing ferroptosis and necroptosis apoptosis and enhances the secretion of IFN- γ and TNF- α , thereby converting ‘cold’ tumors into ‘hot’ tumors (233). Zero-valent iron nanoparticles promote ferroptosis by inducing ferroptosis and cytokine hydrogen peroxide, downregulate PD-1 and CTLA-4 on CD8⁺ T cells and simultaneously reduce PD-L1 expression on tumor cells, thereby enhancing antitumor immunity (234). Moreover, the combination of ferroptosis induction with biologics represents another promising avenue, the combination of erastin and oncolytic viruses increases dendritic cell activation and tumor-specific CD8⁺ T cell responses, enhancing the efficacy of immunotherapy (235).

Combining CAR-T cell therapy with ferroptosis regulation. Compared with combination therapy with ICIs, the combination of CAR-T cell therapy and ferroptosis regulation represents another key pathway, the core of which lies in leveraging the targeting capability of CAR-T cells and the synergistic killing effect of ferroptosis inducers. CAR-T therapy targets and destroys tumors by recognizing tumor-associated antigens; however, because some of these antigens are also expressed in normal tissues, this approach may trigger severe adverse reactions (236). CAR-T technology has evolved through multiple generations: From the first generation, which contained only an activation signal domain, to the second generation, which introduced costimulatory domains such as CD28 or 4-1BB, and on to the third generation, which integrated multiple costimulatory domains; the fourth generation (TRUCKs) incorporates cytokines such as IL-12 to enhance the immune response in the TME, while the fifth generation integrates more complex signaling pathways, including various immunomodulatory factors, to enhance antitumor activity and overcome immune suppression (237,238).

In terms of metabolic regulation, inactivation of the CD73/adenosine A2A receptor signaling pathway promotes the *de novo* synthesis and consumption of GSH in CD8⁺ T cells, leading to the accumulation of oxidized GSH (GSSG) and mitochondrial lipid peroxidation, thereby enhancing T cell efficacy while inducing ferroptosis (239). Multiple studies have shown that the induction of ferroptosis enhances antitumor immunity with CAR-T therapy (240,241). For example, receptor tyrosine kinase like orphan receptor 1 CAR-T cells promote the production of phosphatidylcholine containing a diacyl PUFA tail by secreting IFN- γ , upregulate ACSL4 expression and enhance lipid peroxidation induced by ferroptosis inducers, thereby synergistically inhibiting the growth of non-small cell lung cancer (240,241). Furthermore,

axitinib reverses CAR-T cell exhaustion by activating the Wnt/ β -catenin signaling pathway, thereby enhancing cytokine secretion and antileukemic activity (242).

In a HCC model, atovaquone enhances IFN- γ release by TCR T cells while simultaneously increasing ROS levels in tumor cells, expanding the labile iron pool and damaging mitochondrial membrane integrity, thereby suppressing tumors and activating the immune response via the ferroptosis mechanism (243). Furthermore, IFN κ can induce immunogenic ferroptosis via the IFNAR/STAT1/ACSL4 signaling pathway; CAR-T cells engineered to express IFN κ demonstrated stronger antitumor effects in both antigen-positive and antigen-negative tumor models, suggesting its potential as a potentiating factor (241).

In summary, combination therapy targeting ferroptosis and T cells represents an innovative direction in the field of anticancer therapy. By specifically regulating ferroptosis-related pathways in tumor cells, this approach can reshape the TME, enhance the immunogenicity of tumor cells and simultaneously improve T cell infiltration and cytotoxic activity. This enhances anticancer efficacy and overcomes immune resistance, offering new, highly effective strategies and promising applications for the treatment of clinically refractory tumors.

Challenges

Tumor heterogeneity: Some tumors are insensitive to ferroptosis induction. Tumor heterogeneity is a key challenge limiting the efficacy of ferroptosis therapy. This heterogeneity manifests at multiple levels, including genetic, phenotypic and microenvironmental, and collectively leads to notable differences in the sensitivity of different tumor cells to ferroptosis inducers (244).

At the mechanistic level, there is heterogeneity in the expression and regulation of key ferroptosis proteins (such as GPX4) across different cell lines, and the extent of involvement of auxiliary death pathways, such as autophagy, also varies (245). Furthermore, specific molecules such as hippocalcin-like protein 1 can influence sensitivity by regulating membrane lipid composition (246), while a range of genetic mutations, such as cyclin dependent kinase inhibitor 2A deletion, mex-3 RNA binding family member A overexpression and SREBF2 or hepatic leukemia factor activation, can promote or inhibit ferroptosis through different downstream pathways (247-250).

In addition to molecular alterations within the tumor cells themselves, regulation of the TME is equally key. For example, tumor-associated fibroblasts can secrete metabolites such as kynurenine to upregulate FTH1 in tumor cells, helping them resist ferroptosis while simultaneously creating an immunosuppressive microenvironment (221). This suggests that resistance to ferroptosis is often intertwined with immune evasion mechanisms, further adds to the complexity of combination therapy.

Epigenetic and non-coding RNA networks are also deeply involved; for instance, the long non-coding RNA ADAMTS9-AS1 can inhibit ferroptosis via the miR-587/SLC7A11 axis (251), while levels of the transcriptional co-activator TAZ positively regulate ferroptosis sensitivity (252,253).

In summary, tumor heterogeneity leads to heterogeneous responses to ferroptosis-induced therapy through complex,

multilevel mechanisms. Future research must thoroughly elucidate the determinants of ferroptosis sensitivity across different tumor types and subpopulations and design combination therapy strategies targeting their specific resistance mechanisms to achieve precise and effective immuno-metabolic synergistic therapy.

Toxicity concerns: Ferroptosis may damage normal tissues. Accompanying the problem of disparate therapeutic outcomes resulting from tumor heterogeneity are the accompanying safety concerns. Ferroptosis inducers generally lack specificity; while killing tumor cells, they may also damage various immune cells (such as CD8⁺ T cells and dendritic cells) and normal tissues and organs, thereby weakening antitumor immunity and causing systemic toxicity (254).

Studies have shown that ferroptosis is involved in pathological damage to multiple organ systems. In the lungs, exposure to nanoparticles or pathological factors can lead to ferroptosis in endothelial and epithelial cells (255-257). In the nervous system, heart, lungs and brain, substances such as arsenic or DOX can also induce neurotoxicity or cardiotoxicity by triggering ferroptosis in neurons or cardiomyocytes (258). Chemotherapy drugs such as cisplatin may similarly induce ferroptosis in ovarian cells, affecting reproductive system function (259).

To decrease toxicity, research is focused on developing induction strategies specific to the TME. For example, a Fe (II)-PW₁₁ catalyst can selectively catalyze lipid peroxidation and deplete antioxidants in the acidic tumor environment, while degrading into less toxic components in normal tissue (260). Furthermore, modulating cellular processes such as autophagy may also serve as a pathway to achieve selective ferroptosis (261).

In summary, the non-selective induction of ferroptosis is one of the key challenges limiting its clinical application. Future efforts should focus on developing specific strategies that can precisely target tumor cells while protecting normal tissues and immune function.

Notable differences in the susceptibility to ferroptosis among different T cell subsets. In addition to tumor heterogeneity and off-target toxicity, CD4⁺ and CD8⁺ T cells and their respective subsets exhibit differential sensitivity to ferroptosis, a phenomenon closely associated with their GPX4 expression levels and unique metabolic characteristics (262). A deeper understanding of these subset-specific differences is key for designing precise combination therapy strategies (182,262). On activation, CD8⁺ effector T cells rely more heavily on FA uptake and lipid synthesis than CD4⁺ T cells, leading to greater accumulation of membrane PUFAs) and increased substrates for lipid peroxidation. Distinct iron homeostasis patterns diversify ferroptosis susceptibility: CD8⁺ effector memory and TEMRA T cells harbor an elevated labile iron pool, rendering them more prone to ferroptotic death. By contrast, CD4⁺ T cells maintain relatively high basal GPX4 levels to resist lipid oxidative stress, while activated terminally differentiated CD8⁺ T cells tend to downregulate GPX4, thereby impairing their core antioxidant defense against ferroptosis. Collectively, these intrinsic discrepancies in lipid metabolism, iron homeostasis and GPX4-dependent antioxidant capacity determine the subset-specific ferroptosis vulnerability of T cells (262).

CD8⁺ cytotoxic T cells are highly sensitive to ferroptosis. CD8⁺ T cells are sensitive to GPX4 inhibitors (such as RSL3), and even low doses can induce ferroptosis in these cells. FAs in the TME can induce ferroptosis in CD8⁺ T cells in a CD36-dependent manner (182). Tumor cells gain a competitive advantage in cystine uptake due to their high expression of SLC7A11, leading to cystine deprivation in CD8⁺ T cells. Cystine deprivation disrupts GSH synthesis in T cells but promotes CD36-mediated lipid uptake through dysregulated cystine/glutamate exchange. This process induces T cell exhaustion and ferroptosis, manifested by reduced memory formation and cytokine secretion capacity, as well as increased PD-1 and TIM-3 expression (8). CD8⁺ T cells rely primarily on glycolysis for energy; their rapid proliferation leads to an increased proportion of PUFAs (such as AA) in membrane phospholipids. At the same time, the NADPH produced by glycolysis is insufficient to effectively neutralize lipid peroxidation damage, making them notably more sensitive to GPX4 inhibitors than Tregs (262).

Tregs are resistant to ferroptosis. Contrasting sharply with the high susceptibility of CD8⁺ T cells, Treg cells are a key population of immunosuppressive cells in the TME, and their resistance to ferroptosis is notably higher than that of CD8⁺ effector T cells. GPX4 is highly expressed in Treg cells and prevents ferroptosis in Treg cells by scavenging lipid peroxides (67). When GPX4 is specifically depleted in Treg cells, TCR/CD28 co-stimulation leads to a massive accumulation of lipid peroxides and ferroptosis in Treg cells. GPX4-deficient Treg cells exhibit impaired immunosuppressive function, accompanied by an increased proportion of Th17 cells and an enhanced antitumor immune response (67). Treg cells produce NADPH via the FAO pathway to maintain a high GSH/GSSG ratio and resist lipid peroxidation (157). Simultaneously, Treg cells highly express GLS, which provides enzymatic support for GPX4 through glutamine metabolism (263). This metabolic adaptation confers Tregs a survival advantage in the nutrient-deprived TME.

Long-term survival of memory T cells depends on resistance to ferroptosis. In addition to the differences between effector T cells and Tregs, memory T cells are key to the body's ability to mount a persistent antitumor immune response, and their long-term survival depends on resistance to ferroptosis. The mTORC2-AKT-GSK3 β signaling axis ensures the long-term survival of virus-specific memory CD4⁺ T cells by maintaining GPX4 expression and preventing lipid peroxidation. Inactivation of mTORC2 impairs the phosphorylation of downstream AKT and GSK3 β , inducing the accumulation of mitochondrial ROS and lipid peroxidation, while simultaneously inhibiting GPX4, a major lipid peroxidation-clearing enzyme. Interference with mTORC2 signaling during the memory phase leads to ferroptosis in memory CD4⁺ T cells (164). Furthermore, defects in the mitochondrial FA synthesis gene *MECR* disrupt mitochondrial function, leading to iron accumulation and increased susceptibility to ferroptosis, thereby impairing the survival and function of TEMs (190).

Th cell subsets exhibit varying degrees of sensitivity to ferroptosis. Within the CD4⁺ T-cell subset, different Th cell subsets exhibit varying sensitivities to ferroptosis due to their unique metabolic characteristics. Th1 cells highly

express ACSL4 and are more sensitive to ferroptosis (185). Downregulation of GPX4 promotes the immune response of Th1 cells and exacerbates inflammatory reactions. Th9 cells rely on PPAR- γ -mediated cystine uptake to prevent lipid peroxidation and ferroptosis-like cell death. PPAR- γ inhibition downregulates SLC7A8 and upregulates genes associated with cystine transport and ferroptosis (220). Th17 cells and Treg cells maintain a balance in the regulation of ferroptosis. Th17 cells upregulate ACSL4 by secreting IL-17A, thereby exacerbating ferroptosis in cardiomyocytes; conversely, GPX4-deficient Treg cells promote antitumor Th17 responses by producing IL-1 β (57). Tfh are protected from ferroptosis by the HMGA1/STAT3/GPX4 signaling axis under specific pathological conditions (241).

Tumor-infiltrating CD8⁺ T cells are even more sensitive to ferroptosis than tumor cells themselves (182,264). An ideal therapeutic strategy should achieve 'selective ferroptosis', inducing ferroptosis in tumor cells and Tregs while protecting CD8⁺ effector and memory T cells from ferroptosis-induced damage.

Future directions

Nano-delivery systems: Targeting the TME and decreasing side effects. The fundamental design principle of nanodelivery systems is to exploit the physicochemical characteristics of nanomaterials for the precise delivery of ferroptosis-inducing agents to tumor tissues, thus achieving enhanced efficacy with attenuated systemic adverse effects.

ROS-generating nanoparticles. The essence of ferroptosis is the accumulation of iron-dependent lipid peroxidation, and ROS are the key factors that initiate the lipid peroxidation chain reaction. Based on this chemical principle, the design strategy for ROS-generating nanoparticles involves utilizing the abundant H₂O₂ in the TME to continuously produce highly reactive $\cdot$ OH via Fenton or Fenton-like reactions, which directly attack the PUFAs in membrane phospholipids, thereby triggering a lipid peroxidation chain reaction (265). To enhance the catalytic efficiency of this process, researchers have combined iron-based nanomaterials with other metal ions (such as copper and cobalt) to construct bimetallic or multimetallic nanosystems, utilizing electron transfer between metal ions to synergistically amplify ROS production (266). For example, the use of surface vacancies in transition metal disulfides to catalyze ROS generation has demonstrated the inherent ability of the material to induce cell death (267); stimulus-responsive 'nanolongan' core-shell structures can reduce Fe³⁺ to Fe²⁺ under near-infrared light irradiation, on-demand triggering the Fenton reaction upon illumination (268); and the construction of bimetallic nano-enzyme systems that simultaneously induce ferroptosis and cuproptosis through Fe/Cu synergistic catalysis (269). Tumor cells have higher baseline ROS levels and weaker antioxidant reserves compared with normal cells (269), which provides a therapeutic window for ROS-generating nanoparticles; however, how to further enhance tumor tissue selectivity remains a core challenge for this strategy.

GSH-depleting nanoparticles. As a complement to approaches that directly produce ROS, GPX4 uses GSH as a cofactor to reduce lipid hydroperoxides to non-toxic lipid alcohols, serving as the last line of defense against ferroptosis.

The design strategy for GSH-depleting nanoparticles aims to precisely disrupt the redox balance in tumor cells, by depleting GSH to inactivate GPX4, while simultaneously generating ROS, thereby shifting the balance between the production and clearance of lipid peroxides toward production, thus overcoming the threshold for ferroptosis initiation (270). To achieve efficient GSH depletion, researchers have devised various chemical mechanisms: Utilizing strongly oxidizing components loaded onto nanocarriers to directly undergo redox reactions with GSH; employing nanoenzymes to catalyze the consumption of GSH while simultaneously generating ROS, notably enhancing the synergistic effect (271) or leveraging high concentrations of GSH within tumor cells to trigger the disintegration of nanocarriers, thereby simultaneously releasing ferroptosis inducers and GSH scavengers (272). These strategies include: i) A nanocatalytic system that generates large amounts of ROS while depleting GSH through a cascade of Fenton and enzymatic reactions (219); ii) a combined intervention scheme utilizing glucose oxidase to catalyze the conversion of glucose into H₂O₂ accompanied by GSH depletion (218); and iii) a liquid nanosystem that achieves the simultaneous release of Fe²⁺ and free radicals in the TME through pH-responsive surface modification (273). The advantage of this strategy lies in its precise exploitation of the natural difference in GSH levels between tumor cells and normal cells; however, caution is warranted regarding potential side effects arising from the fact that immune cells in the TME also rely on GSH for antioxidant defense.

TME-responsive delivery vectors. In contrast to the preceding two categories, which emphasize ROS production or GSH depletion, ideal ferroptosis induction should be confined to the interior of tumor tissue to avoid systemic toxicity. The design strategy for TME-responsive delivery carriers involves utilizing physicochemical signals specific to the TME (such as acidic pH, hypoxia, overexpression of specific enzymes and high ATP concentrations) as 'keys' to trigger drug release or activate ferroptosis pathways only at the tumor site. The core chemical principles include: i) pH-responsive release, exploiting the fact that the extracellular pH of tumor tissue (~6.5-6.8) is lower than that of normal tissue (~7.4) to design nanocarriers that undergo structural disintegration or surface charge reversal under acidic conditions, thereby achieving targeted drug release (274); ii) enzyme-responsive release, utilizing MMPs or cathepsins, which are highly expressed in tumor tissues, to cleave sensitive peptide segments on the surface of nanocarriers, thereby exposing target ligands or releasing the encapsulated drug; iii) ultiresponsive systems, integrating pH, redox and photothermal responses to achieve precise spatiotemporal control over ferroptosis induction (examples include smart catalysts that selectively catalyze lipid peroxidation in an acidic TME but become inactive at normal physiological pH) (260); and iv) supramolecular nanosystems that simultaneously achieve reversal of immunosuppression and synergistic induction of ferroptosis/apoptosis through laser excitation (275). This strategy represents a trend toward precision in the development of nanodelivery systems, with the core objective of transforming ferroptosis from a 'systemic toxic side effect' into 'targeted, precise elimination'.

In summary, while nanodelivery strategies have different focuses, they are not mutually exclusive, ideal nanoplatforms

often integrate multiple mechanisms, such as multimodal systems that simultaneously possess ROS generation, GSH depletion and TME responsiveness. Their common goal is to enhance the enrichment coefficient of ferroptosis inducers at the tumor site and reduce off-target damage to normal tissues, particularly effector T cells, by combining physical targeting (EPR effect) with biological targeting (ligand modification). Future research should continue to optimize the biosafety, degradability and large-scale manufacturing processes of nanomaterials to advance the clinical translation of these strategies.

Metabolic intervention: Modulating T cell lipid metabolism to enhance antitumor effects. Nanodelivery systems tackle the issue of ‘how to transport therapeutic agents to the intended site’, while metabolic intervention addresses ‘how to achieve precise modulation upon arrival’. These two strategies are mutually reinforcing and collectively define the future trajectory of ferroptosis combination therapy. Following T cell activation, metabolic patterns undergo notable reprogramming, with lipid and cholesterol synthesis upregulated to support proliferation and effector functions (276). Lipid metabolic pathways influence the susceptibility of T and tumor cells to ferroptosis by regulating membrane lipid composition and antioxidant defenses the higher the content of PUFAs in the membrane, the more abundant the substrates for lipid peroxidation and the more readily ferroptosis occurs (240,277).

Liver X receptor (LXR) pathway. LXR is a key regulator of cholesterol metabolism. In T cells, LXR regulates SREBP-1c-mediated FA synthesis, thereby influencing the proportion of PUFAs in membrane phospholipids (278); moderate inhibition of LXR signaling alters T cell membrane lipid composition, reducing the efficiency of CD36-mediated lipid peroxide uptake, thereby protecting T cells from lipid peroxide-induced ferroptosis in the TME (34). In tumor cells, the combined activation of LXR α and inhibition of Raf-1 proto-oncogene, serine/threonine kinase can induce lethal lipotoxicity in HCC cells; binding of LXR ligands to LXR β activates pannexin 1 channels, releases ATP and mediates cell death in colorectal cancer cells (279). From this, it can be seen that the LXR pathway exhibits cell-type-specific bidirectional regulation, in tumor cells, LXR activation enhances sensitivity to ferroptosis, whereas moderate inhibition of LXR in T cells may produce a protective effect.

PPAR pathway. PPAR γ deficiency impairs the accumulation and function of Tregs (280). PPAR γ activates GPX4 transcription by directly binding to its promoter region, constituting a key defense against ferroptosis (281). In Tregs, the high expression of GPX4 mediated by PPAR γ confers resistance to ferroptosis; by contrast, GPX4-deficient Tregs undergo ferroptosis, which impairs their immunosuppressive function and enhances antitumor immunity (67). In tumor cells, RAB10 activates PPAR γ and its downstream target gene diacylglycerol O-acyltransferase 1 via the PI3K/AKT pathway, thereby inhibiting ferroptosis and promoting tumor survival (282); pharmacological inhibition of PPAR γ rescinds its transcriptional activation of GPX4, reversing immunosuppression and enhancing CD8 $^{+}$ T cell infiltration (283). Differentiated interventions are required for the PPAR pathway, inhibiting PPAR γ in tumor cells to weaken resistance to ferroptosis and inducing GPX4 deficiency in Tregs to reverse immunosuppression.

FAO. Within the TME, there are marked differences in FAO dependence among different T cell subsets. Treg cells are highly dependent on FAO to maintain their suppressive function (284). NADPH produced through FAO supports GSH regeneration and GPX4 function, enhancing the cells’ ability to clear lipid peroxides. CD8 $^{+}$ effector T cells are rich in PUFA-PLs and can undergo ferroptosis in the TME by taking up oxidized lipids via CD36 (34); Tregs are more resistant to ferroptosis due to their high FAO dependence and high GPX4 expression (67). The long-term survival of memory T cells also depends on FAO and efficient mitochondrial respiration. Therefore, selectively inhibiting FAO in Tregs [such as using carnitine palmitoyltransferase 1A (CPT1a) inhibitors] can overcome Treg resistance to ferroptosis (284), thereby enhancing antitumor immunity while attenuating immunosuppression; conversely, for CD8 $^{+}$ effector T cells and memory T cells, protection against TME-induced ferroptosis requires supplementation with MUFA or enhancement of adaptive FAO metabolism (182).

In summary, differentiated metabolic interventions targeting the LXR, PPAR and FAO pathways are based on the core logic of promoting ferroptosis in tumor cells (by activating LXR and inhibiting PPAR γ), inducing ferroptosis in Tregs to reverse immunosuppression (via GPX4 deficiency and CPT1a inhibition) and protecting CD8 $^{+}$ effector T cells and memory T cells from ferroptosis (by modulating LXR signaling, supplementing MUFAs and maintaining adaptive FAO metabolism) (34,284). Future research should develop selective intervention strategies based on the metabolic characteristics specific to T cell subsets to achieve highly effective and low-toxicity immunometabolic synergistic therapy.

Precision combination therapeutic strategies based on molecular mechanisms. Based on the molecular mechanisms of ferroptosis, T cell crosstalk as aforementioned, including the GPX4/SLC7A11 antioxidant defense axis, ACSL4-mediated lipid peroxidation, the IFN- γ /STAT1/IRF1 axis-mediated regulation of System Xc $^{-}$, CD36-mediated ferroptosis in T cells, the bidirectional regulation of MAPK signaling and the differential metabolic features of distinct T cell subsets, future research can be pursued along the following concrete and actionable directions.

Differentiated protection and elimination strategies based on the ferroptosis sensitivity of T cell subsets. Targeting the mechanistic difference that CD8 $^{+}$ effector T cells are sensitive to GPX4 inhibitors while Treg cells exhibit strong resistance (262), subset-selective intervention strategies can be designed accordingly: For CD8 $^{+}$ CTLs, oncolytic viruses loaded with GPX4 can be used to reduce their CD36 expression and alleviate lipid peroxidation, thereby restoring their antitumor function (183). Alternatively, supplementation with MUFAs can lower membrane PUFA content to protect them from ferroptosis (182); for Tregs, GPX4 inhibitors (such as RSL3) combined with nanodelivery systems can be employed to selectively deplete Tregs within the TME, thereby reversing immunosuppression (67). The long-term survival of memory T cells depends on the antioxidant defense maintained by the mTORC2-GPX4 axis (164); therefore, the use of high-dose ferroptosis inducers during the memory T cell enrichment phase should be avoided in therapeutic regimens.

Sequential combination therapy based on the IFN- γ /STAT1/ACSL4 pathway. IFN- γ upregulates ACSL4 expression through STAT1 and increases the PUFA content in tumor cell membranes, thereby enhancing ferroptosis sensitivity (87). IFN- γ can upregulate AGPAT3 by activating the transcription factor IRF1, driving lipid remodeling and accumulation of polyunsaturated ether phospholipids, which notably increases the sensitivity of tumor cells to ferroptosis (285). In addition, pre-activation of T cell immunity enhances IFN- γ production, which works with AA to trigger ACSL4-mediated ferroptosis in tumor cells. Based on this mechanism, oncolytic viruses or genetically engineered outer membrane vesicles can be used to pre-activate T cell immunity and induce IFN- γ release in the TME (286), thereby inducing tumor cells to elevate their ACSL4 levels and membrane PUFA content, followed by administration of ferroptosis inducers to achieve synergistic killing. This hypothesis has been preliminarily validated by CAR-T cells engineered to express IFN- κ (241).

Metabolic intervention based on tumor SLC7A11-mediated and T cell cystine competition. Tumor cells overexpressing SLC7A11 outcompete T cells for cystine, leading to impaired GSH synthesis and increased CD36-mediated lipid uptake in T cells, which results in ferroptosis and functional exhaustion (8). In osteosarcoma research, the SLC7A11 inhibitor IKE induces tumor cell ferroptosis through the p53/xCT/GPX4 pathway; concurrently, damage-associated molecular patterns (DAMPs) released from ferroptotic cells activate the NLRP3 pathway, promoting M1-type tumor-associated macrophages (TAMs) polarization and CTL infiltration, thereby establishing a ferroptosis-immunity positive feedback loop (287). In pancreatic cancer, to counter yes-associated protein (YAP)-driven SLC7A11 overexpression, copper-verteporfin coordination nanoparticles inhibit YAP activity to downregulate SLC7A11 transcription and synergize with IKE to block the System Xc⁻-GSH-GPX4 defense axis, effectively reversing ferroptosis resistance (288). Future efforts could focus on developing tumor-targeted nanodelivery systems for SLC7A11 inhibitors, which would inhibit cystine uptake by tumor cells while avoiding off-target suppression of T cells (88).

T cell protection strategies based on the CD36-oxidized lipid pathway. Oxidized lipids in the TME are taken up by CD8⁺ T cells via the CD36 receptor, directly inducing lipid peroxidation and ferroptosis in these cells (34). Oncolytic viruses loaded with GPX4 can downregulate CD36 expression and alleviate lipid peroxidation, thereby restoring the anti-tumor function of CD8⁺ T cells both *in vitro* and *in vivo* (183). In addition, CD36 blockade can protect CD4⁺ T cells from palmitic acid-induced ferroptosis and dysfunction (289). Future efforts could focus on developing CD36 neutralizing antibodies combined with GPX4 overexpression strategies or employing CRISPR-Cas9 screening to identify key transcriptional regulators of CD36 expression (214), thereby providing novel targets for protecting T cells from ferroptosis.

Bidirectional regulation strategy based on branch-specific differences of the MAPK pathway. The JNK/p38 pathway promotes ferroptosis (by upregulating TFR1 and enhancing ferritinophagy) (199), whereas the ERK pathway can inhibit ferroptosis under certain conditions. p38 MAPK activation promotes ferroptosis by downregulating Nrf2, while the ERK/Nrf2 axis exerts a protective role by upregulating GPX4

and SOD (290,291). Future efforts could explore combination regimens of JNK/p38 agonists and ERK inhibitors to synergistically promote ferroptosis in tumor cells, while leveraging the enhancing effect of ERK inhibitors on T cell function (208) to preserve antitumor immunity. Attention should be paid to the differential activity of MAPK branches across distinct T cell subsets to achieve cell-type-specific regulation.

Personalized therapeutic strategies based on TME metabolic features. Metabolic features such as high lactate in the TME profoundly influence ferroptosis sensitivity (92). Recent studies have shown that stimulator of interferon response CGAMP interactor 1 (STING)-thymocyte selection-associated high mobility group box (TOX)-HO-1-mediated ferroptosis in tumor-infiltrating CD8⁺ T cells is triggered by lactate as a key microenvironmental driver (292). This finding provides precise targets for personalized therapy: LDH inhibitors can be combined for high-lactate TME to relieve lactate-mediated inhibition of ACSL4 (61); HIF-1 α inhibitors can be combined for hypoxic TME to relieve its upregulation of GPX4 (52); and iron chelators can be combined for high-iron TME to avoid T cell damage caused by excessive Fenton reaction activation (54). Of note, the selective GPX4 degrader N6F11 can specifically eliminate GPX4 protein in tumor cells without affecting T cells, DCs or NK cells, demonstrating a feasible strategy for differential ferroptosis induction within the TME (293).

Regulatory role of the TME in the efficacy of immunotherapy
Precision combination therapeutic strategies based on molecular mechanisms. Based on the molecular mechanisms of ferroptosis-T cell crosstalk aforementioned including the GPX4/SLC7A11 antioxidant defense axis, ACSL4-mediated lipid peroxidation, the IFN- γ /STAT1/IRF1 axis-mediated regulation of System Xc⁻, CD36-mediated ferroptosis in T cells, the bidirectional regulation of MAPK signaling and the differential metabolic features of distinct T cell subsets, future research can be pursued along concrete and actionable directions.

Dual role of immune cells in the TME. Immune cell populations in the TME possess both antitumor and pro-tumor potential, and their functional orientation profoundly influences the efficacy of immunotherapy (294).

TAMs are among the most abundant immune cells in the TME. In esophageal squamous cell carcinoma, single-cell RNA sequencing analysis has revealed marked heterogeneity within the TME (295). Macrophages impair the immune response and promote tumor progression through efferocytosis, the process of phagocytosing apoptotic tumor cells (296). In this process, TP63 transcriptionally activates RAC2 to enhance macrophage efferocytosis, thereby driving M2 macrophage polarization and immune suppression (297). From the perspective of ferroptosis, immunotherapy combination therapy, there is a potential interface between TAM efferocytosis and ferroptosis. DAMPs released by ferroptotic tumor cells can induce DC maturation and cross-priming of CD8⁺ T cells (298). However, if ferroptotic cells are phagocytosed by TAMs via efferocytosis, immunogenic signals may be masked by inhibitory phagocytic pathways. In addition, nanoplateforms targeting M2-like TAMs can remodel the immunosuppressive microenvironment by inducing ferroptosis in TAMs (192), suggesting that combined blockade of TAM efferocytosis and induction of ferroptosis may synergistically enhance antitumor immunity.

In glioblastoma, tripartite motif containing (TRIM) 29 drives tumor progression by degrading neurofilament light chain and activating the PI3K/AKT pathway (299). From the perspective of ferroptosis regulation, sustained activation of the PI3K/AKT pathway can enhance ferroptosis resistance by activating antioxidant pathways such as Nrf2 (300), suggesting that tumors with high TRIM29 expression may be concurrently resistant to ferroptosis inducers, and that the combination of PI3K/AKT inhibitors with ferroptosis inducers holds synergistic potential.

Regulatory roles of cytokines and tumor-associated factors. Cytokines and chemokines derived from CAFs can promote tumor growth and metastasis by regulating tumor immune evasion. Notably, *in situ* CAF engineering, converting immunosuppressive CAF subtypes into an immune-activating state, is a promising strategy for reshaping the TME and enhancing immunotherapy for triple-negative breast cancer (301).

From the perspective of ferroptosis regulation, CAFs can upregulate GPX4 and SLC7A11 expression in tumor cells by secreting cytokines such as TGF- β and IL-6, thereby enhancing their ferroptosis resistance. In addition, CAFs can modulate ferroptosis sensitivity by altering the lipid composition of the TME through the secretion of lipid metabolites (such as FAs), which affects the PUFA content in tumor cell membranes (302). Therefore, while reversing immunosuppression, CAF engineering may also eliminate the ferroptosis-protective effects on tumor cells by altering the secretory profile of CAFs, thereby creating a more favorable therapeutic window for ferroptosis inducers.

In pancreatic cancer, special AT-rich sequence-binding protein 2 (SATB2) is expressed at markedly higher levels in tumor tissues than in normal tissues. Its overexpression inhibits T lymphocyte cytotoxicity, promotes pancreatic cancer cell migration and increases the proportion of S-phase cells. Transcriptomic analysis revealed a total of 1,997 differentially expressed genes following SATB2 overexpression and knockout; these genes are involved in immune-related processes such as B cell chemotaxis and T cell differentiation. SATB2 has been identified as a potential target for improving immunotherapy in pancreatic cancer (303).

SATB2-regulated genes involved in T cell differentiation may indirectly influence the metabolic features and GPX4 expression levels of T cell subsets, thereby altering their sensitivity to ferroptosis. Targeting SATB2 may not only enhance the antitumor function of T cells but also reshape the T cell differentiation landscape to modulate the proportions of distinct T cell subsets within the TME, thereby creating a favorable immune cell composition for differentiated intervention with ferroptosis inducers (303).

Immune regulation by intrinsic tumor drivers. Various molecules expressed by tumor cells influence treatment response by directly or indirectly regulating the immune microenvironment. In HCC, WD repeat domain 54 (WDR54) is overexpressed in liver cancer tissues and is positively associated with unfavorable patient prognosis. WDR54 plays a key role in promoting the malignant proliferation and metastasis of HCC by enhancing the NF- κ B signaling pathway. Sustained activation of the NF- κ B pathway can transcriptionally upregulate a series of antioxidant enzyme genes, including superoxide dismutase 2 and GPX4, thereby enhancing the capacity of tumor

cells to clear lipid peroxides and conferring marked resistance to ferroptosis (304). In addition, enhancer of zeste homolog 2 (EZH2)-mediated epigenetic regulation has been identified as a key node linking epigenetic modification, tumorigenesis, immune control and ferroptosis, suggesting that in tumors with WDR54/NF- κ B axis activation, the combination of epigenetic inhibitors (such as EZH2 inhibitors) with ferroptosis inducers may synergistically relieve ferroptosis resistance and enhance antitumor immunity (305). The STING-TOX axis induces ferroptosis in tumor-infiltrating CD8⁺ T cells by suppressing HO-1 expression, thereby mediating resistance to immunotherapy (292), further indicating that intrinsic tumor drivers can influence immunotherapy outcomes by directly modulating the ferroptosis sensitivity of T cells.

Role of the JAK/STAT pathway. The JAK/STAT signaling pathway shapes an immunosuppressive TME by driving PD-L1 upregulation, recruiting MDSCs and inducing M2 polarization of TAMs and promoting T cell exhaustion (306). The JAK/STAT pathway and ferroptosis share clear molecular crosstalk: STAT3 can directly transcriptionally regulate the expression of GPX4 and SLC7A11, enhancing ferroptosis resistance in tumor cells (57); whereas IFN- γ upregulates IRF1 through STAT1 phosphorylation, which in turn directly suppresses the transcription of SLC7A11 and SLC3A2, limiting cystine uptake and inducing ferroptosis in tumor cells (88). In animal models, combined treatment with IFN- γ and the ferroptosis inducer RSL3 eradicated heterogeneous tumors composed of antigen-positive melanoma cells and their antigen-loss variants (88), validating the bridging role of the JAK/STAT pathway in ferroptosis-immunotherapy combination strategies (307). Therefore, strategies combining JAK inhibitors, PD-1 blockade and ferroptosis inducers are expected to achieve more potent antitumor immune responses through multi-level synergy.

In summary, the present review outlined the key metabolic regulatory mechanisms of ferroptosis in the TME. Lipid, iron and amino acid metabolism collectively determine cellular sensitivity to ferroptosis. Affected by their intrinsic metabolic phenotypes, distinct T cell subsets exhibit substantial differences in responses to ferroptosis. Ferroptosis and T cell immunity form a complex bidirectional regulatory loop: on the one hand, ferroptosis can activate anti-tumor T cell responses via immunogenic cell death; on the other hand, it can directly trigger ferroptosis in tumor-infiltrating T cells and aggravate T cell exhaustion. Effector molecules secreted by activated T cells modulate the susceptibility of tumor cells to ferroptosis, and nutrient competition between tumor cells and immune cells further participates in this regulatory process. Although strategies combining ferroptosis modulation with immune checkpoint blockade and CAR-T cells have demonstrated anti-tumor potential in preclinical models, tumor heterogeneity, off-target toxicity, and heterogeneous responses of T cell subsets remain major obstacles to clinical translation. The TME regulates immunotherapy efficacy at multiple levels. An ideal intervention strategy should consider the complexity of the TME, inducing ferroptosis in tumor cells while protecting effector T cells. Nano-delivery systems and differentiated metabolic interventions targeting T cell subsets may facilitate the clinical translation of high-efficiency, low-toxicity immuno-metabolic anti-tumor therapy.

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Availability of data and materials

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Authors' contributions

ST, HL, QiaL and WX conceived the study and wrote and edited the manuscript. YL and CL wrote and edited the manuscript. WL, QiaL and HS wrote the manuscript. RL and ZW were responsible for reviewing and editing the manuscript. LS edited the manuscript. QiyL and HL were responsible for critical revision of the manuscript, and final approval of the version to be published. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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