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Review Article

The ferroptosis-tumor microenvironment nexus: bidirectional regulation in cancer pathogenesis and therapeutic opportunities

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Abstract: This review systematically dissects the mechanisms of the bidirectional ferroptosis-tumor microenvironment (TME) regulation. The TME modulates ferroptosis susceptibility in immune cells through metabolic reprogramming and transcriptional regulation, while immune cells induce tumor cells ferroptosis via cytokine signaling and redox disruption. Intercellular crosstalk among immune and stromal cells further shapes ferroptotic responses through multidimensional mechanisms, forming a complex regulatory network. Paradoxically, ferroptosis exerts dual effects on the TME: it enhances antitumor immunity via damage-associated molecular patterns (DAMPs)-mediated dendritic cells (DCs) activation and T cell priming, yet promotes immune evasion through immunosuppressive niche formation and checkpoint upregulation. Current therapeutic strategies focus on glutathione peroxidase 4 (GPX4) inhibitors, synergistic combinations with immune checkpoint inhibitor (ICI), and nanotechnology-enabled targeted delivery systems. Persistent challenges include tumor heterogeneity, off-target toxicity, and deficiency in pharmacokinetics. Future research should prioritize two strategies: ferroptosis biomarker-guided patient stratification and TME-responsive smart drug delivery systems, optimizing personalized therapies to improve survival outcomes. By elucidating the ferroptosis-TME nexus, this review provides novel insights for advancing precision oncology and immunotherapeutic paradigms.

Keywords: Ferroptosis, lipid peroxidation, TME, $CD8^+$ T cell, immunotherapy, cancer therapy

Introduction

In recent years, ferroptosis, a novel form of cell death identified by Dixon, Scott J, et al. in 2012, has garnered increasing attention [1, 2]. Unlike apoptosis, autophagy, necrosis, and pyroptosis, ferroptosis is characterized by iron-dependent lipid peroxidation accumulation, with prominent features of subsequent rupture of the cell membrane due to damage and cell death [1-3]. Since its initial identification, significant advancements have been made in understanding ferroptosis, particularly within the realm of oncology [4-6]. Accumulating evidence indicates that ferroptosis plays a pivotal role in tumor progression and treatment resistance [4-6]. The mechanisms underlying ferroptosis predominantly involve the inhibition of GPX4, iron accumulation, and the buildup of lipid peroxides (LPO) [2, 3, 7]. These mechanisms underscore the pivotal role of ferroptosis in the pathophysiological processes of various diseases, including cancer, neurological disorders, and ischemia-reperfusion injuries [3, 6-8]. In the context of cancer, ferroptosis is regarded as a potential mechanism for inhibiting tumor growth. Research has demonstrated that ferroptosis can impede tumor progression by inducing oxidative stress and lipid peroxidation within tumor cells [4-6]. Interestingly, the tumorigenesis and progression, as well as ferroptosis-mediated regulation of tumor cells, are intrinsically linked to the TME [5, 6, 9]. The TME, comprising cancer cells, non-cancerous cells (such as immune cells and stromal cells), extracellular matrix, metabolites, and cytokines, constitutes a complex ecosystem that underpins the growth, proliferation, and metasta-

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sis of tumor cells [9]. Notably, the TME is crucial in shaping cancer cells' susceptibility to ferroptosis [5, 9, 10]. Furthermore, the interplay between ferroptosis and the TME has increasingly emerged as a focal point of research [5, 9, 10]. Elements within the TME, including immune cells, metabolites, and signaling molecules, can profoundly impact the induction of ferroptosis and the subsequent fate of tumor cells [5, 9, 10].

This review aims to explore the bidirectional regulation between ferroptosis and the TME, uncover the molecular mechanisms involved, and discuss its implications for cancer therapy. By understanding the complex relationship between ferroptosis and the TME, we aim to provide new perspectives and approaches for future tumor treatment strategies [5, 9, 10] (**Figure 1**).

Molecular mechanism of ferroptosis

Distinct from classical cell death modalities, ferroptosis exhibits unique morphological characteristics including cell volume shrinkage, mitochondrial cristae reduction, and increased membrane density [11]. These distinctive morphological features stem from ferroptosis-specific molecular mechanisms. Current evidence indicates that ferroptosis regulation involves a complex network of factors and signaling pathways, with well-established key components including iron overload, lipid peroxidation, and the GPX4-mediated antioxidant defense system [12]. Consequently, the regulatory pathways of ferroptosis have emerged as potential therapeutic targets [13]. Elucidating the mechanisms and regulatory networks underlying ferroptosis may provide novel therapeutic strategies for related diseases.

Iron homeostasis dysregulation

Disrupted iron metabolism is a key driver of ferroptosis [14, 15]. In this process, cells take up iron primarily through transferrin receptor 1 (TfR1). Once inside the cell, iron is stored within ferritin. An imbalance in iron levels can trigger ferritinophagy-an autophagic process mediated by nuclear receptor coactivator 4 (NCOA4) - which breaks down ferritin and releases free Fe^{2+} [16]. This excess iron catalyzes the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH + OH^-$), generating highly reactive hydroxyl radicals that attack and peroxidize polyunsaturated fatty acids (PUFAs) in cellular membranes. The resulting LPO accumulate, leading to membrane damage and ferroptotic cell death [16, 17].

The cystine/glutamate antiporter system (System Xc^-)-glutathione (GSH)-GPX4 axis: core antioxidative machinery

The System Xc^- transporter is essential for maintaining cellular redox balance. This complex, formed by solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2) subunits, imports extracellular cystine while exporting intracellular glutamate [18]. Inside the cell, cystine is rapidly converted to cysteine, the rate-limiting precursor for synthesizing GSH [18, 19]. As a major cellular antioxidant, GSH serves as a crucial cofactor for the enzyme GPX4. GPX4 then utilizes GSH to reduce toxic lipid hydroperoxides into harmless lipid alcohols, thereby halting the lipid peroxidation chain reactions that drive ferroptosis and preserving membrane integrity [11]. Consequently, inhibiting System Xc^- (e.g., with erastin) depletes GSH, inactivates GPX4, and triggers the lethal lipid peroxidation characteristic of ferroptosis [18].

The activity of this axis is tightly regulated. The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) enhances ferroptosis resistance by upregulating the expression of both SLC7A11 and GPX4 [20, 21]. At the protein level, the deubiquitinase OTUB1 stabilizes SLC7A11, preventing its degradation and further promoting cell survival [22]. Within the TME, cancer cells often exploit these mechanisms, overexpressing System Xc^- components to bolster their antioxidant defenses and resist therapy [22]. The critical role of this pathway presents clear therapeutic opportunities. Targeting this axis through System Xc^- inhibitors (e.g., erastin) or direct GPX4 inhibitors (e.g., RSL3), often in combination with metabolic interventions, represents a prominent strategy to induce ferroptosis in cancer cells [12].

Lipid peroxidation

The execution of ferroptosis is marked by the iron-dependent accumulation of LPO, which arises from the oxidation of PUFAs within membrane phospholipids (PLs) [23, 24]. This peroxidation cascade is catalyzed by enzymes such

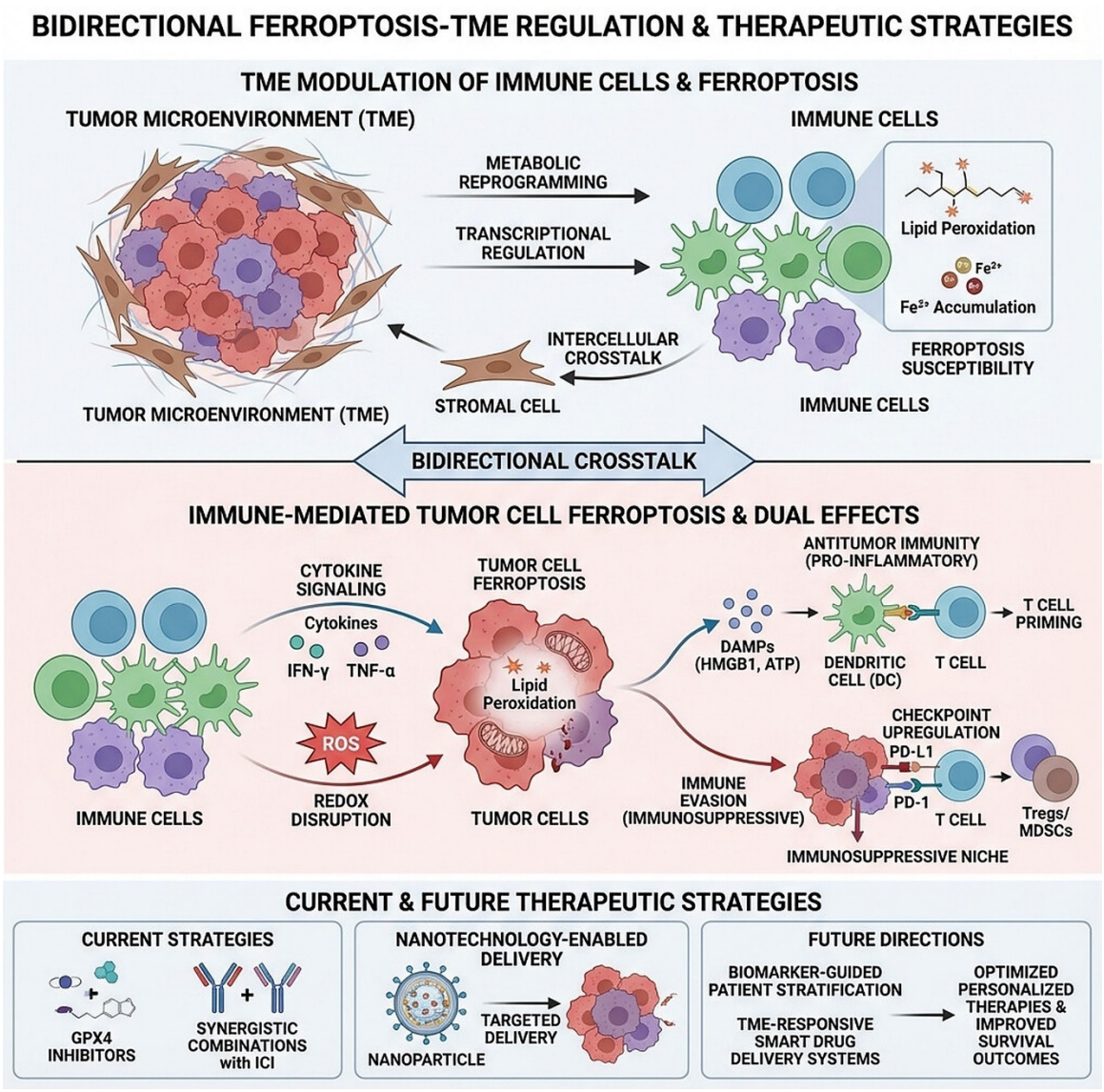

Figure 1. Visual summaries.

as lipoxygenases (LOXs), which primarily target phosphatidylethanolamine (PE)-bound PUFAs [25]. A key regulator of this process is acyl-CoA synthetase long-chain family member 4 (ACSL4). ACSL4 primes cells for ferroptosis by esterifying free PUFAs into membrane PLs, thereby enriching the membranes with substrates susceptible to peroxidation [26-28]. This function is enhanced by the PKCβII-mediated phosphorylation of ACSL4 [29]. By supplying PUFAs for oxidation, ACSL4 cooperates with LOXs to generate lethal oxidized PL derivatives, such as oxidized PE, which propagate ferroptotic signaling [30, 31]. Consequently, the cellular level of ACSL4 is a critical determinant of ferroptosis sensitivity, and its inhibition has been shown to attenuate ferroptotic damage in disease models, highlighting its therapeutic relevance [31, 32] (**Figure 2**).

Regulation of ferroptosis by the TME

TME, comprising blood vessels, immune cells, fibroblasts, signaling molecules, and extracellular matrix, plays crucial roles in tumor growth, progression, and metastasis. Beyond providing nutritional and oxygen support, the TME dynamically interacts with tumor cells to regulate their proliferation, apoptosis, and migratory capacities [33]. This microenvironment modulates ferroptosis through dual mechanisms: pro-ferroptotic effects driven by oxidative stress

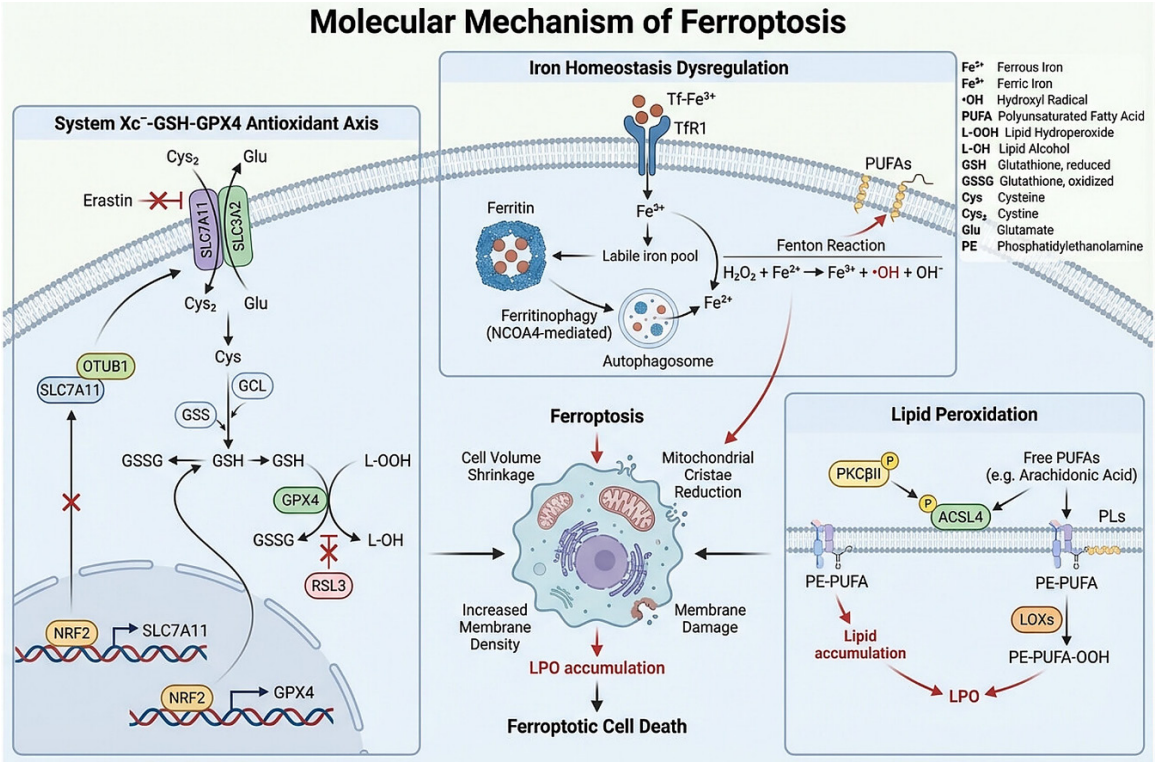

Figure 2. Core molecular mechanisms and regulatory network of ferroptosis. Ferroptosis is driven by three interconnected pathways: (1) Dysregulation of the System Xc^--GSH-GPX4 axis: The System Xc^- imports cystine for GSH synthesis, which is essential for GPX4-mediated reduction of LPO. Pharmacological inhibitors such as Erastin block System Xc^-, depleting GSH and inactivating GPX4, while RSL3 directly targets GPX4's selenocysteine residue to suppress its enzymatic activity. (2) Iron overload: NCOA4-mediated ferritinophagy releases labile Fe^{2+}, which fuels Fenton reactions to generate hydroxyl radicals (OH), exacerbating lipid peroxidation. (3) Lipid peroxidation cascade: ACSL4 esterifies PUFAs into membrane PLs, providing substrates for LOXs to generate lipid hydroperoxides (L-OOH). Liproxstatin-1 inhibits lipid peroxidation by targeting 15-LOX. The transcription factor NRF2 counteracts ferroptosis by upregulating antioxidant genes (e.g., GPX4).

and iron metabolism dysregulation, and anti-ferroptotic effects mediated through antioxidants and iron chelators [34]. Immune components and cytokines within the TME further influence ferroptosis by altering iron homeostasis and oxidative stress levels [35]. These regulatory mechanisms highlight the TME's potential as a therapeutic target for modulating ferroptosis in cancer treatment [34]. Within the TME, immune cell subsets constitute the most dynamic regulators of ferroptotic cell death [35].

Immune cell regulation of ferroptosis: mechanisms and implications

$CD8^+$ T cells: a dual role in regulating and undergoing ferroptosis

$CD8^+$ T cells are central executors of antitumor immunity and key modulators of ferroptosis within the TME. Their influence is dualistic: they can induce ferroptosis in tumor cells but are also susceptible to it themselves, creating a complex interplay that shapes immunotherapy outcomes [36].

$CD8^+$ T cell-induced tumor ferroptosis: A primary mechanism by which $CD8^+$ T cells kill tumor cells is through the secretion of interferon-gamma (IFN-γ). Upon recognizing a tumor cell, activated $CD8^+$ T cells release IFN-γ, which binds to receptors on the tumor cell surface. This triggers the JAK-STAT signaling pathway, leading to the transcriptional suppression of SLC7A11 [26]. The downregulation of SLC7A11 depletes intracellular cysteine, impairing the synthesis of the antioxidant GSH. GSH deficiency, in turn, inactivates the enzyme GPX4, resulting in the lethal accumulation of LPO and ferroptotic cell death [37]. This process is

amplified by ICIs (e.g., anti-PD-1/PD-L1), which reinvigorate exhausted T cells, enhancing their production of IFN-γ and thus strengthening the ferroptotic signal [26, 36]. Furthermore, a self-reinforcing cycle of immunity is established: dying ferroptotic tumor cells release DAMPs, which activate DCs to prime more $CD8^+$ T cells, sustaining the anti-tumor response [38].

Ferroptosis susceptibility of $CD8^+$ T cells: Paradoxically, $CD8^+$ T cells within the TME can also fall victim to ferroptosis, which dampens their anti-tumor function. In lipid-rich environments, $CD8^+$ T cells overexpress the scavenger receptor CD36, leading to excessive uptake of oxidized lipids. This promotes intracellular lipid peroxidation and activates stress pathways that suppress T cell effector functions [39, 40]. Compounding this, tumor cells can outcompete T cells for cystine via their own SLC7A11 transporters, creating a cystine-depleted microenvironment that starves T cells of the precursors needed for GSH synthesis, thereby inducing their ferroptosis [41]. This vulnerability presents a therapeutic opportunity; protecting $CD8^+$ T cells from ferroptosis may enhance the efficacy of cancer immunotherapies.

Context-dependent role of TNF-α: The cytokine TNF-α, also secreted by $CD8^+$ T cells, exerts a context-dependent effect on ferroptosis. Short-term exposure can promote cell survival by activating the nuclear factor-κB (NF-κB) pathway and enhancing antioxidant defenses [42]. However, chronic TNF-α signaling drives ferroptosis by increasing reactive oxygen species (ROS) production through NADPH oxidases and mitochondrial dysfunction, and by disrupting iron metabolism to promote Fenton reactions [42, 43].

Crosstalk with other immune cells: The regulation of ferroptosis is further fine-tuned by crosstalk between $CD8^+$ T cells and other immune components. For instance, IL-1β from macrophages and IL-17 from Tc17 $CD8^+$ T cell subsets can exacerbate oxidative stress and promote a pro-ferroptotic environment [44]. Conversely, IL-21 signaling can sensitize tumor cells to ferroptosis by modulating lipid metabolism and suppressing SLC7A11 [45, 46].

In summary, $CD8^+$ T cells sit at the crossroads of ferroptosis and antitumor immunity, capable of both initiating and falling prey to this form of cell death. A detailed understanding of these bidirectional regulatory mechanisms is crucial for developing strategies that maximize their tumor-killing potential while preserving their function in the harsh TME (**Figure 3**).

The dual regulatory effects of $CD4^+$ T cell on ferroptosis

$CD4^+$ T cell exhibit dual regulatory effects on ferroptosis through cytokine-mediated mechanisms. Mechanistically, these lymphocytes can indirectly promote ferroptosis via secretion of IFN-γ, which induces metabolic reprogramming in tumor cells characterized by enhanced lipid peroxidation [26]. Notably, $CD4^+$ T cell-derived helper signals are indispensable for optimizing $CD8^+$ T cell-mediated antitumor immunity. Emerging evidence suggests this helper signaling pathway may potentiate antitumor immune responses by augmenting ferroptosis [6]. The immunomodulatory role of $CD4^+$ T cell in ferroptosis regulation presents a paradoxical nature. While promoting ferroptosis could enhance tumor elimination through amplified immunogenic cell death, the concomitant release of immunosuppressive mediators during this process might paradoxically dampen antitumor immunity. This dual functionality underscores the necessity for comprehensive investigation into $CD4^+$ T cell-ferroptosis crosstalk [47]. Future research should prioritize deciphering the dynamic balance between pro-ferroptotic immunostimulation and ferroptosis-associated immunosuppression, which may unveil novel combinatorial strategies for cancer immunotherapy. The antitumor effects of $CD8^+$ T cell are counterbalanced by immunosuppressive cellular components.

Immune-stromal crosstalk modulates ferroptotic vulnerability in the TME

Treg cells employ JAK2/STAT3 signaling to upregulate SLC7A11, conferring ferroptosis resistance while secreting IL-10/TGF-β to inhibit cytotoxic $CD8^+$ T cell function [48]. M1-polarized macrophages induce tumor ferroptosis through TNF-α/ROS overproduction and IFN-γ-driven SLC7A11 suppression, with DAMPs from dying cells reinforcing M1 activation via TLR4/NF-κB [49, 50]. In contrast, M2 macrophages utilize

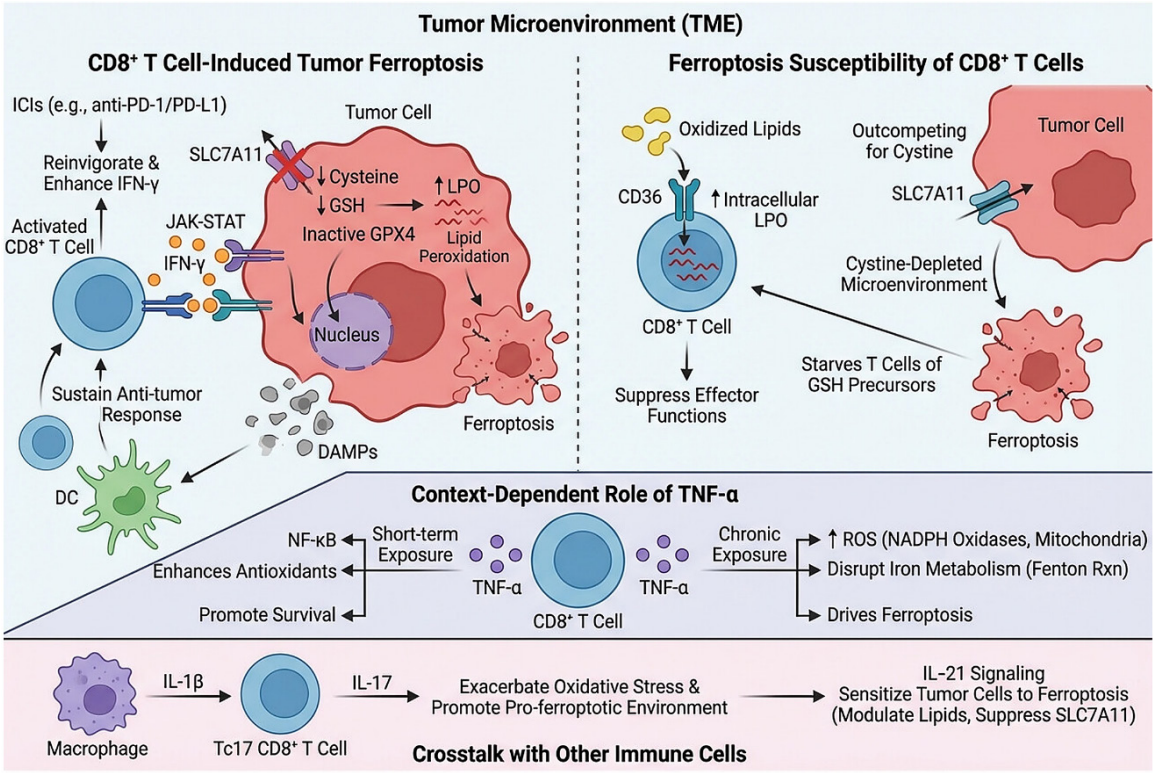

Figure 3. CD8⁺ T cells in ferroptosis: inducers and targets. Within the TME, CD8⁺ T cells both trigger and undergo ferroptosis. Activated CD8⁺ T cells secrete IFN-γ, which activates JAK-STAT signaling in tumor cells to suppress SLC7A11, depleting cysteine and GSH, inactivating GPX4, and driving lipid peroxidation (LPO) and tumor ferroptosis; ICIs (anti-PD-1/PD-L1) amplify IFN-γ. Ferroptotic tumor cells release DAMPs that activate DCs, reinforcing antitumor immunity. Conversely, CD36-dependent uptake of oxidized lipids and tumor competition for cystine increase LPO in CD8⁺ T cells, suppressing effector function and inducing T-cell ferroptosis. TNF-α signaling is biphasic, with short-term NF-κB-mediated cytoprotection but chronic ROS/iron dysregulation that promotes ferroptotic death.

IL-10 and FAO/OXPHOS metabolism to attenuate lipid peroxidation [51, 52]. Cancer-associated fibroblasts (CAFs) exhibit dual regulatory roles: exosomal miR-522 inhibits arachidonate 15-LOX to limit lipid ROS, while NRF2 activation upregulates GPX4/Trx antioxidant systems [53, 54]. Paradoxically, CAF-derived ferritin/PDGF promotes iron-mediated Fenton reactions, sensitizing NK cells to ferroptosis [55]. Hypoxia-induced HIF-1α cooperates with CAFs to elevate stearoyl-CoA desaturase 1 (SCD1)/FASN-dependent monounsaturated fatty acid (MUFA) synthesis, displacing peroxidation-prone PUFAs in membranes [56, 57].

Immunosuppressive neutrophils (N2-TANs) recruit Tregs via CCL2/CXCL1 and impair T cells through arginine 1 (Arg1)/ROS, despite intrinsic ferroptosis susceptibility from metabolic hyperactivity [58, 59]. PMN-MDSCs maintain ferroptosis resistance via GPX4/SLC7A11 under normoxia but succumb to hypoxic ROS accumulation, whereas M-MDSCs suppress tumor ferroptosis by Arg1-mediated ACSL4 downregulation [60, 61]. Reciprocal TGF-β/CCL17 signaling between MDSCs and TANs establishes a self-reinforcing immunosuppressive network [62]. Collaborative NET formation activates HMGB1-RAGE/TLR pathways, facilitating angiogenesis and immune escape [63].

Metabolic reprogramming of glucose and lipids modulates ferroptosis susceptibility in the TME

The interplay between glucose and lipid metabolic reprogramming in regulating tumor cell ferroptosis susceptibility within the TME has emerged as a pivotal research focus. Tumor cells predominantly utilize aerobic glycolysis (Warburg effect), resulting in excessive lactate production. Lactate influx via monocarboxylate

transporters (MCTs) activates the pentose phosphate pathway (PPP), thereby upregulating GSH and GPX4 expression to suppress lipid peroxidation and ferroptosis [64]. Notably, lactate-induced TME acidification may concurrently inhibit LOX activity, reducing PUFA oxidation [65].

Lipid metabolic rewiring further critically modulates ferroptosis dynamics. Increased low-density lipoprotein receptor (LDLR)-mediated cholesterol uptake enriches membrane cholesterol content, reducing fluidity and promoting lipid raft formation. These alterations spatially restrict lipid peroxide diffusion, thereby attenuating ferroptotic signaling [66]. MUFAs, synthesized via SCD1, preferentially incorporate into cellular membranes to displace peroxidation-susceptible PUFAs, establishing an anti-ferroptotic lipid architecture [66]. Paradoxically, tumor cells exploit PUFA metabolic plasticity to evade ferroptosis: downregulation of ACSL4 reduces pro-ferroptotic PUDA incorporation, while upregulation of ACSL3 promotes MUFA synthesis [67, 68]. Collectively, these glucose and lipid metabolic adaptations cooperatively govern ferroptosis susceptibility, providing novel therapeutic perspectives for developing cancer therapies targeting ferroptosis regulatory nodes [69, 70].

Cytokine-signaling networks in the TME: orchestrating ferroptosis regulation

TGF-β regulates TME fibrosis and tumor progression while modulating ferroptosis via Hippo pathway crosstalk [71, 72]. IL-6 activates NF-κB to promote inflammatory survival signals and therapeutic resistance, correlating with aggressive tumor phenotypes [73, 74]. TNF-α exhibits dual roles: NF-κB activation transiently enhances antioxidant defenses (e.g., γ-GCS), while chronic signaling drives ferroptosis through PI3K-AKT-mTOR-mediated ROS accumulation and iron overload [74, 75]. The Hippo pathway maintains ferroptosis sensitivity by balancing proliferative and apoptotic signals, with its dysregulation conferring resistance [75]. Conversely, hyperactivated PI3K-AKT-mTOR suppresses ferroptosis via redox homeostasis and lipid peroxidation inhibition [75]. NF-κB integrates inflammatory and survival responses by upregulating antioxidant genes (e.g., GPX4, SOD2), creating a protective barrier against ferroptotic death [76].

Collectively, TGF-β/IL-6/TNF-α signaling and Hippo/PI3K-AKT-mTOR/NF-κB pathways form an interconnected network that fine-tunes ferroptosis susceptibility. Targeting these axes - particularly cytokine-driven metabolic checkpoints and pathway crosstalk - offers therapeutic opportunities to exploit ferroptosis vulnerabilities in malignancies (**Figure 4**).

Impact of ferroptosis on the TME

Ferroptosis-triggered immune activation: mechanisms and therapeutic implications

Ferroptosis is intrinsically linked to the release of DAMPs, endogenous molecules that activate immune responses upon their release into the TME. These DAMPs play pivotal roles in modulating immune tolerance and antitumor immunity. Tumor cells undergoing ferroptosis release HMGB1, ATP, and calreticulin, which activate DCs via pattern recognition receptors (PRRs) such as TLR4 and cGAS-STING. Mature DCs enhance tumor antigen presentation, subsequently priming $CD8^+$ T cell to secrete IFN-γ and granzyme B. IFN-γ further amplifies ferroptosis by suppressing SLC7A11/SLC3A2 and GPX4 expression in tumor cells, thereby impairing antioxidant defenses [77, 78]. For instance, BQR@MLipo-induced ferroptosis in bladder cancer cells activates the cGAS-STING pathway to promote DAMP release, DC activation, and $CD8^+$ T cell infiltration [79]. Similarly, FeGd-HN@TA-Fe^{2+}-SN38 nanoparticles trigger ferroptosis via endoplasmic reticulum stress, releasing DNA-containing exosomes that activate the cGAMP-STING-TBK1 axis to induce DC maturation and IFN-β secretion, ultimately potentiating $CD8^+$ T cell responses [80]. Targeting DCs to enhance antigen presentation is critical for optimizing cancer vaccines and immunotherapies [6].

The crosstalk between ferroptosis-induced DAMPs and DC activation underscores the therapeutic potential of leveraging ferroptosis to augment cancer immunotherapy. DAMPs from ferroptotic cells enhance antitumor T cell immunity by promoting DC-mediated antigen presentation and T cell priming [12]. Chemotherapy-induced immunogenic cell death fur-

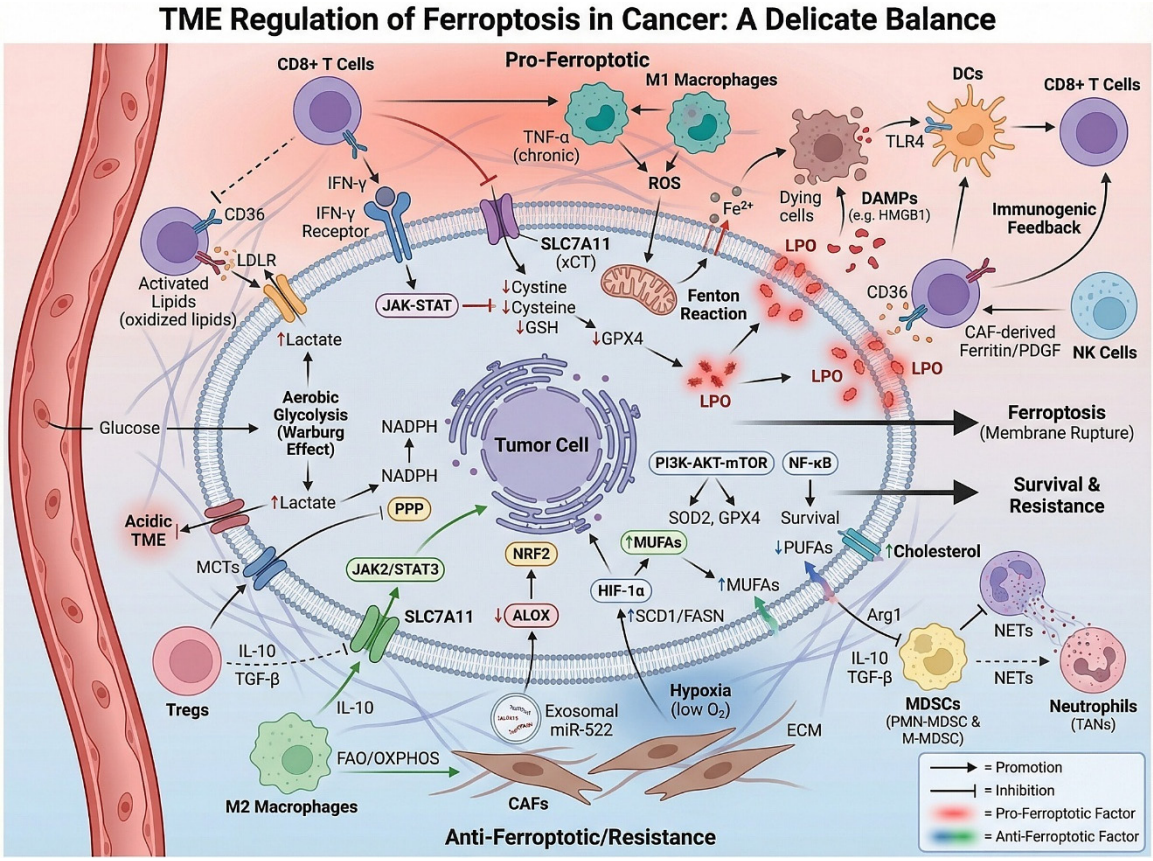

Figure 4. TME regulation of ferroptosis in cancer. The TME balances pro- and anti-ferroptotic cues that determine tumor cell fate. Pro-ferroptotic inputs include $CD8^+$ T-cell IFN-γ/IFN-γR-JAK-STAT signaling that inhibits xCT (SLC7A11), chronic TNF-α and ROS from M1 macrophages, and Fe^{2+}-driven Fenton reactions that accelerate LPO accumulation; DAMPs from dying cells activate TLR4 on dendritic cells to sustain immunogenic feedback. Anti-ferroptotic/resistance pathways arise from Warburg glycolysis-derived lactate (MCT influx) fueling the PPP/NADPH antioxidant program, NRF2 and NF-κB/PI3K-AKT-mTOR survival signaling, hypoxia (HIF-1α) - driven SCD1/FASN MUFA remodeling, and immunosuppressive cells (Tregs, M2 macrophages, MDSCs/NET-forming neutrophils) that supply IL-10/TGF-β or deplete metabolites.

ther synergizes with this process by increasing tumor antigen availability [81]. Beyond antigen presentation, ferroptosis remodels the TME to activate antitumor immunity. For example, HMGB1 released during ferroptosis polarizes macrophages toward the M1 phenotype via TLR4 signaling, increasing pro-inflammatory cytokines (e.g., TNF-α, IL-1β) that enhance $CD8^+$ T cell cytotoxicity [77, 82]. Ferroptosis inducers (e.g., COF-919) reduce M2 macrophage abundance by inhibiting GPX4 or FSP1, thereby reversing immunosuppression [82]. Cu/ZIF-8@U-104@siNFS1-HA-induced ferroptosis in osteosarcoma cells promotes M1 macrophage polarization and antitumor immunity [83]. Additionally, ferroptosis inducers suppress Treg and MDSC activity via DAMP release, alleviating $CD8^+$ T cell inhibition [84].

Metabolic reprogramming synergizes with ferroptosis to activate immunity. Lipid peroxidation products (e.g., oxidized PUFAs) generated during ferroptosis disrupt tumor cell membranes, releasing antigens captured by DCs for T cell activation [85]. Fe^{2+}-mediated Fenton reactions exacerbate oxidative stress, activating PERK-eIF2α signaling to release DAMPs and promote DC maturation [80]. Collectively, ferroptosis establishes a "ferroptosis-immune positive feedback loop" through DAMP release, TME remodeling, and metabolic rewiring. Integrating ferroptosis into immunotherapeutic strategies may enhance treatment effi-

cacy by fostering robust and sustained antitumor immunity [86, 87].

Ferroptosis-driven immune evasion: metabolic reprogramming and immunosuppressive niche formation

The interplay between ferroptosis and immune suppression in the TME involves multifaceted signaling networks and cellular adaptations [88, 89]. While DAMPs (e.g., HMGB1, calreticulin) from ferroptotic tumor cells initially activate DCs and T cells, late-stage ferroptosis exhibits diminished immunogenicity, facilitating immune escape [90, 91]. Paradoxically, ferroptosis-derived DAMPs recruit immunosuppressive factors such as 8-hydroxyguanosine (8-OHG), KRAS G12D exosomes, and prostaglandin E2 (PGE2) to establish an immunosuppressive niche [77]. HMGB1 binding to AGER on macrophages activates NF-κB and inflammasome pathways, inducing IL-6/CXCL1 secretion while promoting DC apoptosis or phenotypic switching, thereby impairing antigen presentation [92, 93].

Ferroptosis directly suppresses antitumor immune cell function. Lipid-rich TME conditions upregulate CD36 on $CD8^+$ T cell, driving excessive lipid uptake that culminates in LPO and ferroptosis, thereby reducing IFN-γ/TNF-α production and cytotoxic capacity [36, 94]. MDSCs evade ferroptosis via SLC7A11 and ASAH2 overexpression, depleting cystine to impair $CD8^+$ T cell function [90]. RSL3-induced ferroptosis triggers PPARG-mediated lipid accumulation in DCs, suppressing their maturation and promoting exhaustion [78]. Early ferroptotic LPO inhibit DC phagocytosis and T cell activation, while ROS neutralization of NK cell-derived granzyme B (GrB) limits tumor killing [78, 95].

Ferroptosis-associated miR-181 and 8-OHG induce M2 macrophage polarization via TLR2 signaling, fostering taurine-mediated ferroptosis resistance and immunosuppression [38, 78]. STAT3 activation in ferroptotic tumor cells enhances fatty acid oxidation in macrophages, promoting M2 polarization and IL-10/TGF-β secretion to suppress $CD8^+$ T cell [77]. KRAS G12D exosomes from pancreatic ductal adenocarcinoma (PDAC) cells activate STAT3 to drive M2 polarization and tumor progression [96]. GPX4 inhibition by RSL3 selectively reduces M2 macrophage ferroptosis, skewing TME toward immunosuppression [82]. MDSCs deplete Arg and tryptophan (Trp) to inhibit T cell proliferation [65, 78].

Ironically, IFN-γ-induced ferroptosis upregulates PD-L1 expression in tumor cells, engaging the PD-1/PD-L1 axis to inhibit $CD8^+$ T cell [77, 97]. Oxidized PLs (e.g., AA-PLs) from ferroptotic cells activate PPARγ to upregulate T cell exhaustion markers (TIM-3, LAG-3) [98]. Lipid peroxidation byproducts (e.g., 4-HNE) directly impair NK cell cytotoxicity [96]. Fe^{2+}/ROS-mediated Fenton reactions damage DCs and NK cells, attenuating immune responses [77].

The dual immunological role of ferroptosis: current controversies and knowledge gaps

The paradoxical role of ferroptosis in promoting both immune activation and evasion stems from several core controversies and knowledge gaps in current research. A fundamental question remains which specific oxidized lipid species act as key immunomodulators, as systematic lipidomics studies to precisely identify and track these molecules are lacking. Conflicting evidence exists regarding whether these lipids function as immunostimulatory DAMPs or immunosuppressive mediators [99, 100]. A plausible hypothesis suggests different lipid products may exert opposing functions, with the net effect determined by their relative abundance, spatiotemporal distribution, and corresponding receptor expression in the tumor microenvironment.

Ferroptosis demonstrates remarkable context dependency. The immunological consequences of “early” versus “late” ferroptosis may differ substantially [101], yet clear definitions and distinctions between these phases remain elusive. In vivo, where cell death occurs asynchronously, this dynamic progression complicates assessment of overall immune response. Furthermore, tumor heterogeneity significantly influences both susceptibility to ferroptosis and subsequent immunological outcomes, suggesting that inducing ferroptosis in “hot” versus “cold” tumors may yield fundamentally different results.

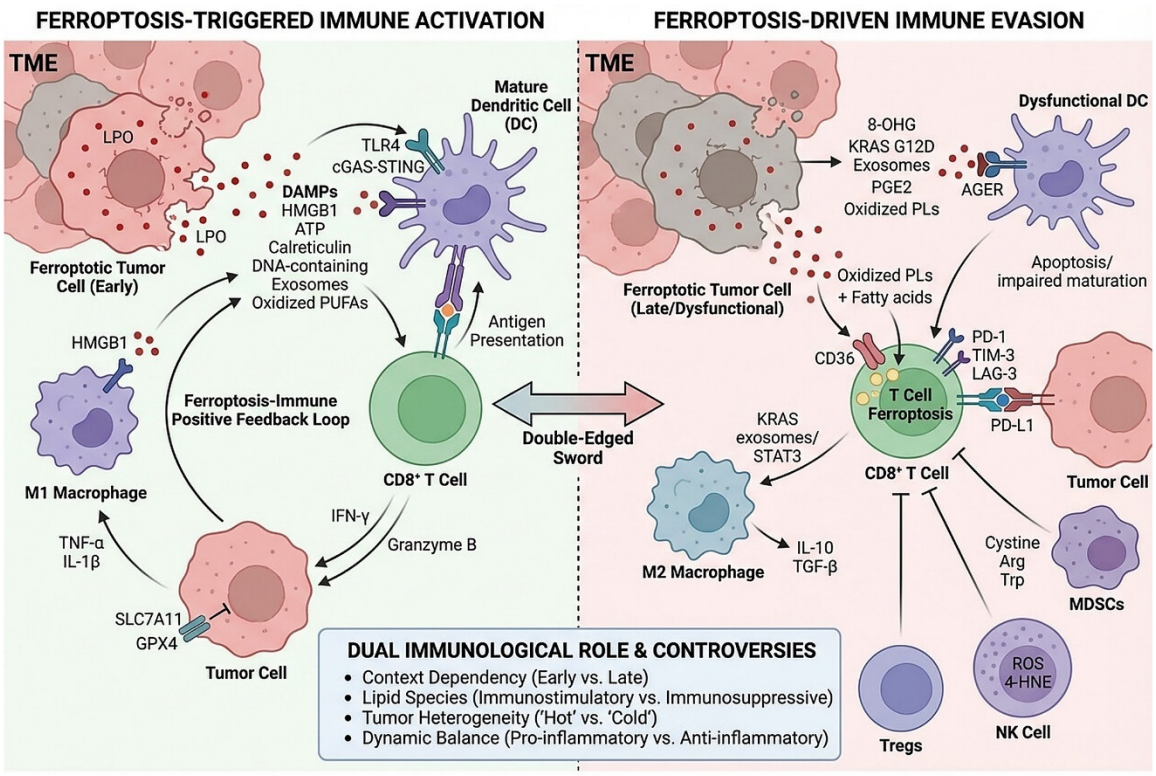

Figure 5. Ferroptosis shapes the TME: immune activation vs immune evasion. Ferroptosis remodels the TME as a "double-edged sword". Left: Early ferroptotic tumor cells release DAMPs (HMGB1, ATP, calreticulin), oxidized PUFAs and DNA exosomes that activate dendritic cells through TLR4 and cGAS-STING, enhancing antigen presentation and $CD8^+$ T-cell priming. $CD8^+$ T cells then secrete IFN-γ and granzyme B to suppress SLC7A11/GPX4 in tumor cells, reinforcing a ferroptosis-immune positive feedback loop; HMGB1 also promotes M1 macrophage activation (TNF-α/IL-1β). Right: Late/dysfunctional ferroptosis can foster immune evasion via 8-OHG, KRASG12D exosomes, PGE2 and oxidized phospholipids that impair DC maturation (AGER), drive CD36-dependent T-cell lipid overload/ferroptosis with exhaustion markers, and recruit suppressive M2 macrophages, Tregs and MDSCs that starve effector cells.

Collectively, ferroptosis represents a sharp double-edged sword in tumor immunology. The ultimate immunological consequence reflects a dynamic balance between pro-inflammatory and anti-inflammatory forces, governed by complex interactions among temporal, spatial, tumor-type, and microenvironmental factors. Systematically investigating these variables to establish predictive models for ferroptosis immunology represents the crucial next step toward its precise therapeutic application (**Figure 5**).

The potential applications of ferroptosis in anticancer therapy

Clinical translation of ferroptosis-targeted anticancer therapy

As of the end of 2025, despite substantial achievements in basic research, the translation of ferroptosis-targeted therapies from laboratory to clinic remains profoundly challenging. As pioneering compounds in ferroptosis research, Erastin and RSL3 have effectively validated the anticancer concept of ferroptosis in vitro and in animal models [102]. Erastin primarily induces ferroptosis by inhibiting system Xc^- to deplete intracellular GSH, while RSL3 directly suppresses GPX4 activity [12, 103]. These agents demonstrate tumor growth inhibition across various models, including colorectal, prostate, and non-small cell lung cancers [12, 102].

However, inherent limitations of these canonical tool compounds present major obstacles for clinical development. Core regulatory pathways of ferroptosis, particularly GPX4, are essential for maintaining homeostasis in numerous normal tissues. For instance, renal

cells and specific neuronal populations critically depend on GPX4 to defend against lipid peroxidation damage [2]. Consequently, systemic administration of potent GPX4 inhibitors like RSL3, or compounds broadly affecting GSH synthesis like Erastin, inevitably generates toxicity in these normal tissues. This explains why clinical trials for ferroptosis inducers have been delayed despite abundant preclinical data, with in vivo efficacy and insurmountable toxicity representing primary concerns [104].

Classical ferroptosis inducers including Erastin and RSL3 exhibit dismal pharmacokinetic profiles, characterized by poor solubility, low metabolic stability, inadequate bioavailability, and short half-lives with rapid clearance. These properties hinder the achievement and maintenance of effective therapeutic concentrations in vivo while complicating toxicity assessment [105]. Furthermore, critical human pharmacokinetic parameters remain largely unknown. The absence of dedicated clinical trials means no data exist regarding plasma concentration-time curves or elimination half-lives for any ferroptosis inducer in humans. Detailed reports on administration routes, dosing regimens, and corresponding pharmacokinetic limitations for clinical-stage ferroptosis inducers are completely lacking. This systematic knowledge gap forces all clinical applications to proceed blindly, preventing rational dosing design, complicating drug interaction predictions, and severely impeding Investigational New Drug applications.

Moreover, the lack of validated biomarkers for predicting patient sensitivity or resistance to ferroptosis therapy continues to hamper precise patient selection [106]. Without reliable biomarkers to guide patient enrollment, future clinical trials would need to adopt inefficient screening approaches, potentially diluting efficacy signals, increasing trial failure risks, and exposing unsuitable patients to unnecessary toxicity. Promisingly, the FerrDb database is systematically organizing potential regulators and markers, including TFRC expression levels and LOX family activities, which may provide valuable resources for advancing ferroptosis therapy toward precision medicine [107].

A central technical challenge involves directing ferroptosis specifically toward tumor cells while minimizing damage to normal tissues. Current research explores multidimensional solutions, with targeted delivery systems that alter the biodistribution of ferroptosis inducers to achieve tumor-specific enrichment emerging as the most active and promising strategy for enhancing efficacy while reducing toxicity. Additionally, prodrug design and combination therapies represent classical approaches for improving drug selectivity.

For ferroptosis therapy to benefit patients, its fundamental issues of targeting and safety must first be addressed through disciplined science and clinical trial design.

Ferroptosis-mediated radiotherapy and chemotherapy sensitization

Ferroptosis induction represents a promising strategy to enhance conventional cancer therapies, though its clinical translation requires careful evaluation of both mechanisms and limitations. Radiotherapy promotes ferroptosis through dual pathways: generating ROS that drive PUFA peroxidation while simultaneously activating ataxia telangiectasia mutated (ATM) kinase to suppress SLC7A11 expression, thereby reducing cystine uptake and GSH synthesis [108]. Preclinical evidence supports this concept, with studies showing Erastin significantly enhancing radiosensitivity in breast and lung cancer models, and RSL3 improving radiotherapy efficacy by 30%-50% in glioma models [109]. However, these impressive results must be interpreted with consideration of the inherent toxicity profiles of these first-generation ferroptosis inducers and the challenges of achieving similar effects in human tumors with their complex microenvironments.

Similarly, certain chemotherapeutic agents demonstrate ferroptosis-inducing capabilities. Cisplatin and paclitaxel trigger ferritinophagy-mediated iron release, while artemisinin derivatives downregulate SLC7A11 expression [110, 111]. In colorectal cancer models, artemisinin combined with cisplatin achieved substantial tumor reduction through ATF4-CHOP pathway activation [110]. Nevertheless, the relative contribution of ferroptosis to overall treatment efficacy remains difficult to quantify, as these agents simultaneously activate multiple cell death pathways.

These findings collectively highlight ferroptosis modulation as a viable approach for therapy sensitization. Future work should prioritize developing less toxic ferroptosis inducers and establishing biomarkers to identify tumors most likely to respond to these combination strategies, thus enabling more precise clinical translation.

Combination of ferroptosis and immunotherapy

Accumulating evidence indicates that ferroptosis not only directly kills tumor cells but also transforms immunologically "cold" tumors into "hot" ones by releasing DAMPs, establishing a foundation for combination therapy with ICIs [112]. Pioneering studies highlight a central mechanism: ferroptosis inducers upregulate PD-L1 expression on tumor cells via the ROS-NF-κB signaling axis, thereby "priming" tumors and enhancing their sensitivity to subsequent PD-1/PD-L1 blockade [113, 114].

Beyond PD-L1 modulation, ferroptosis represents a form of immunogenic cell death. Dying tumor cells release DAMPs such as ATP and HMGB1, which promote dendritic cell maturation and antigen presentation, initiating adaptive antitumor immunity [115]. These signals further recruit and activate $CD8^+$ T cells, facilitating cytotoxic T lymphocyte infiltration into tumor cores for targeted tumor clearance [116].

Notably, ferroptosis inducers and ICIs engage in a reciprocal amplification loop: enhanced T-cell recruitment and function by ferroptosis synergizes with T-cell-driven ferroptosis promotion, creating a self-reinforcing antitumor cycle [36]. Additionally, ferroptosis remodels the tumor microenvironment by depleting myeloid-derived suppressor cells and reprogramming immunosuppressive M2-like tumor-associated macrophages toward the antitumor M1 phenotype, overcoming ICI resistance and augmenting therapeutic efficacy [117].

In a preclinical study on head and neck squamous cell carcinoma (HNSCC), allograft models in immunocompetent C57BL/6 mice demonstrated that combining the ferroptosis inducer FIN56 with anti-PD-L1 antibodies (αPD-L1) significantly reduced tumor volume and weight and extended overall survival compared to monotherapies, highlighting robust synergistic effects [113].

The combination of ferroptosis inducers and ICIs leverages dual mechanisms of "immune sensitization" and "target enhancement", demonstrating synergistic antitumor potential, particularly in ICI-resistant cold tumors. As of the end of 2025, while this innovative strategy remains in the preclinical stage with no large-scale clinical trial data reported, its potential to overcome resistance and broaden therapeutic applicability positions it as a promising cornerstone for future solid tumor treatments. Future efforts should prioritize developing highly targeted and minimally toxic ferroptosis inducers while designing innovative clinical trials incorporating comprehensive biomarker analyses to bridge the gap between basic research and clinical application.

Ferroptosis and nanotechnology: navigating the hype and roadblocks to clinical translation

The convergence of nanotechnology and ferroptosis is frequently framed as a paradigm shift for precision cancer therapy. In theory, nanocarriers exploit the enhanced permeability and retention (EPR) effect and TME features like acidity and redox imbalance for targeted drug delivery [118, 119]. However, the clinical reality of the EPR effect is highly variable and often overstated, casting doubt on the universal applicability of this passive targeting strategy. While nanocarriers can indeed improve the pharmacokinetics of small-molecule inducer like Erastin and RSL3-addressing short half-life and nonspecific distribution-their active targeting efficacy through ligands (e.g., lactoferrin/RGD) is frequently hampered by biological barriers and inconsistent target antigen expression in human tumors [118].

Preclinically, the promise is evident. Systems such as lipid-coated iron oxide nanoparticles co-delivering doxorubicin have demonstrated compelling synergy, achieving significant tumor growth inhibition and reduced cardiotoxicity in murine models by concurrently suppressing SLC7A11 and GPX4 [120]. Yet, these results, while mechanistically elegant, are constrained by the limitations of animal models, which poorly recapitulate the heterogeneity and stromal complexity of human cancers. The very TME factors (e.g., pH, ROS) that enable "smart" drug

release are often dysregulated and heterogeneous within a single tumor, potentially leading to incomplete and uneven ferroptosis induction.

The most formidable challenges, however, lie in clinical translation and regulation. The scalable and reproducible manufacturing of complex, multi-functional nanocarriers presents a significant industrial hurdle [121]. Moreover, the regulatory pathway for these "ferroptosis-inducing nanomedicines" is ill-defined. Regulators lack specific guidelines for this novel modality, forcing developers into a framework designed for conventional drugs or first-generation nanotherapeutics [121]. Critical questions regarding the unique immunogenicity, long-term fate of metallic nanoparticles, and appropriate biomarkers to demonstrate in vivo ferroptosis efficacy in patients remain largely unanswered. Therefore, future progress hinges not merely on optimizing nanocarrier architecture, but on conducting rigorously designed preclinical studies that better model human disease and on engaging regulatory agencies early to collaboratively define a clear and feasible approval pathway [121, 122].

Artificial intelligence (AI)-driven advancements in ferroptosis research and therapeutics

The integration of AI into ferroptosis research offers promising tools for deciphering complex TME dynamics, yet its practical utility remains constrained by several fundamental limitations [123]. While AI-driven frameworks can systematically integrate multi-omics data to map ferroptosis-associated gene networks [123, 124], the predictive value of these models heavily depends on data quality and appropriate feature selection. Graph neural networks (GNNs) theoretically enable dynamic modeling of ferroptosis signaling cascades [125]; however, their biological relevance requires rigorous validation against experimental data, as simulated equilibria between lipid peroxidation and antioxidant systems may not accurately reflect the dynamic nature of cellular redox states in vivo.

In drug discovery, AI approaches also face significant translational hurdles. Although generative adversarial networks (GANs) can rapidly populate virtual compound libraries, the hit-to-lead success rate remains modest due to inadequate prediction of pharmacokinetic properties and target specificity in biological systems [126]. Similarly, while reinforcement learning algorithms propose optimized combination regimens based on TME iron metabolism profiling, their clinical implementation is hampered by the technical challenge of obtaining real-time metabolic data from patients and the algorithms' limited adaptability to tumor evolution and heterogeneity [127].

For biomarker discovery, AI demonstrates potential but faces validation barriers. Convolutional neural networks (CNNs) can extract quantitative features from histopathology and medical imaging, yet their generalizability across different healthcare systems and imaging protocols remains questionable [128]. Multimodal data fusion approaches, such as random forest models integrating clinical and molecular parameters, show promise for patient stratification but require prospective validation in large, independent cohorts to establish clinical utility [129]. The field must address these critical gaps in model robustness and clinical applicability before AI can fulfill its potential in advancing ferroptosis-based therapeutics.

Collectively, while AI enhances ferroptosis research across target identification, drug design, and patient stratification, its transition from an exploratory tool to a clinical asset faces three progressively difficult barriers: interpretability ("black box" predictions), reproducibility (across heterogeneous datasets), and regulatory compliance. As of 2025, mature applications directly guiding clinical decisions for ferroptosis remain limited. Forging a path forward requires that interpretable AI techniques, standardized reporting, and regulatory considerations be integrated from the outset of development [130]. Only by systematically addressing these gaps can the field ensure that AI-powered insights translate into safe, effective, and responsible patient care.

Challenges and prospects of ferroptosis modulation in clinical oncology

The translation of ferroptosis into clinical oncology is fraught with substantial and interconnected hurdles that extend beyond its mecha-

Table 1. Comparative table summarizing therapeutic strategies (monotherapy vs. combination)

Therapeutic Strategy	Core Mechanisms & Representative Agents	Advantages	Disadvantages
Ferroptosis Inducer Monotherapy	Mechanisms: Directly inhibits GPX4 or system Xc^-, depleting glutathione and accumulating lethal lipid peroxides. Representatives: Erastin; RSL3; Sorafenib; Sulfasalazine.	• Clear mechanism of action. • Straightforward pharmacology. • Relatively simple toxicity profile.	• Limited efficacy and prone to drug resistance. • Poor pharmacokinetics of many inducers. • Slow clinical translation.
Combination with Radiotherapy/Chemotherapy	Mechanisms: Synergistic action; conventional therapies increase cellular susceptibility to ferroptosis. Representatives: Erastin/RSL3 + Cisplatin/Radiation.	• Strong synergistic effect. • Overcomes therapeutic resistance. • Potential for dose reduction.	• Risk of cumulative toxicity. • Complex regimen optimization needed.
Combination with ICIs	Mechanisms: Ferroptosis releases DAMPs to activate immunity; ICIs enhance T cell function. Representatives: FIN56 + anti-PD-L1 antibody.	• Mutual reinforcement creates potent synergy. • Expands applicability of ICIs. • Remodels immunosuppressive microenvironment.	• Potential overlapping toxicity. • Complex patient stratification. • Limited clinical evidence.
Integration with Nanodelivery Systems	Mechanisms: Nanocarriers enable targeted delivery to tumors. Representatives: Liposomal Erastin/RSL3; iron oxide nanoparticles.	• Improved pharmacokinetics and bioavailability. • Enhanced tumor-specific accumulation. • Reduced off-target toxicity.	• Complex manufacturing process. • Potential long-term toxicity of nanomaterials. • Significant regulatory hurdles.

nistic appeal. A paramount, yet inadequately addressed, challenge is the inherent lack of specificity, which poses a significant risk of systemic toxicity. Ferroptosis induction can cause collateral damage to iron-rich healthy tissues, potentially leading to organ dysfunction and chronic inflammation, thereby threatening the therapeutic window [131]. This risk is compounded by profound intertumoral heterogeneity. For instance, while hematologic malignancies often exhibit marked vulnerability, solid tumors such as PDAC display robust resistance, a disparity largely attributable to divergent expression of antioxidant defenses (e.g., GPX4, FSP1) and iron metabolism networks [132, 133]. This heterogeneity is not merely an observation but a fundamental obstacle that current one-size-fits-all approaches fail to overcome, highlighting an urgent need for mechanism-based patient stratification [132].

Pharmacological limitations present another critical barrier. Many current ferroptosis inducers suffer from suboptimal pharmacokinetics, poor bioavailability, and on-target, off-tumor toxicity, severely limiting their clinical utility [134]. While nanotechnology-enabled delivery systems, designed to exploit TME features like acidity and elevated GSH, offer a promising avenue for spatiotemporal control, their clinical translation remains in its infancy. Critical questions regarding long-term stability, biocompatibility, and reproducible manufacturing scalability are yet to be satisfactorily resolved [133]. Therefore, simply concentrating therapeutics within tumors is insufficient; a more sophisticated understanding of the TME's dynamic nature is required to outmaneuver adaptive resistance mechanisms.

In conclusion, the trajectory of ferroptosis from a compelling concept to a cornerstone of cancer therapy is neither straightforward nor guaranteed. Its future hinges not on incremental improvements, but on a concerted effort to dismantle these core translational barriers. This necessitates a triad of focused innovation: first, a deeper mechanistic elucidation of resistance pathways; second, the rigorous development and validation of predictive biomarkers; and third, the engineering of smarter, adaptive delivery platforms. The field must commit to this disciplined, translational-focused agenda to unlock the definitive clinical potential of ferroptosis modulation (**Table 1**).

Summary and prospect

Ferroptosis, an iron-dependent regulated cell death driven by lipid peroxidation, has emerged as a pivotal therapeutic target in oncology through its bidirectional interaction with the TME. This review systematically outlines its core molecular mechanisms and emphasizes their critical dependence on redox homeostasis. TME components, including immune cells, stromal cells, metabolites, and physicochemical features, modulate ferroptosis susceptibility via transcriptional regulation and metabolic reprogramming. Conversely, ferroptosis dynamically remodels the TME through DAMP-mediated immunostimulation or metabolic niche-driven immunosuppression, establishing a complex bidirectional regulatory network. Preclinical studies demonstrate that ferroptosis-targeted strategies synergistically enhance chemotherapy, immunotherapy, and radiotherapy by overcoming therapeutic resistance and immunosuppressive TME barriers. However, unresolved crosstalk between ferroptosis and TME pathways governing immune infiltration and treatment response necessitates further investigation. Future research must address the spatiotemporal heterogeneity of TME composition and ferroptosis pathways across cancer types, disease stages, and intratumoral regions, necessitating advanced tools such as single-cell and spatial transcriptomics to map dynamic regulatory landscapes.

Current limitations in ferroptosis inducer specificity, systemic toxicity, and acquired resistance demand innovative solutions. Developing TME-responsive smart drug delivery systems, such as pH- or ROS-sensitive nanoparticles, combined with biomarker-driven patient stratification, may enhance therapeutic precision. Concurrently, the immunogenic potential of ferroptosis warrants rigorous validation of its synergy with PD-1/PD-L1 inhibitors, alongside investigations into potential pro-metastatic risks and mitigation strategies. Translational advancements will rely on integrating patient-derived organoids, potential AI-driven prediction platforms, and real-time metabolomic monitoring of TME ferroptosis markers to enable personalized regimens.

Table 2. Glossary of key terms

Term	Definition
AI	Artificial intelligence
ACSL4	Acyl-CoA synthetase long-chain family member 4
Arg1	Arginine 1
ATM	Ataxia telangiectasia mutated
CAFs	Cancer-associated fibroblasts
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
FAO/OXPHOS	Fatty acid oxidation/oxidative phosphorylation
FASN	Fatty acid synthase
FerrDb	Ferroptosis Database
FSP1	Ferroptosis suppressor protein 1
GPX4	Glutathione peroxidase 4
GSH	Glutathione
HMGB1-RAGE	High mobility group box 1-receptor for advanced glycation end-products
HNSCC	Head and neck squamous cell carcinoma
ICI	Immune checkpoint inhibitor
LOX	Lipoxygenase
LPO	Lipid peroxides
M-MDSCs	Monocytic myeloid-derived suppressor cells
MUFA	Monounsaturated fatty acid
N2-TANs	Immunosuppressive neutrophils
NADPH	Nicotinamide adenine dinucleotide phosphate
NCOA4	Nuclear receptor coactivator 4
NET	Neutrophil extracellular traps
NF-κB	Nuclear factor-κB
NRF2	Nuclear factor erythroid 2-related factor 2
OTUB1	Ovarian tumor domain-containing ubiquitin aldehyde-binding protein 1
PDGF	Platelet-derived growth factor
PE	Phosphatidylethanolamine
PKCβII	Protein kinase C βII
PL	Phospholipid
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
SCD1	Stearoyl-CoA desaturase 1
SLC3A2	Solute carrier family 3 member 2
SLC7A11	Solute carrier family 7 member 11
System Xc^-	Cystine/glutamate antiporter system
TfR1	Transferrin receptor 1
TGF-β	Transforming growth factor-β
TLR4	Toll-like receptor 4
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
TANs	Tumor-associated neutrophils

In conclusion, the integration of ferroptosis biology with TME dynamics not only deepens our understanding of tumor pathogenesis but also opens transformative therapeutic ave-

nues. Addressing these challenges through multidimensional, cross-scale investigations will accelerate the translation of ferroptosis research from bench to bedside, ultimately redefining cancer treatment paradigms (**Table 2**).

Disclosure of conflict of interest

None.

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