

Immune network remodeling driven by ferroptosis: Bidirectional interaction mechanisms among multiple immune cells in the lung cancer immune microenvironment (Review)

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Abstract. The efficacy of immunotherapy for lung cancer is largely constrained by the highly complex and dynamically evolving tumor immune microenvironment (TIME). Previous studies have mainly focused on single immune checkpoints or individual immune cell types, thus hindering the comprehensive elucidation of variations in immune responses and the emergence of resistance. Ferroptosis, a form of programmed cell death characterized by iron-dependent lipid peroxidation imbalance, has emerged as a pivotal hub linking tumor metabolism, cellular fate and immune regulation due to high dependence on metabolic states and its capacity to release multiple immunomodulatory signals. The unique environment of lung tissue, characterized by high oxygen levels, active lipid metabolism and easily disrupted iron homeostasis, provides a distinct biological foundation for the initiation and amplification of ferroptosis within the lung cancer TIME. Increasing evidence indicates that ferroptosis affects not only tumor cell survival, but also immune regulation. Through lipid peroxidation products, iron-related metabolites and damage-associated molecular patterns, it forms bidirectional regulatory networks with multiple immune cell subsets, including CD8⁺ T-cells, dendritic cells, macrophages, natural killer cells and neutrophils, thereby shaping the functional state of the immune

microenvironment. Distinct from previous reviews that broadly discuss ferroptosis in cancer immunity or the tumor microenvironment, the present review specifically focuses on the lung cancer-specific immune microenvironment and integrates ferroptosis-mediated bidirectional interactions across multiple immune cell subsets. The present review emphasizes that ferroptosis should not be viewed merely as a tumoricidal form of cell death, but as a context-dependent immunometabolic hub that drives immune network remodeling in lung cancer. By this conceptual perspective, the present review aimed to provide a novel framework for understanding heterogeneous immunotherapy responses and for designing rational ferroptosis-based combination strategies.

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1. Introduction

Lung cancer ranks among the most burdensome malignant tumors globally, with its high incidence and mortality rates posing persistent public health challenges (1-3). In the era of immunotherapy, treatment outcomes for lung cancer are largely constrained by the highly complex and heterogeneous tumor immune microenvironment (TIME) (4,5). The TIME comprises immune cells, stromal cells, myeloid-derived inflammatory cells, extracellular matrix and diverse soluble signaling molecules. Its cellular composition, spatial distribution and functional state exhibit significant heterogeneity, systematically shaped by multidimensional factors (e.g., tumor genetic background and metabolic reprogramming) (5-8). Although immune checkpoint inhibitors (ICIs) have

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significantly improved survival outcomes for some patients, the overall response rate remains limited with prevalent resistance, suggesting that single-target strategies struggle to reverse the overall immunosuppressive TIME (9,10). Increasing evidence indicates that immune escape in lung cancer is not driven by a single pathway, but results from the complex regulatory network formed by the interaction between tumor cells and multiple immune components (11).

Therefore, current focus is gradually shifting from single immune checkpoint interventions toward identifying and modulating key hubs that integrate metabolic, immune, and microenvironmental signals (12,13). Traditional forms of programmed cell death (PCD), such as apoptosis, have long been regarded as key mechanisms for antitumor therapy. However, their immunological effects are relatively limited, often accompanied by immune quiescence or even immune tolerance. This creates difficulties in inducing sustained and effective immune remodeling in the highly immunosuppressive TIME (14). By contrast, ferroptosis, a novel PCD pathway characterized by iron-dependent lipid peroxidation imbalance, is highly dependent on cellular metabolic states, particularly the fine-tuned regulation of iron homeostasis, lipid composition and antioxidant systems (15,16). Notably, ferroptosis is not solely determined by intrinsic tumor cell programs; it can be dynamically regulated by immune factors, oxidative stress signals and multiple metabolic pathways. This process is accompanied by the release of lipid peroxidation products and metabolically derived signals, naturally embedding ferroptosis within the TIME (17). This highly coupled metabolic-immune characteristic endows ferroptosis with the potential to coordinate tumor cell fate and immune regulation within specific microenvironmental contexts.

Ferroptosis has particular immunoregulatory significance in lung cancer. Lung tissue is chronically exposed to a high oxygen tension environment, resulting in elevated baseline oxidative stress levels. Exogenous factors, such as smoking and air pollution further exacerbate iron homeostasis disruption and lipid peroxidation risks (18,19). Against this backdrop, lung cancer cells commonly exhibit iron metabolism imbalance, polyunsaturated fatty acid (PUFA) accumulation and a high dependence on antioxidant systems, rendering them more sensitive and plastic to ferroptotic stress (19,20). These tissue and metabolic characteristics provide a structural foundation for ferroptosis to serve as a pivotal hub linking tumor cell fate and immune regulation in lung cancer. However, existing studies predominantly focus on utilizing ferroptosis for direct tumor cell elimination or investigating its regulation by individual immune cell types. A systematic integration of how diverse immune cells within the TIME dynamically interact with tumor ferroptosis at the systemic level remains lacking, at least to the best of our knowledge (21-23). The present review focuses on lung cancer and systematically discusses the bidirectional interactions between ferroptosis and multiple immune cell subsets within the TIME. It is proposed that ferroptosis should be understood not merely as a form of tumor cell death, but as a context-dependent driver of immune network remodeling that may shape both immune activation and immunosuppressive adaptation (Fig. 1).

2. Regulation of the TIME by ferroptosis

Ferroptosis represents a non-apoptotic form of cell death driven by the combined effects of iron homeostasis imbalance and lipid peroxidation reactions, involving multi-level metabolic and redox regulation. In the tumor context, ferroptosis-related molecular events not only influence tumor cell survival, but also change metabolic and oxidative stress conditions within the tumor microenvironment (TME). Lung cancer tissues frequently exhibit marked oxidative stress, iron metabolism abnormalities and chronic inflammation, providing a specific biological context for the occurrence of ferroptosis-related processes.

Characteristics and molecular mechanisms of ferroptosis. Cell death is a crucial biological process for maintaining homeostasis and tissue renewal. PCD encompasses forms such as apoptosis, necrosis, autophagy, pyroptosis and ferroptosis, each exhibiting distinct morphological features, biochemical processes and regulatory mechanisms (24-26). Ferroptosis, a regulated form of cell death proposed in 2012 (15), is characterized by the lethal accumulation of iron-dependent lipid peroxides on the cell membrane. Its hallmark features include mitochondrial shrinkage, the loss of cristae architecture and impaired membrane lipid integrity, while lacking classic apoptotic phenotypes, such as chromatin condensation and apoptotic body formation (27,28). Due to its unique molecular mechanisms and pathological significance, ferroptosis has rapidly emerged as a major focus in cell death research and has been demonstrated to be extensively involved in various pathological processes, including tumors, neurodegenerative diseases and cardiovascular diseases (29-31).

The occurrence of ferroptosis primarily involves key mechanisms, such as iron homeostasis imbalance, reactive oxygen species (ROS) accumulation, enhanced lipid peroxidation and the failure of antioxidant defense systems (32). At the molecular level, ferroptosis depends on the excessive oxidation of PUFA-containing phospholipids, with the inactivation of glutathione peroxidase 4 (GPX4) and the depletion of its substrate glutathione (GSH) considered decisive events (33,34). Beyond the GPX4-dependent pathway, the FSP1-coenzyme Q10 axis exerts GPX4-independent protective effects by scavenging lipid peroxyl radicals. On the other hand, ferritinophagy further amplifies lipid peroxidation by elevating cellular free iron levels, thereby regulating ferroptosis thresholds at multiple hierarchical levels (35-37).

Mechanistically, ferroptosis in the tumor context can be viewed as a hierarchical process involving: i) Altered cystine uptake and antioxidant failure, represented by the system Xc⁻-GSH-GPX4 axis; ii) lipid remodeling and peroxidation, including acyl-CoA synthetase long chain family member 4 (ACSL4)-dependent PUFA incorporation and ROS propagation; and iii) iron mobilization and ferritinophagy, which amplify oxidative injury. These events collectively determine whether ferroptotic stress remains cell-intrinsic or is converted into extracellular immunoregulatory signals such as damage-associated molecular patterns (DAMPs), oxidized lipids and iron-related metabolites.

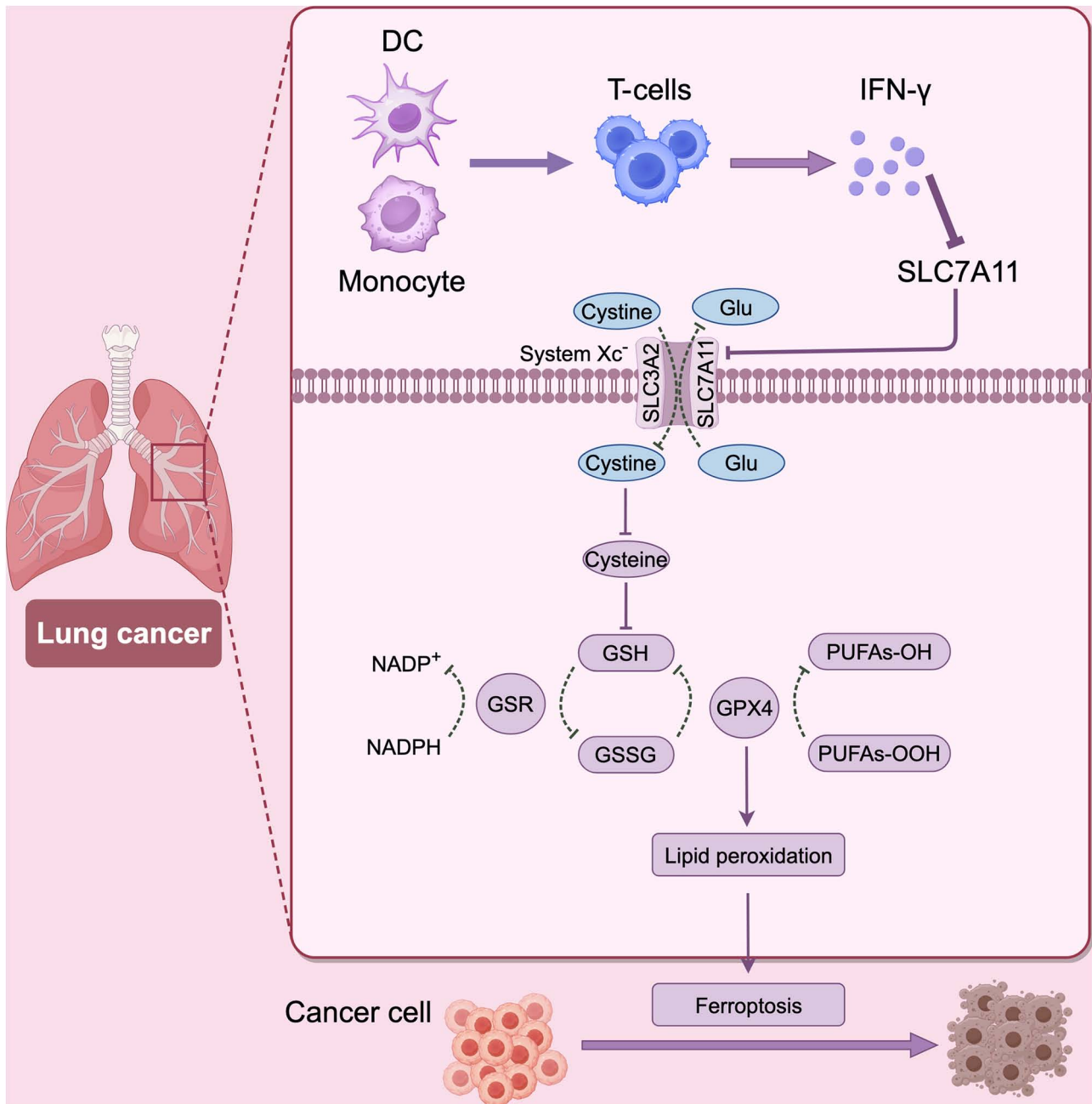


Figure 1. Immune cell-driven induction of iron-deficiency necrosis in lung cancer: DCs and macrophages present tumor antigens to CD8⁺ T-cells, thereby promoting T-cell activation and IFN- γ secretion. IFN- γ signals through the JAK-STAT1 pathway in lung cancer cells, inhibiting the cystine/glutamate antiporter system Xc⁻ (SLC7A11), thereby restricting cystine uptake and reducing intracellular GSH synthesis. GSH depletion reduces GPX4 activity, allowing accumulation of lipid peroxides derived from PUFAs. Excessive lipid peroxidation disrupts redox homeostasis, ultimately inducing ferroptosis in tumor cells. This pathway links adaptive immune activation to the metabolic vulnerability of lung cancer cells. DCs, dendritic cells; GSH, glutathione; GPX4, glutathione peroxidase 4; PUFAs, polyunsaturated fatty acids; SLC7A11, solute carrier family 7 member 11; Glu, glutamate; GSR, glutathione disulfide reductase; GSSG, glutathione disulfide.

Regulatory role of ferroptosis in the TME. In the tumor context, ferroptosis not only serves as an effector endpoint for eliminating tumor cells, but also functions as a critical regulatory node shaping the TIME (38-40). Multiple studies have indicated that inducing ferroptosis in tumor cells significantly suppresses tumor growth, demonstrating particular efficacy in models of apoptosis-resistant tumors (16,17,40). Notably, immune responses are tightly coupled with ferroptosis: Activated CD8⁺ T-cells suppress solute carrier family (SLC) 7 member 11 (SLC7A11)-mediated cysteine uptake in

tumor cells via IFN- γ signaling, thereby weakening the GPX4 antioxidant axis and enhancing tumor cell susceptibility to ferroptosis (41).

Concurrently, ferroptosis-induced lipid peroxidation products, iron-related metabolites and altered membrane structures serve as DAMPs continuously sensed by immune cells within the TIME (42-45). These signals not only influence immune cell recruitment, but also modulate their phenotypic differentiation and functional states. For instance, in environments rich in oxidized lipids, neutrophils, tumor-associated macrophages

(TAMs) and myeloid-derived suppressor cells are more likely to acquire immunosuppressive characteristics, while effector T-cells may undergo functional exhaustion due to lipid peroxidation stress (46,47). Thus, ferroptosis is not a singular, transient cellular clearance event, but rather participates in the dynamic remodeling of the TIME through sustained metabolic and oxidative signaling.

From an immune-regulatory perspective, these pathways do not function in parallel without order. Instead, antioxidant failure and iron-driven lipid peroxidation represent upstream molecular triggers, whereas DAMP release, oxidized lipid accumulation and inflammatory mediator production constitute downstream signals that reshape immune cell recruitment, activation, exhaustion, or polarization.

Environment-specific mechanisms of ferroptosis regulation by the TIME in lung cancer. The unique physiological environment of lung tissue provides a distinct context for the initiation and amplification of ferroptosis in lung cancer. Due to its continuous role in gas exchange, the partial pressure of oxygen around alveoli is maintained at ~100 mmHg, significantly higher than that in other solid tissues (48). This places lung cancer cells under persistent oxidative stress. This hyperoxic environment lowers the threshold for the initiation of ferroptosis by promoting ROS production and Fenton reactions. On the other hand, it drives lung cancer cells to establish more robust antioxidant and iron metabolism adaptation mechanisms, such as the upregulation of transferrin receptor 1 (48,49). Against this backdrop, when CD8⁺ T-cells infiltrate and release IFN- γ , the delicate redox homeostasis is easily disrupted, triggering a cascade of ferroptotic responses.

Lipid metabolism characteristics further amplify the susceptibility of lung cancer to ferroptosis. The lung is rich in phospholipids, and the complex composition of pulmonary surfactant provides abundant substrates for lipid peroxidation. Lung cancer cells frequently upregulate fatty acid transporters such as CD36 to extensively uptake PUFAs, particularly arachidonic acid, from the microenvironment, thereby supplying 'fuel' for ferroptosis (50,51). However, tumor cells can remodel membrane lipid composition by downregulating ACSL4 or enhancing monounsaturated fatty acid synthesis, thereby increasing tolerance to lipid peroxidation. Immune cell-mediated IFN- γ signaling can partially reverse this adaptation process by upregulating ACSL4, re-sensitizing tumor cells to ferroptosis (52,53).

Notably, in lung cancer, a tumor type chronically exposed to hypoxia, susceptible to iron homeostasis disruption and frequently accompanied by chronic inflammatory stimulation, ferroptosis often exhibits regional, sublethal and recurrent kinetic characteristics (33,51,54). Tumor cells can persistently reside in a state of 'sublethal ferroptotic stress', continuously releasing oxidized lipids, iron-related metabolites and inflammatory signals that are repeatedly sensed by immune cells within the TIME (51,55). This chronic, low-intensity oxidative stress progressively drives metabolic reprogramming and functional polarization of immune cells, ultimately facilitating the establishment of an immunosuppressive TIME and laying the groundwork for immune evasion in lung cancer (Table I).

3. Interactions between antitumor immune cells and ferroptosis in lung cancer

Within the TIME, ferroptosis and immune responses are deeply intertwined, forming a bidirectional regulatory network. On the one hand, multiple antitumor immune cells, including CD8⁺ T-cells, dendritic cells (DCs) and natural killer (NK) cells can directly induce ferroptosis in tumor cells. On the other hand, lipid peroxides, iron metabolites and inflammatory signals released during ferroptosis feedback-regulate the recruitment, polarization and function of these immune cells. Within the lung cancer-specific microenvironment characterized by hypoxia and active lipid metabolism, this 'immunity-ferroptosis-microenvironment remodeling' coupling is concretely manifested and dynamically maintained through the actions of key immune subpopulations.

CD8⁺ T-cells and ferroptosis. CD8⁺ T-cells serve as core effector cells executing cytotoxic responses in adaptive immunity, activated through the T-cell receptor recognition of antigen peptides presented by major histocompatibility complex (MHC)-I (56,57). Upon activation, CD8⁺ T-cells directly induce tumor cell apoptosis through the perforin/granzyme pathway and Fas-FasL signaling (58,59). At the same time, they extensively remodel the TIME by secreting cytokines, such as IFN- γ (17,60).

For lung cancer, IFN- γ released by activated CD8⁺ T-cells exerts antitumor effects by inducing ferroptosis. IFN- γ binds to receptors on the tumor cell surface, activating the JAK-STAT1 pathway. Phosphorylated STAT1 translocates to the nucleus and inhibits SLC7A11 transcription, thereby downregulating system Xc⁻ function. This reduces cystine uptake, depletes glutathione and ultimately leads to the accumulation of lipid peroxides (17,23,60,61). Furthermore, IFN- γ induces the expression of ACSL4 in the presence of arachidonic acid, promoting the incorporation of PUFAs into membrane phospholipids. This provides additional substrates for lipid peroxidation, further amplifying ferroptosis signaling (62). Lung tissue, chronically exposed to high oxygen partial pressure and rich in PUFAs, provides a unique physiological substrate for lipid peroxidation reactions. This places lung cancer cells under sustained oxidative stress, amplifying the potential effects of CD8⁺ T-cell-mediated ferroptosis. A similar mechanism has been validated in melanoma. Immunotherapy-induced CD8⁺ T-cells downregulate GPX4 expression or function via IFN- γ , diminishing tumor cell tolerance to lipid peroxidation. This renders ferroptosis a critical executor of antitumor immune effects, with its occurrence level closely associated with CD8⁺ T-cell infiltration and treatment efficacy (17,63). Furthermore, tumor metabolic programs also influence CD8⁺ T-cell-mediated ferroptosis sensitivity in colorectal cancer. Apolipoprotein L3 synergistically enhances CD8⁺ T-cell antitumor effects by promoting L-lactate dehydrogenase A ubiquitination and degradation (65). Although similar mechanisms have been reported in melanoma and colorectal cancer (17,63,64), direct validation of the full regulatory hierarchy in lung cancer remains limited.

Ferroptosis in lung cancer cells exerts complex regulatory effects on CD8⁺ T-cell immunity by reshaping the lipid and inflammatory signaling networks within the TME. DAMPs

and oxidized lipid metabolites released during ferroptosis constitute an immunologically active signaling axis: DAMPs, such as high-mobility group box 1 (HMGB1) enhance antigen presentation and promote CD8⁺ T-cell activation, while simultaneously inducing inhibitory signals such as IL-10, limiting the intensity and persistence of T-cell responses (23,65). Moreover, ferroptosis is often accompanied by COX-2 upregulation and increased prostaglandin E2 (PGE₂) production, with PGE₂ directly suppressing CD8⁺ T-cell recruitment, differentiation and cytotoxic function (23). Beyond inflammatory signals, TME signals induce CD8⁺ T-cells to express FABP7 at the metabolic level, thus leading to imbalanced lipid uptake and triggering lipid toxicity. This further weakens T-cell functional persistence (40). Thus, ferroptosis in lung cancer dynamically shapes an immune state characterized by coexisting CD8⁺ T-cell activation and functional decline through the 'lipid peroxidation-inflammation-metabolic reprogramming' circuit. The combined induction of ferroptosis and immune checkpoint blockade holds promise as a potential strategy to enhance anti-lung cancer immune responses (17). Taken together, the interaction between CD8⁺ T-cells and ferroptosis appears inherently dual-faced in lung cancer: CD8⁺ T-cell-derived IFN- γ can enhance tumor ferroptosis, whereas persistent lipid peroxidation may also impair T-cell persistence and effector function. This suggests that therapeutic strategies should increase tumor ferroptosis susceptibility without aggravating T-cell dysfunction.

Ferroptosis signaling in DCs. DCs, as the most specialized antigen-presenting cells in the immune system, play a central role in the immune defense against lung cancer. They can detect tumor necrosis or apoptosis signals, uptake and process tumor antigens, and present them to T-cells via MHC molecules to initiate cytotoxic immune responses. Interactions between DCs and T-cells prompt the latter to release IFN- γ . This cytokine downregulates the expression of system Xc⁻ [SLC7A11, also known as systemic Xc⁻ transporter (xCT)] and GPX4 in tumor cells, disrupting their redox homeostasis and inducing ferroptosis (66,67). In this process, DCs not only regulate tumor metabolic fate through cytokine signaling, but also recognize DAMPs released during ferroptosis, such as ATP and HMGB1. This further promotes DC maturation and immune activation, enhancing antigen presentation capacity (68). This forms a 'DC-T-cell-ferroptosis' positive feedback loop, constituting DC-induced ferroptosis a key mechanism for the immune system to eliminate tumor cells. Concurrently, it has been reported that DC dysfunction is closely associated with intracellular lipid accumulation; excessive lipid deposition reduces the antigen processing capacity and migratory potential of DCs (69,70).

Within the TME, while ferroptosis can eliminate tumor cells, the accompanying lipid oxidative stress also impairs DC function. Lipid peroxidation products not only disrupt DC membrane structure, but also block antigen presentation pathways, suppressing T-cell activation and thereby weakening overall antitumor immunity (45,71). Specifically, DCs selectively internalize oxidized lipids from the TME, forming lipid droplets rich in oxidized truncated lipids. These droplets directly interfere with peptide-MHC-I complex formation and transport, significantly reducing cross-presentation

capacity (46,69). Furthermore, lipid peroxidation is closely linked to endoplasmic reticulum stress. Persistent oxidative stress activates the unfolded protein response pathway (e.g., IRE1 α -XBP1) in DCs, exacerbating lipid metabolism disorders and lipid droplet accumulation, thereby promoting the shift of DCs toward an immune-tolerant phenotype (72). Moreover, excessive PPAR γ activation promotes the uptake of PUFAs by DCs, while suppressing the GSH-GPX4 antioxidant system, increasing DC susceptibility to ferroptosis and thereby impairing their immune function (73). Notably, the immunological effects of ferroptosis are context-dependent. Unlike classical immunogenic cell death, under certain conditions, ferroptosis fails to activate protective immunity and may suppress DC function by releasing lipid peroxidation products, thereby limiting immune responses (45,74). Therefore, in lung cancer immunotherapy, precisely regulating the intensity and timing of ferroptosis induction, promoting ferroptosis in tumor cells while preserving stable DC function, may prove to be a crucial strategy for enhancing therapeutic efficacy. However, a considerable amount of the available evidence is still derived from non-lung tumor models or *in vitro* systems, and direct validation in human lung cancer remains limited. Therefore, ferroptosis should not be uniformly regarded as immunostimulatory in the context of dendritic cells. From the authors' perspective, its therapeutic value partly depends on whether tumor cell ferroptosis can be enhanced, while preserving DC antigen-processing and cross-presentation capacity.

Macrophage iron homeostasis and ferroptosis. Macrophages in the TME can induce ferroptosis in tumor cells by regulating iron and lipid metabolism, thereby influencing tumor growth and metastasis through modulation of iron uptake, storage and release (66,75). In lung cancer, alveolar macrophages exert antitumor effects through multiple mechanisms: On the one hand, M1-type alveolar macrophages secrete pro-inflammatory factors such as TNF- α , upregulate ACSL3 in tumor cells to accumulate polyunsaturated lipids and induce ferritin expression to reduce iron efflux via ferroportin internalization. This leads to iron overload and lipid peroxidation, triggering ferroptosis (76). Conversely, ROS/RNS generated by AMs deplete tumor cell GSH and impair GPX4 activity, suppressing antioxidant defenses and inducing ferroptosis (76). Additionally, alveolar macrophages deliver pattern recognition molecules via exosomes to activate the cGAS-STING signaling pathway in tumor cells, promoting autophagic ferroptosis and thereby inhibiting lung tumor growth (66).

Ferroptosis significantly influences macrophage polarization and immune function by regulating iron metabolism and lipid peroxidation within the TME. M1 macrophages exhibit a higher iron content, possessing pro-inflammatory and anti-tumor properties; conversely, M2 macrophages display lower iron levels, exhibiting immunosuppressive and pro-tumor functions, while being more sensitive to iron deprivation (76-79). Iron homeostasis directly regulates macrophage polarization: Iron deficiency promotes M2 conversion, while appropriate iron supplementation helps maintain the antitumor phenotype. Multiple mechanisms facilitate ferroptosis-driven M1 polarization. Ferroptosis inducers (e.g., HMGB1 release and TNF- α upregulation) activate macrophage inflammatory responses, promoting M1 phenotype conversion (80). The

radiation therapy-induced bystander effect releases irradiated tumor cell-derived microparticles that trigger macrophage ferroptosis and reprogram M2-TAMs toward an M1 phenotype, enhancing their antitumor effects (81). In lung cancer, dihydroartemisinin induces ferroptosis in TAMs and promotes their phenotypic shift toward M1 macrophages by activating NF- κ B signaling, providing a novel strategy for anti-lung cancer immunotherapy (82). Furthermore, the absence of the systemic xCT in macrophages enhances the response to ICIs, thereby improving the efficacy of immunotherapy in lung cancer (83). Additionally, upon uptake by macrophages, oxidized lipids and exosomes released by ferroptotic cells can trigger their transition to an inflammatory phenotype (47). In summary, ferroptosis synergistically shapes the immune activation state of macrophages by regulating iron homeostasis and inflammatory signaling within the lung cancer TME, positioning it as a critical target for future antitumor immunotherapy. These findings suggest that macrophages are not merely passive responders to ferroptotic stress, but active regulators of iron availability, inflammatory tone and ferroptosis sensitivity within the lung cancer microenvironment.

NK cell-mediated ferroptosis. Lung NK cells, as core effector cells of the innate immune system, play a pivotal role in anti-lung cancer immune surveillance. One key mechanism involves inducing ferroptosis in tumor cells to exert cytotoxic effects. Activated pulmonary NK cells secrete large amounts of IFN- γ , which downregulates the cystine transporters, SLC7A11 and SLC3A2, on the surface of lung cancer cells via the JAK1/2-STAT1 signaling pathway (84). This disrupts intracellular redox balance, directly initiating the ferroptosis pathway. Furthermore, NK cells enhance tumor cell sensitivity to ferroptosis by regulating key genes, such as ACSL4 (85) and modulating critical ferroptosis signaling axes including Keap1/NRF2/GPX4 (86). Within the TME, NK cells synergistically amplify tumor ferroptosis sensitivity when combined with other immune cells, such as chimeric antigen receptor (CAR) T-cells (87). Research further indicates that certain interventions (e.g., the Sophora alopecuroides-Taraxacum decoction) can synergistically inhibit non-small cell lung cancer growth with NK cells by inducing ferroptosis and altering the TIME (88).

On the contrary, ferroptosis in tumor cells dynamically modulates NK cell function, creating a bidirectional interaction. On the one hand, the ferroptotic process generates excessive lipid peroxides, which may impair NK cell function within the TME (89); activating the NRF2 antioxidant pathway of NK cells can reverse such functional suppression and restore their antitumor activity (89). On the other hand, DAMPs released by ferroptotic cells, such as HMGB1 and oxidized lipids, can upregulate NKG2D ligands (e.g., ULBP) on tumor cell surfaces, thereby enhancing NK cell recognition and killing (90). This establishes a 'ferroptosis-immune activation' positive feedback loop: In models combining nanoferric agents with NK therapy, enhanced NK cell function accompanies tumor regression, confirming that this feedback improves local immune responses (90). Furthermore, ferroptosis inducers (e.g., erastin) promote peripheral blood monocyte differentiation into NK cells via lipid peroxidation (91), suggesting potential effects on NK cell sources. Clinical analyses further

support the significance of this interaction: The elevated expression of ferroptosis-related genes (e.g., WDFY4) in lung cancer is associated with increased NK cell infiltration and improved patient survival (92). Collectively, tumor ferroptosis precisely modulates NK cell function through multiple pathways, regulating oxidative stress in the TME, releasing immune signals and influencing cellular differentiation, providing rationale for targeting ferroptosis to enhance immunotherapy. Nevertheless, several of these observations are still based on indirect analyses, combination models, or non-lung tumor systems, and direct mechanistic confirmation in lung cancer remains incomplete. From a therapeutic perspective, this bidirectional interaction suggests that ferroptosis-based strategies may synergize with NK-cell-mediated immunity only when oxidative stress is controlled within a range that preserves NK-cell fitness.

Neutrophil-driven regulation of ferroptosis. Recent studies have indicated that tumor-infiltrating neutrophils (TANs) exert antitumor effects in the lung cancer microenvironment by inducing ferroptosis (93,94). TANs generate large amounts of ROS and pro-oxidative enzymes, such as myeloperoxidase (MPO), directly attacking tumor cell membrane lipids and inducing lipid peroxidation (93,94). Similarly, in glioblastoma, neutrophils drive lipid peroxidation accumulation and ferroptosis-like death by delivering MPO-containing granules to tumor cells (94). Furthermore, neutrophil-secreted ferric-binding protein lipocalin-2 induces ferroptosis in surrounding cells, suggesting that secreted proteins regulate the iron metabolism and death susceptibility of neighboring cells (95). Notably, in lung cancer, the neutrophil-like population polymorphonuclear myeloid-derived suppressor cells highly express ferroptosis-related genes, and their iron accumulation correlates with potent T-cell suppression and immune evasion (96). Moreover, neutrophil extracellular traps suppress ferroptosis and impair CD8⁺ T-cell function by stabilizing SLC2A3 mRNA and other mechanisms, thereby promoting tumor growth (97). This demonstrates the bidirectional regulatory potential of neutrophil-derived factors on ferroptosis.

Conversely, ferroptosis in tumor cells dynamically regulates neutrophil behavior and function within the TIME. For instance, when cisplatin induces ferroptosis in non-small cell lung cancer, tumor cells upregulate and secrete chemokines, such as CXCL1/CXCL2 and other DAMPs, extensively recruiting neutrophils to the tumor site (98). Ferroptosis can also alter the functional state of neutrophils by affecting their iron metabolism and lipid peroxidation processes, thereby regulating immune evasion and tumor progression (47,99). Furthermore, ferroptosis may induce neutrophil apoptosis, further promoting the formation of an immunosuppressive microenvironment (100,101). This suggests that ferroptosis and neutrophils form a feedback pathway from cell death to immune regulation, jointly shaping the immune microenvironment landscape of lung cancer (Fig. 2).

It should be noted that the evidence supporting ferroptosis-mediated immune remodeling is uneven across different immune cell populations and tumor types. For CD8⁺ T-cells and selected macrophage pathways, relatively direct mechanistic evidence is available. By contrast, for several DC-,

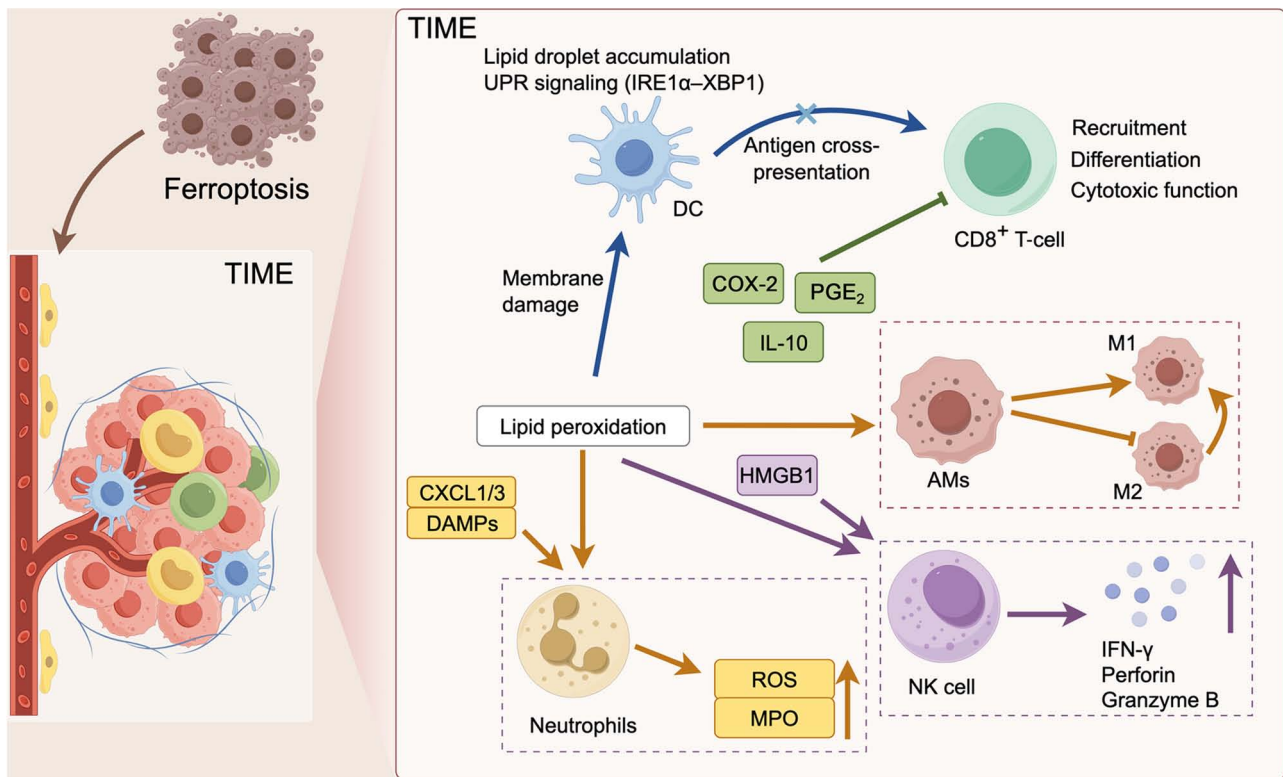


Figure 2. Regulation of the lung cancer tumor microenvironment driven by ferroptosis: Iron depletion in lung cancer cells generates abundant oxidized lipids, DAMPs, and inflammatory mediators, collectively reshaping the TIME. Lipid peroxidation induces membrane damage, activating lipid droplet accumulation and IRE1 α -XBP1-mediated the UPR in DCs, thereby impairing antigen cross-presentation and limiting effective CD8⁺ T-cell activation. Concurrently, COX-2-derived PGE₂ and IL-10 suppress CD8⁺ T-cell recruitment, differentiation and cytotoxic function. Iron-depleted debris reprograms alveolar macrophages toward an inflammatory phenotype, while oxidized lipids and HMGB1 stimulate NK cells to release IFN- γ , perforin and granzyme B. Concurrently, CXCL1/CXCL2-mediated neutrophil recruitment and ROS/MPO production further amplify lipid peroxidation, establishing a feedforward iron-depletion-inflammation cycle. The synergistic effects of iron depletion establish a lipid-driven immunometabolic network that simultaneously promotes tumor cell killing and immune dysfunction in lung cancer. DAMPs, damage-associated molecular patterns; TIME, tumor immune microenvironment; UPR, unfolded protein response; DC, dendritic cell; NK cell, natural killer cell; ROS, reactive oxygen species; MPO, myeloperoxidase; HMGB1, high-mobility group box 1; AMs, alveolar macrophages.

NK- and neutrophil-related mechanisms, a substantial proportion of the literature is still derived from non-lung tumor models, co-culture systems, or associative transcriptomic analyses. Therefore, caution is required when extrapolating these findings to the human lung cancer TIME.

4. Prospects for ferroptosis-immune cell combination therapy

Combined strategies of ferroptosis and immunotherapy. In lung cancer, the combination of ferroptosis and immunotherapy extends beyond enhancing the function of a single immune effector cell. Instead, it achieves synergistic effects by reshaping the anti-tumor network involving multiple immune cells. First, inducing ferroptosis in tumor cells to enhance the efficacy of ICIs represents the most well-established strategy to date. Ferroptosis induction promotes dendritic cell maturation and antigen presentation by releasing DAMPs and oxidized lipids, thereby enhancing initial T-cell activation efficiency (102). Concurrently, IFN- γ secreted by CD8⁺ T-cells downregulates anti-ferroptotic molecules such as SLC7A11 in tumor cells, forming a positive feedback loop that promotes ferroptosis and enhances anti-PD-1 treatment response (103). This process is accompanied by the recruitment and activation

of NK cells; TNF- α and IFN- γ secreted from these cells then further increases tumor cell sensitivity to ferroptosis (65).

Secondly, ferroptosis strategies can synergize with adoptive cell therapies. The inflammatory microenvironment induced by ferroptosis helps reduce the solid tumor matrix barrier and enhance immune cell infiltration. Moreover, engineered immune cells (such as CAR T-cells) can significantly increase tumor cell susceptibility to ferroptosis inducers by secreting IFN- γ , which upregulates ACSL4 expression in tumor cells (87). Furthermore, differentially regulating the ferroptosis of immune cells themselves provides a new dimension for combination therapy. Studies have indicated that immunosuppressive cell populations (e.g., M2 macrophages and Tregs) exhibit distinct characteristics in lipid metabolism and iron homeostasis regulation, potentially rendering them more susceptible to ferroptosis under specific conditions. Selectively attenuating these cells can indirectly enhance the antitumor effects of CD8⁺ T-cells and NK cells (104,105). In summary, the ferroptosis-immunotherapy combination strategy exhibits systemic characteristics involving the coordinated participation of multiple immune cell types.

However, the translational value of such combinations depends not only on antitumor efficacy, but also on whether ferroptotic stress can be restricted to tumor-promoting

Table I. Lung cancer-specific microenvironmental and metabolic features that sensitize tumors to ferroptosis.

Feature category	Lung cancer-specific features	Impact on ferroptosis	(Refs.)
Hyperoxic environment	Alveolar oxygen partial pressure=100 mmHg, placing lung cancer cells under chronic oxidative stress	Enhances ROS and Fenton reactions, significantly lowering ferroptosis thresholds	(48)
Iron homeostasis adaptation	Tumor cells upregulate TFR1 to adapt to the hyperoxic environment	Increases the pool of free Fe ²⁺ , amplifying lipid peroxidation	(48,49)
Lipid supply environment	Alveolar surface active substances and phospholipids are abundant, with ample PUFAs in the microenvironment	Provides ample substrates for lipid peroxidation, heightening ferroptosis susceptibility	(50,51)
PUFA-enriched environment	Lung cancer cells upregulate CD36, extensively uptake AA and other PUFAs	Boosts membrane lipid peroxidation potential, promoting ferroptosis onset	(50,51)
Sublethal iron death stress	Ferroptosis occurs regionally, recurrently, and non-lethally	Establishes sustained oxidative signaling involving lipids and iron	(33,51, 54,55)

ROS, reactive oxygen species; PUFAs, polyunsaturated fatty acids; TFR1, transferrin receptor 1; AA, arachidonic acid.

compartments without damaging protective immune populations.

Challenges and translational priorities for ferroptosis-immunotherapy combinations. Despite demonstrating significant potential in lung cancer, the clinical translation of ferroptosis-immunotherapy combinations faces multifaceted challenges. Treatment safety is a primary concern, as ferroptosis inducers may disrupt iron homeostasis in normal tissues, while immune-related inflammatory responses could amplify toxicity risks (106). Therefore, limiting the effects of ferroptosis through targeted delivery or localized activation strategies is a critical prerequisite for the feasibility of combination regimens. Secondly, the heterogeneous response of immune cells to ferroptosis adds to the complexity of regulation. Beyond tumor cells, CD8⁺ T-cells, DCs and NK cells may also sustain functional impairment in high lipid peroxidation environments, and PD-1 signaling has been demonstrated to promote ferroptosis in CD8⁺ T-cells and impair their effector function (107). Concurrently, tumor cells can acquire ferroptosis tolerance by upregulating pathways, such as FSP1 and NRF2-HO-1, further limiting the sustained efficacy of combination therapies (108). Furthermore, the lack of reliable predictive and monitoring biomarkers remains a critical barrier to the precise implementation of combination therapies. Existing studies suggest that GPX4 expression levels and the proportion of iron-killed immune cells are associated with the treatment response; however, their predictive accuracy and universality require further validation (102,109). Future efforts are required to integrate multi-omics analyses with liquid biopsy technologies to establish comprehensive models for dynamically assessing iron-killed sensitivity and immune status.

Another key issue is the uneven strength and reproducibility of the current evidence. Although some mechanisms, such as the IFN- γ -mediated suppression of SLC7A11/system

Xc⁻ and enhanced tumor ferroptosis are supported by multiple functional studies (17,62), others remain based largely on single-model observations or pharmacological induction without sufficient genetic validation. Thus, the key question is not simply whether ferroptosis should be induced, but in which cells, at what stage, and to what extent it should be modulated. Future studies are required to prioritize more precise and cross-validated strategies to maximize tumor killing, while minimizing collateral damage to antitumor immune cells (110).

Clinical translation and early trial signals. The clinical translation of ferroptosis-based therapy in lung cancer remains at an early stage. At present, the majority of the available evidence is still preclinical, and lung cancer-specific clinical validation is limited (111,112). Nevertheless, early-phase clinical exploration has begun in advanced solid tumors. For example, ClinicalTrials.gov lists trials, such as NCT06048367 and NCT07433283, which evaluate iron-based formulations designed to induce ferroptosis in patients with advanced solid malignancies, potentially including lung cancer cases. These trials highlight growing translational interest in ferroptosis-targeting strategies, but also indicate that the field is still primarily focused on safety, feasibility, and delivery optimization rather than biomarker-guided precision application (113). Therefore, before ferroptosis-based combinations can be broadly integrated into lung cancer immunotherapy, key issues such as tumor-selective targeting, dose-limiting toxicity, immune-compatible scheduling and patient stratification need to be addressed (114).

5. Conclusion and future perspectives

In lung cancer, ferroptosis does not merely function as an effector form of cell death for tumor clearance. Rather, it is deeply embedded within the dynamic regulation of the

TIME due to its high dependence on metabolic state and redox balance. In lung cancer, a tumor type chronically exposed to high oxygen tension, active lipid metabolism and easily disrupted iron homeostasis, ferroptosis often persists regionally, sublethally and recurrently. It is repeatedly sensed by diverse immune cells through the release of lipid peroxidation products, iron-related metabolites and inflammatory signals. CD8⁺ T-cells, DCs, macrophages, NK cells and neutrophils participate in this process, both inducing ferroptosis in tumor cells and being feedback-regulated by ferroptosis-related signals, forming a complex and dynamic immune-metabolic interaction network. This network can amplify antitumor immune responses under specific conditions, while also promoting the formation of TIME in the context of chronic oxidative stress and metabolic reprogramming. A systematic understanding of this bidirectional regulatory system may provide insight beyond single-target or single-cell-type therapeutic approaches. In the future, by precisely modulating the intensity, spatial distribution and interaction patterns of ferroptosis with different immune cells, combined with biomarker-guided patient stratification, ferroptosis holds promise as a key regulatory module for enhancing the efficacy of lung cancer immunotherapy.

To fully decode the immunometabolic hub of ferroptosis within the TIME, future research should transition from static, isolated models to high-resolution, multidimensional frameworks. Recent advances in single-cell sequencing and spatial transcriptomics have fundamentally transformed our ability to map TIME heterogeneity, providing detailed spatial landscapes of lung cancer immunity (115,116). Concurrently, evaluating the immense complexity of these interactions requires drawing inspiration from broader systems biology methodologies. For instance, the integration of multi-modal artificial intelligence algorithms has significantly advanced precision prognostic modeling (117), while network pharmacology and bioinformatic topologies provide powerful tools for deciphering multi-target mechanisms, environmental stress responses, and complex therapeutic networks (118,119).

Applying these systemic analytical approaches to lung cancer will help clarify the dynamic feedback loops between ferroptotic tumor cells and the immune system. Furthermore, precisely defining the roles of specific immune subsets, such as the emerging impact of memory T-cell signatures in enhancing cancer immunotherapy (120), alongside the critical role of innate immune sensing (e.g., STING or TLR pathway activation triggered by ferroptotic damage) (121,122) is essential. Ultimately, integrating these cross-disciplinary computational methods with deep innate and adaptive immune profiling may provide the necessary foundation for biomarker-guided patient stratification and rational ferroptosis-based therapeutic combinations.

In conclusion, these findings suggest that ferroptosis should be viewed not merely as a tumoricidal event, but as a context-dependent immunometabolic hub that shapes both antitumor immunity and immunosuppressive remodeling in lung cancer.

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Competing interests

The authors declare that they have no competing interests.

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