

Emerging dual role of ferroptosis in lung cancer (Review)

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Received November 14, 2024; Accepted July 4, 2025

DOI: 10.3892/or.2025.8974

Abstract. Lung cancer (LC) is the second most frequently diagnosed malignancy worldwide and has the highest mortality rate among all types of cancer. Despite advancements in treatment strategies, the overall survival rate for affected individuals remains low. Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation and accumulation of reactive oxygen species, serves a role in LC. The present review aimed to explore the dual role of ferroptosis in LC, examining both its pathological and therapeutic implications. Ferroptosis contributes to tumor progression, modulates the immune microenvironment and influences treatment resistance. Conversely, it also enhances the efficacy of immunotherapy, increases radiosensitivity and decreases chemotherapy resistance. The present study aimed to summarize the potential of ferroptosis-based strategies, including the use of nanomaterials and combination therapy, to inform future research and therapeutic approaches.

Contents

1. Introduction
2. Molecular mechanisms of ferroptosis

3. Ferroptosis: A double-edged sword in LC
4. Conclusion

1. Introduction

Lung cancer (LC) is the second most common malignancy globally and the leading cause of cancer-associated deaths, accounting for 11.4% of new cases and 18% of overall cancer mortality (1). Of newly diagnosed LC cases, ~85% are small cell lung cancer (SCLC) and 15% are non-SCLC (NSCLC) (2). Standard treatment options include surgery, chemotherapy, radiation and targeted therapies. However, >50% of patients succumb to the disease within the first year of diagnosis, with a 5-year survival rate <18% (3). Drug resistance remains a challenge in treatment, as most patients with advanced NSCLC develop resistance to current therapies, leading to disease progression (4). These factors highlight the need for novel therapeutic targets, strategies to overcome drug resistance and approaches to improve survival of patients with LC.

Ferroptosis is distinguished from other forms of oxidative iron-dependent programmed cell death (PCD), such as necrosis, autophagy and apoptosis (5). Ferroptosis is characterized by membrane rupture, reduced mitochondrial volume, loss of mitochondrial cristae and chromatin condensation (6). This process is initiated by the accumulation of pro-ferroptotic molecules that induce lipid peroxidation through the generation of reactive oxygen species (ROS) facilitated by iron (7). Ferroptosis predominantly relies on lipid-derived ROS production but does not engage key regulators of other PCD processes, such as caspases, mixed lineage kinase domain-like protein or Gasdermin-D (GSDMD) (5).

Ferroptosis has emerged as a key mechanism in tumor suppression: Extensive research has explored its role in malignancy, with studies indicating that ferroptosis inhibits cancer progression through pharmacological and cytokine-induced pathways (8-11). Notably, drug-resistant cancer cells, particularly those with high metastatic potential, are more susceptible to ferroptosis (12). Furthermore, incorporating ferroptosis into conventional therapy has been investigated in various cancers, including hepatocellular carcinoma and glioblastoma (13). Ferroptosis has shown

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Key words: ferroptosis, lung cancer, mechanism, iron, therapeutic strategy

promise in LC as well, with studies demonstrating its effectiveness in eliciting therapeutic responses to experimental reagents such as erastin and (1S,3R)-2-(2-chloroacetyl)-2,3,4,9-tetrahydro-1-[4-(methoxycarbonyl)phenyl]-1H-pyrido[3,4-b]indole-3-carboxylate, approved drugs such as sulfasalazine and artemisinin, ionizing radiation (IR) and cytokines such as IFN- γ and TGF β 1 (14-17). This leads to tumor suppression in various cancer types (18). Consequently, the induction of ferroptosis offers an advancement in cancer treatment strategies. The present review aimed to examine the dual role of ferroptosis in LC, analyzing the molecular mechanisms, prognostic implication and therapeutic potential of ferroptosis regulators.

2. Molecular mechanisms of ferroptosis

Ferroptosis is characterized by iron-dependent peroxidation of unsaturated phospholipids and the subsequent accumulation of ROS. Its molecular mechanisms primarily involve lipid, iron and amino acid metabolism (Fig. 1).

Lipid metabolism and ferroptosis. Lipid metabolism serves a critical role in ferroptosis, a form of regulated cell death driven by the accumulation of lipid peroxides due to the oxidation of polyunsaturated fatty acids (PUFAs). PUFAs, including ω -3 and -6 Fas (19), possess multiple double bonds and are involved in various physiological functions in cells, such as maintaining cell membrane fluidity, modulating inflammatory responses, regulating gene expression and serving as precursors for bioactive lipid mediators (prostaglandins, leukotrienes, and resolvins) that mediate immune and metabolic processes (20). Enzymes involved in lipid metabolism regulate ferroptosis by promoting lipid peroxidation. In phospholipid metabolism, acyl-CoA synthetase long chain family member 4 (ACSL4) activates PUFAs, such as arachidonoyl and adrenal acid, facilitating their conversion into PUFA-CoA (21). The subsequent incorporation of PUFAs into phospholipids is driven by lysophosphatidic acid transferase 3 (22). Arachidonoyl- and adrenal-linked phospholipids are then oxidized by ALOX15, generating lipid peroxides that trigger ferroptosis (23).

Iron metabolism and ferroptosis. Iron metabolism imbalance is associated with pathological conditions such as neurodegenerative disease (24), hereditary hemochromatosis (24) and cancer progression (25), and serves a pivotal role in ferroptosis. Ferroptosis is associated with iron-dependent lipid peroxidation. Iron is primarily absorbed from dietary sources or released through the natural breakdown of red blood cells during aging. When transferrin (TF) binds to Fe³⁺ on the cell membrane, it forms TF-Fe³⁺, which is internalized by transferrin receptor 1 (TFR1). This is followed by the release of Fe³⁺ from the endosome into the cytosol via divalent metal transporter 1, facilitated by the six-transmembrane epithelial antigen of prostate 3 (26,27). Ferroportin releases Fe²⁺ from ferritin, and ferroptosis results from the disruption of the iron absorption, depletion and recycling balance, leading to the generation of highly reactive lipid peroxides via interaction of free Fe²⁺ with hydrogen peroxide (26,27). Several proteins and regulatory factors involved in iron metabolism influence ferroptosis. TFR1, a key iron transporter, is regulated

by hypoxia-inducible factor-1 and iron regulatory protein, leading to increased cellular iron uptake and susceptibility to ferroptosis. Conversely, ferroptosis is inhibited by decreasing iron intake (28). In the absence of TFR1, ZIP14, a metal cation transporter, mediates iron entry and induces ferroptosis (29). Additionally, autophagy is associated with ferroptosis. Nuclear receptor coactivator 4 (NCOA4) serves a role in ferritin degradation, helping to maintain intracellular iron balance by modulating ferritin autophagy (30). When NCOA4 engages in ferritin autophagy, cells become more susceptible to ferroptosis (31). Furthermore, CDGSH iron-sulfur domain 1 (CISD1) and CISD2 are key for mitochondrial iron transport, with inhibition of CISD1 promoting erastin-dependent ferroptosis and iron-mediated mitochondrial lipid peroxidation (32). By contrast, CISD2 inhibition accelerates sulfasalazine-induced ferroptosis by increasing mitochondrial ferrous iron and lipid ROS levels (33). These findings highlight the impact of iron metabolism on ferroptosis.

Amino acid metabolism and ferroptosis. Almost every cell in the body contains the tripeptide glutathione, composed of L-glutamyl-L-cysteinylglycine (34). The enzyme γ -glutamylcysteine synthetase (γ -GSH) serves a pivotal role in glutathione synthesis by catalyzing the conversion of glutamate and cysteine into γ -glutamylcysteine. A key aspect of ferroptosis is the ability of GSH to convert lipid hydroperoxides, produced during cell metabolism, into less harmful lipid alcohols (35,36). GSH exists in two forms: Reduced glutathione (GSH) and oxidized glutathione disulfide (GSSG) (34). Numerous pathways facilitate glutathione synthesis. One such pathway involves the conversion of NADPH to NADH via the action of glutathione reductase. Alternatively, GSH is efficiently synthesized by utilizing intracellular cysteine (L-cysteine), glycine and glutamate, with the assistance of specific enzymes (37,38). Cysteine is an essential precursor, obtained either via the transsulfuration pathway during methionine synthesis or the conversion of extracellular cysteine. The glutamate-cystine antiporter (system Xc-), a complex of SLC3A2 and SLC7A11, facilitates cystine uptake into cells. Glutaminase 2 converts glutamine into Glu, a precursor for various organic molecules. Additionally, SLC38A1 and SLC1A5 receptors mediate the entry of glutamine into cells from the extracellular environment. GSH serves a pivotal role in converting potentially toxic lipid hydroperoxides into less harmful lipid alcohols, thus preventing cell damage (39).

Several compounds are being investigated for their ability to modulate amino acid metabolism, including glutathione peroxidase 4 (GPX4) and cysteine (40). Various pathways regulate cysteine availability, with much research focusing on the regulation of SLC7A11 (41). In HT-1080 fibrosarcoma cells, upregulation of SLC7A11 enhances resistance to ferroptosis, while downregulation of this gene increases susceptibility to ferroptosis (41).

Tumor suppressor gene p53 influences immune response, metabolism and neurodegeneration in a context-dependent manner, modulating ferroptosis either by inhibiting or promoting its activation (42-44). P53 downregulates SLC7A11 expression, which limits cystine uptake via system Xc-, thereby reducing the antioxidant capacity of cells, increasing lipid ROS levels and triggering ferroptosis.

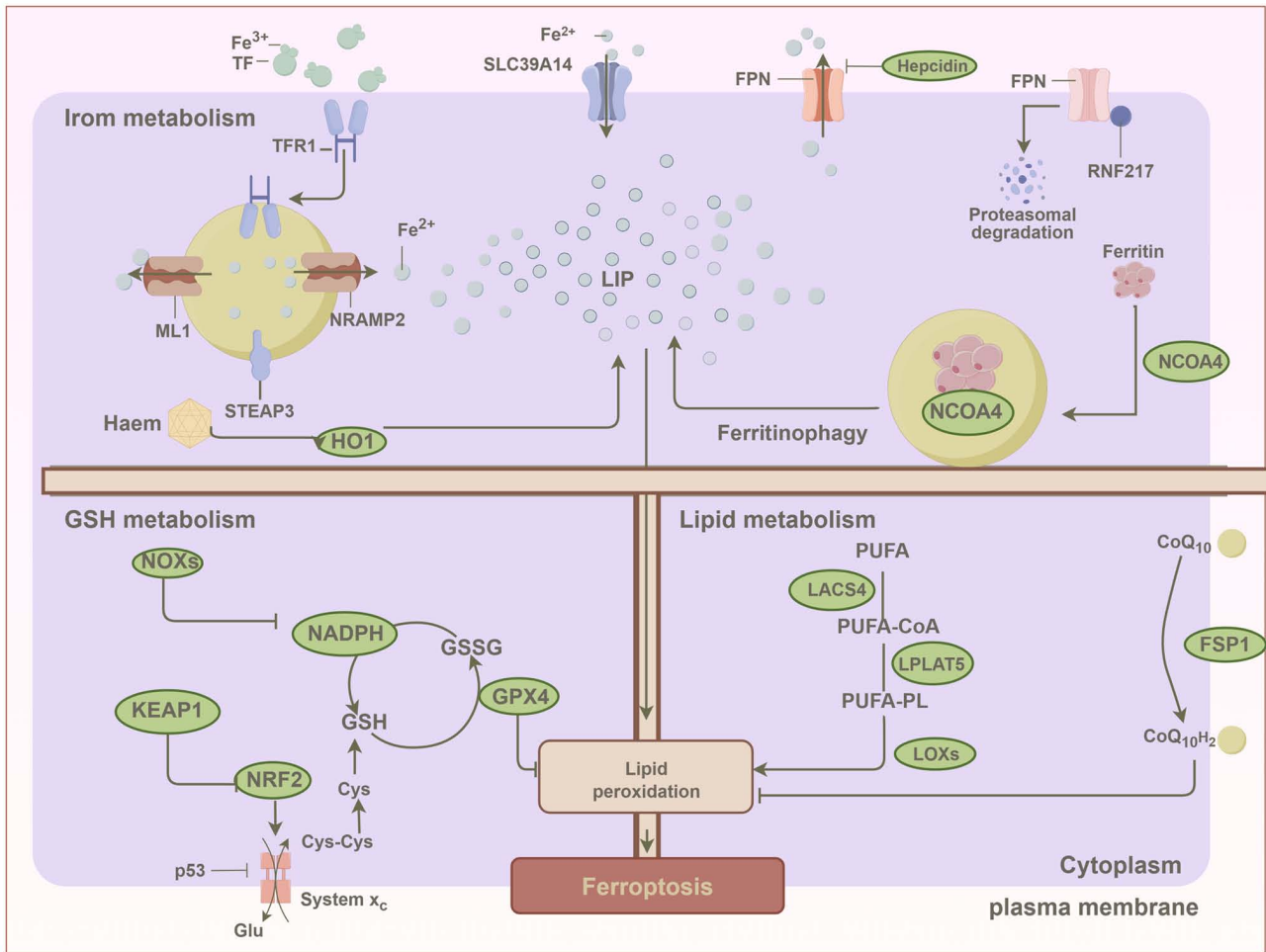


Figure 1. Molecular mechanisms of ferroptosis. Iron is taken up via TFR1 and released into the labile iron pool (LIP) through various transporters and reductases. Excess iron can promote the generation of reactive oxygen species (ROS), which contribute to lipid peroxidation. Iron export is mediated by ferroportin (FPN), and its regulation involves hepcidin and other proteins. Polyunsaturated fatty acids (PUFAs) are activated by acyl-CoA synthetase (LACS4) and incorporated into phospholipids (PLs) in the membrane. Lipid peroxidation is initiated by enzymes like lipoxygenases (LOXs) and can be amplified by the depletion of GSH and the inactivation of glutathione peroxidase 4 (GPX4). CoQ10 and ferroptosis suppressor protein 1 (FSP1) act as antioxidants to counteract lipid peroxidation. GSH metabolism: The system Xc- (composed of SLC3A2 and SLC7A11) imports cystine for GSH synthesis, which is crucial for GPX4 activity. NRF2 regulates antioxidant responses, while p53 can modulate ferroptosis sensitivity. Additionally, proteins like NCOA4 mediate ferritinophagy, releasing iron from ferritin to increase LIP and promote ferroptosis. TFR, Transferrin receptor; NRAMP, Natural resistance-associated macrophage protein; ML, Metal transporter STEAP, Six-transmembrane epithelial antigen of the prostate; HO, Heme oxygenase; LIP, Labile iron pool; SLC39A14, Solute carrier family 39 member 14; FPN, Ferroportin; RNF, Ring finger protein; NCOA, Nuclear receptor coactivator; GSH, Glutathione; NOX, NADPH oxidase; PUFA, Polyunsaturated fatty acid; LACS, Long-chain acyl-CoA synthetase; PL, phospholipid; LOX, Lipoxygenase; CoQ, Coenzyme Q; FSP, Ferroptosis suppressor protein.

Nuclear factor erythroid 2-related factor 2 (Nrf2) serves a critical role in regulating lipid peroxidation. It controls genes such as heme oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO1), which are involved in cell iron metabolism and oxidative stress responses. Activation of the Nrf2-HO-1 axis upregulates system Xc-, increasing cell resistance to ferroptosis. Furthermore, the protein p62 stabilizes Nrf2 by preventing its degradation, thereby enhancing its accumulation. When p62 is knocked down via RNA interference, the expression of NQO1, HO-1 and ferritin heavy chain is decreased, exacerbating erastin-induced ferroptosis (45,46). To delay ferroptosis, the p53/p21 axis decreases GSH consumption, although further studies are needed to elucidate how p21 contributes to increased GSH synthesis (47). Erastin inhibits system Xc-, decreasing GSH uptake and GPX4 activity, ultimately triggering ferroptosis by lowering cell antioxidant defenses and increasing lipid

ROS. Ras synthetic lethal 3 inactivates GPX4, further promoting ferroptosis (48).

3. Ferroptosis: A double-edged sword in LC

Pathogenic role of ferroptosis in LC

Ferroptosis and the development of LC. Epidemiological and laboratory studies have established an association between iron consumption and the development of LC (49,50). Increased dietary iron intake is associated with a 13% decrease in the risk of developing LC over an average follow-up period of 7 years (51).

A case-control study in the USA, involving 923 patients and 1,125 healthy controls, found an association between heme iron intake and decreased risk of LC, suggesting that dietary iron consumption may serve a significant role in LC development (52). Iron, along with other essential minerals, is key

for maintaining DNA integrity, as it helps prevent oxidative DNA damage (52). Conversely, both iron excess and deficiency contribute to oxidative DNA damage (53), which may increase the risk of cancer development (54). Epidemiological data have further highlighted a link between DNA repair capacity and an increased risk of LC (55,56). High iron levels induce apoptosis, necrosis and ferroptosis in experimental settings (57). Erastin, initially identified as a ferroptosis inducer (FIN), promotes iron-dependent cell death by reducing antioxidants via the inhibition of cystine-glutamate antiporters (58). In a BALB/c mouse model of LC, overexpression of TFR1 accelerates tumor growth, decreases survival time and enhances iron uptake by LC cells (59). Additionally, heat shock protein (HSP) B1 acts as a negative regulator of ferroptosis, preventing iron accumulation by inhibiting TFR1 production (60). Despite these findings, the mechanisms by which iron influences LC remain unclear, although its potential to trigger ferroptosis and generate ROS via the Fenton reaction suggests a significant role in the disease process.

The GPX family has been recognized as a key contributor to cancer progression, with elevated levels of GPXs, including GPX8 and GPX4, observed in LC cell lines (61). The increased expression of GPX8 is associated with poorer clinical outcomes in patients with NSCLC. Mechanistically, GPX8 inhibits tumor cell death and promotes cell motility and invasion, thereby facilitating tumor progression (62). Elevated GPX4 levels enhance LC cell proliferation and confer resistance to ferroptosis (63). By contrast, RSL3 inhibits GPX4 function, thereby decreasing LC cell migration and invasion (64). Ferrostatin-1 (Fer-1) effectively reverses these effects, highlighting its potential therapeutic value (65). Inhibiting GPX4 has emerged as a promising strategy to induce ferroptosis in LC cells, providing new avenues for LC treatment. Ferroptosis suppressor protein 1 (FSP1) is a key regulator of ferroptosis, acting independently of the GPX4 pathway (66). FSP1 inhibits ferroptosis via its interaction with ubiquinone, also known as coenzyme Q10 (CoQ10) (67). When GPX4 gene expression is downregulated, FSP1 undergoes cardamom acylation and modulates NAD(P)H to decrease CoQ10 levels, preventing lipid peroxidation and inhibiting ferroptosis (67). The expression of FSP1 in LC cells enhances resistance to ferroptosis, whereas inhibiting FSP1 counteracts this resistance (67). The advent of EGFR tyrosine kinase inhibitors (EGFR-TKIs) and the identification of EGFR-activating mutations have revolutionized LC therapy (68). Ferroptosis-inducing therapies could be used to treat solid tumors, including LC, particularly in cases where the cells exhibit intrinsic or acquired resistant to EGFR-TKIs (69).

Ferroptosis and tumor immune microenvironment (TIME) of LC. The tumor microenvironment (TME) is a complex and dynamic multicellular ecosystem primarily composed of cancer and immune cells and the extracellular matrix (ECM) (70). Within this environment, tumor cells thrive and propagate. Immune cells, including T cells, tumor-associated macrophages, myeloid-derived suppressor cells, dendritic cells (DCs), B cells and natural killer cells, collectively form the TIME (71). These immune cells are key in tumorigenesis, recurrence and metastasis. While immune cells in the TIME regulate cancer cell proliferation, cancer cells, in turn, can influence TIME by secreting signaling molecules that

induce immune tolerance. Ferroptotic cancer cells modulate anti-cancer immunity by releasing signaling molecules into the ECM (72-74). By secreting IFN- γ , CD8⁺ T lymphocytes within the TIME trigger ferroptosis and enhance lipid peroxidation, which promotes anti-tumor responses. Ferroptosis in immune cells within TIME also influences anti-cancer immunity (75). These findings indicate the complex association between ferroptosis and TIME, highlighting the importance of understanding how ferroptosis regulates TIME to develop novel immunotherapeutic strategies for LC.

Immunogenic cell death refers to the death of tumor cells that may be triggered either genetically or pharmacologically. Ferroptotic tumor cells typically undergo plasma membrane rupture, releasing immunostimulatory signals that include 'find me' and 'eat me' signals. These signals, such as damage-associated molecular patterns, including high mobility group box 1 protein (HMGB1), ATP and DNA (76,77), help immune cells such as DCs and macrophages identify and target dying tumor cells, thereby activating anti-tumor immunity and recruiting additional immune cells (78,79). For example, certain FINs prompt tumor cells to secrete HMGB1, which binds to receptors for advanced glycosylation end-products, modulating macrophage inflammatory responses (73). Additionally, early ferroptotic tumor cells induce phenotypical changes in DCs, triggering effects akin to vaccination (76). Ferroptotic cancer cells are more likely to provoke tumor-specific immune responses, enhancing the efficacy of immune checkpoint inhibitors (ICIs) (80,81).

While ferroptotic tumor cells stimulate immune responses, the molecules they release may also contribute to pro-tumor immunity. Studies in LC have demonstrated that ferroptosis facilitates an immunosuppressive microenvironment (82,83). The release of oxidized phospholipids such as 1-stearoyl-2-15(S)-HpETE-sn-glycero-3-PE (15-HpETE-PE), oxidized arachidonoids and 4-Hydroxynonenal (4-HNE) (72,79,84) impairs antigen cross-presentation and effective antitumor immunity (85,86). These lipids suppress immune responses in multiple ways. Notably, oxidized phosphatidylcholine activates Nrf2 and promotes the differentiation of T helper 17 cells, inhibiting DC maturation (87,88). The TME can become saturated with 15-HpETE-PE, both before and after the death of ferroptotic tumor cells. Exposure of epithelial and immune cells to 15-HpETE-PE accelerates ferroptosis, contributing to a pro-tumor immune environment (89,90) (Fig. 2).

Ferroptosis and therapy resistance of LC. Ferroptosis contributes to tumor development, proliferation and immune evasion through multiple pathways. Ferroptosis has been associated with immune infiltration in LC, facilitating leukocyte transendothelial migration, modulating M2 macrophages and promoting effective immune milieu infiltration (91). This exerts an immunosuppressive effect, accelerating cancer progression (91). An inverse association exists between most immune checkpoint proteins and GAPDH expression. Although GAPDH is highly expressed in LC, its levels decrease during ferroptosis. This suggests the increased production of immune checkpoint proteins during ferroptosis may help tumor cells evade immune surveillance (92). However, the precise regulatory role of GAPDH in ferroptosis remains unclear. Further

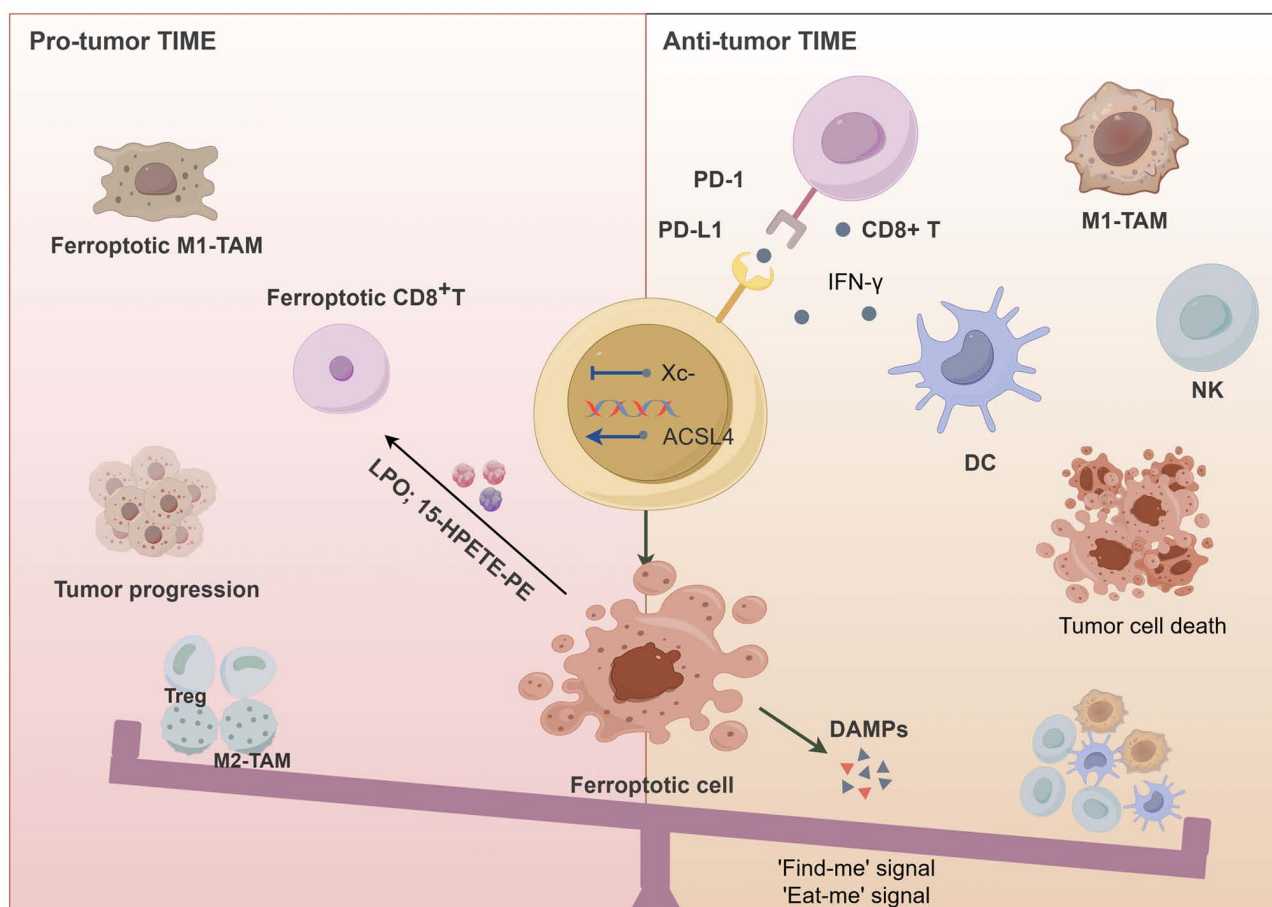


Figure 2. Ferroptosis and TIME of lung cancer. Ferroptotic M1-TAMs and ferroptotic CD8⁺ T cells contribute to tumor progression. Lipid peroxidation (LPO) products like 15-HPETE-PE are released, which may promote an immunosuppressive environment. Tregs and M2-TAMs further support tumor growth and immune evasion. Ferroptotic tumor cells release damage-associated molecular patterns (DAMPs), which act as 'find-me' and 'eat-me' signals to recruit and activate immune cells. Natural killer (NK) cells, dendritic cells (DCs), and M1-TAMs are involved in recognizing and eliminating tumor cells. CD8⁺ T cells are activated by interferon-gamma (IFN- γ) and can recognize tumor cells expressing PD-L1, with the interaction between PD-1 and PD-L1 being a key checkpoint in the immune response. TIME, Tumor immune microenvironment; TAM, Tumor-associated macrophage; Treg, Regulatory T cell; LPO, Lipid peroxidation; HPETE-PE, Hydroperoxy eicosatetraenoic acid-phosphatidylethanolamine; DAMP, damage-associated molecular pattern; NK, Natural killer cell; DC, Dendritic cell; PD-L, programmed death-ligand.

research into its specific role and mechanisms may reveal novel therapeutic strategies for LC.

Ferroptosis has been observed in NSCLC cells exposed to IR and other harsh environmental factors, as these stressors promote the production of ACSL4 and ROS (93). Another adaptive response induced by IR is the upregulation of ferroptosis inhibitors, such as GPX4 and SLC7A11. This inhibition of ferroptosis contributes to radioresistance, triggered by SLC7A11 expression in response to IR-induced stress (93). The use of FINs can decrease radioresistance in resistant cell lines and xenograft tumors. Additionally, radiation-induced ferroptosis is associated with an enhanced response to treatment and improved survival in patients with esophageal cancer undergoing radiotherapy (93).

Value of ferroptosis in LC. Although the precise physiological function of ferroptosis remains unclear, its involvement in numerous types of human disease has been well-documented (94-98). Pharmacological modulation of ferroptosis has emerged as a promising therapeutic approach for cancer and ischemia-reperfusion injury (IRI) in various preclinical rat models (94,95). Ferroptosis is implicated in a wide array

of diseases. For example, in neurodegenerative conditions such as Alzheimer's, Parkinson's and Huntington's diseases, elevated iron levels in the central nervous system are linked to oxidative stress, lipid peroxidation and cell death, all characteristic features of ferroptosis (96). In cardiovascular disease, ferroptosis contributes to IRI, where blood flow restoration following ischemia triggers iron influx and the generation of ROS, leading to ferroptotic cell death (97). In cancer, ferroptosis has emerged as a potential therapeutic target (95). The metabolic imbalance caused by GSH depletion or the inactivation of GPX4 can induce ferroptosis in cancer cells (98). Small molecule-induced ferroptosis has demonstrated significant inhibition of tumor growth and enhances the sensitivity of chemotherapeutic drugs, particularly in drug-resistant conditions (95). For example, in breast cancer, inducing ferroptosis significantly suppresses cancer cell proliferation and invasion (99).

Directly inducing ferroptosis in cancer cells is a viable strategy. Numerous studies have shown that enhancing ferroptosis in combination with standard therapy improves therapeutic efficacy and offers a novel approach to LC treatment (100-103). Ferroptosis is frequently used alongside

chemotherapy, radiation and immunotherapy in various therapeutic regimens (100-103).

Combination treatment options targeting ferroptosis in LC

Reversing chemotherapy resistance. The persistent challenge of drug resistance is a notable obstacle in cancer therapy, particularly with treatments such as platinum-based chemotherapy for LC. Increasing empirical evidence highlights the potential of ferroptosis in overcoming drug resistance in LC treatment (95,104). The combination of ferroptosis-targeting agents with established drug resistance therapies presents a promising strategy for tackling drug-resistant LC. Erastin and sorafenib effectively induce ferroptosis in cisplatin-resistant cancer cells, as demonstrated by Li *et al* (105). Whether used alone or in combination with lower doses of cisplatin, these agents substantially decrease the proliferation of NSCLC cells possessing cisplatin-resistant characteristics (N5CP cells). The combination of gefitinib with betulinol offers a novel therapeutic approach to overcome gefitinib resistance in EGFR wild-type/KRAS-mutated NSCLC cells (106). Thus, FINs may represent a breakthrough in the treatment of EGFR-TKI-resistant LC. Recent studies have identified a novel NQO1-mediated strategy for targeting drug-resistant NSCLC cells, which may induce ferroptosis via NQO1 inhibition (107).

The observation that the ferroptosis inhibitor Fer-1 mitigates the effects of erianin on LC cell sphere formation suggests that erianin may suppress stemness in LC by facilitating ferroptosis (108). Isoorientin ($C_{21}H_{20}O_{11}$ with a molecular weight of 448.4 g/mol, can overcome drug resistance in LC by activating the Nrf2/GPX4 pathway, thereby inducing ferroptosis (104). Isoorientin enhances the anti-tumor effects of cisplatin by decreasing the survival of drug-resistant cells, depleting glutathione levels and significantly increasing intracellular iron, malondialdehyde and ROS levels. Isoorientin counters drug resistance by downregulating sirtuin 6/Nrf2/GPX4 expression (104). The use of small molecules and compounds that regulate ferroptosis represents an innovative approach to improving chemotherapy outcomes (109), potentially serving as a solution to chemotherapy resistance (110). FIN56 promotes ferroptosis via the inhibition of autophagy-dependent protein degradation of GPX4, acting as a type 3 FIN, which represent a distinct class of ferroptosis-inducing agents that promote cell death by selectively inhibiting autophagy-dependent degradation of GPX4, rather than directly targeting GPX4 activity or GSH synthesis (111). When combined with cisplatin, FIN56 enhances its cytotoxic effect on LC cells, suggesting that inducing ferroptosis may be an effective strategy for resistant cancer cells (112). Similarly, RSL3, through the inhibition of GPX4, triggers ferroptosis and enhances antitumor activity of cisplatin both *in vitro* and *in vivo* (113). Previous research has also highlighted the potent anti-tumor effects of propofol, a commonly used intravenous anesthetic (114,115). Propofol enhances cytotoxic effects of cisplatin in LC (116-118) by modulating cisplatin resistance through FIN via the upregulation of the microRNA (miR)-7445p/miR-615-3p pathway and inhibition of GPX4.

Increasing radiosensitivity. IR has been shown to induce ferroptosis (93). The protein RNA-binding motif Single-Stranded Interacting Protein 1 (RBMS1) is associated with radioresistance in LC by regulating the expression

of SLC7A11. A previous study have identified a potential therapeutic strategy for LC, demonstrating that N-desmethyl imipramine hydrochloride modulate RBMS1 levels in IR-resistant LC cells, thereby enhancing their susceptibility to radiation therapy (119). Moreover, heme, known for its ability to neutralize free radicals and protect cells from oxidative damage, increases the initial generation of ROS in LC cells exposed to radiation (120). This enhancement of ROS production accelerates lipid breakdown, promoting ferroptosis and increasing LC cell vulnerability to radiation (120).

Ongoing studies consistently reveal an association between LC radiation sensitivity and ferroptosis (121-123). Research using compounds such as 4-chlorobenzoic acid has shown that the radiation tolerance of KEAP1, triggered sporadically (in a non-constant manner and under selective pressure), can be enhanced to treat lung tumors with KEAP1 mutations, which is achieved through the sporadic activation of a CoQ-FSP1 antioxidant axis (124). Currently, no pharmaceuticals specifically targeting the CoQ/FSP1 pathway have reached clinical trials. Investigating this pathway offers a promising direction for advancing LC therapy. Additionally, as nanotechnology evolves, the integration of nanomedicine, radiation and ferroptosis is emerging as a novel strategy for treating LC (125-127). Chronic hypoxia, a hallmark of the TME, serves a key role in treating LC (124). Angiopoietin-like 4, produced under hypoxic conditions, inhibits ferroptosis via both intracellular and exosomal routes, contributing to radiation resistance in LC (128). Focusing on ferroptosis as a means to improve radiation therapy outcomes is a promising approach that warrants further exploration (Fig. 3).

Enhancing immunotherapy. Immunotherapy, widely recognized as the third revolution in cancer treatment, holds potential, particularly in managing advanced NSCLC (129). Ferroptosis enhances tumor immunotherapy by downregulating ferroptosis resistance genes via the action of FINs or immune cells (129). This downregulation increases ferroptosis, thereby amplifying immunogenic cell death and activating immune cell-mediated attacks. A novel approach to treating LC may involve combining immunotherapy with ferroptosis induction. The therapeutic response in NSCLC improves when statin drugs are used in conjunction with ICIs (130). Tumor cells tend to create an immunologically 'cold' environment when ferroptosis is inhibited or occurs at low levels (131). Statins, which induce ferroptosis by limiting PD-L1 expression, have emerged as a potential treatment for immune-cold tumors in NSCLC, promoting the efficacy of anti-PD-1 therapy in LC (132).

Several factors, including the expression of SLC7A11/SLC3A2, CD8⁺ T cell levels and IFN- γ concentrations, can influence the prognosis of patients with LC (133). T cell-mediated immunity serves a key role in tumor development. As part of immunotherapy, tumor cells may undergo enhanced lipid peroxidation through ferroptosis induced by activated CD8⁺ effector T cells (134). Furthermore, anti-tumor effects of immunotherapy may be potentiated by ferroptosis activation. CD8⁺ effector T cells secrete IFN- γ , which inhibits cystine uptake and promotes lipid peroxidation, thereby triggering ferroptosis (134). Additionally, ferroptosis may enhance the effectiveness of tumor immunotherapy by modulating the expression of immune checkpoint molecules, such as PD-L1

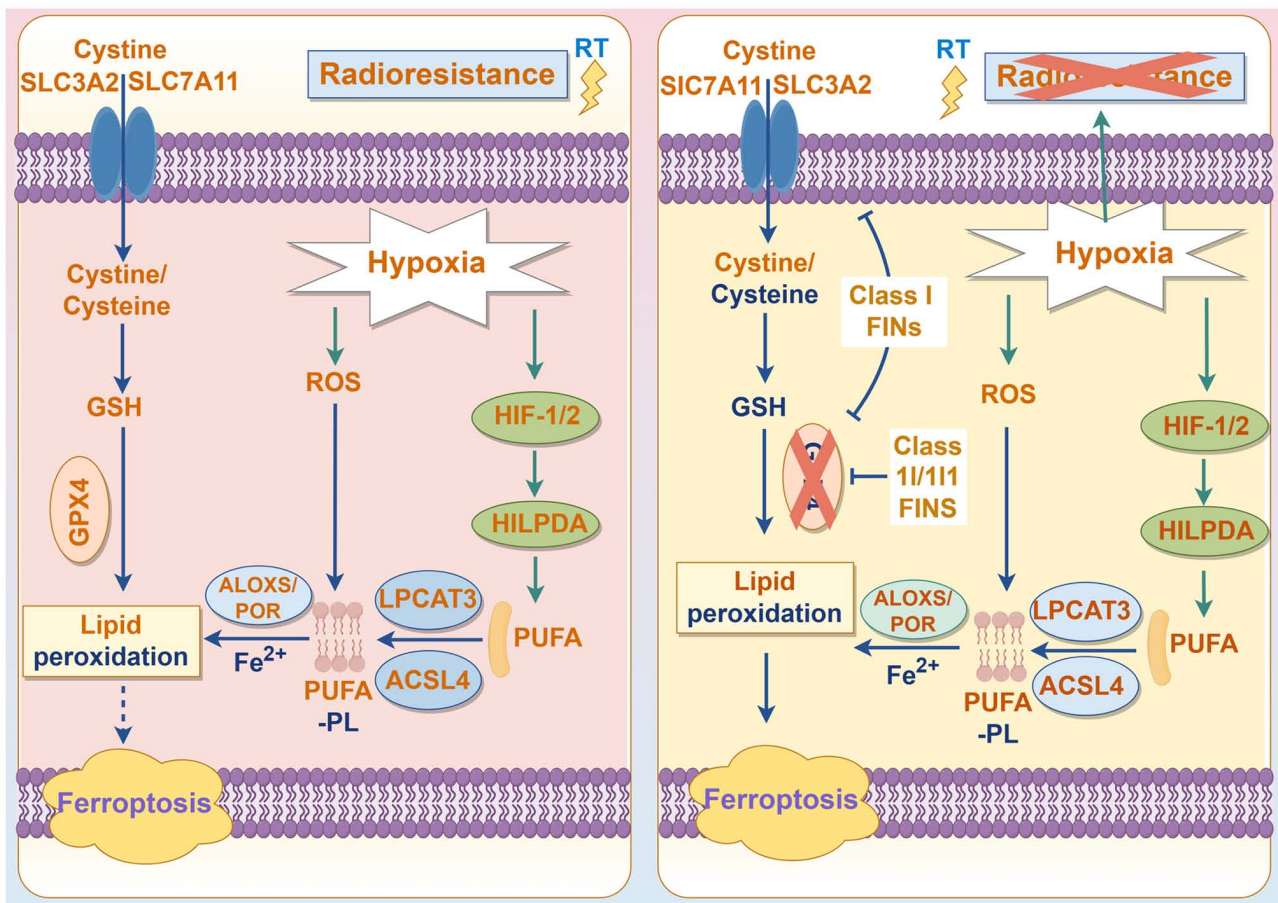


Figure 3. Ferroptosis and radioresistance. High expression of SLC3A2/SLC7A11 leads to increased cystine uptake, which boosts glutathione (GSH) synthesis. GSH then inhibits lipid peroxidation by activating GPX4, protecting cells from ferroptosis. Under hypoxia, HIF-1/2 and HILPDA further suppress ferroptosis, promoting radioresistance. Inhibition of SLC7A11/SLC3A2 (e.g., by Class I ferroptosis inducers, FINs) reduces cystine uptake and GSH levels, making cells more susceptible to lipid peroxidation and ferroptosis. Hypoxia still induces HIF-1/2 and HILPDA, but the overall effect is increased ferroptosis due to reduced antioxidant capacity, potentially overcoming radioresistance. SLC3A2, Solute carrier family 3 member 2; SLC7A11, Solute carrier family 7 member 11; RT, Radiotherapy; GSH, Glutathione; ROS, Reactive oxygen species; HIF, Hypoxia-inducible factor; HILPDA, Hypoxia-inducible lipid droplet-associated protein; PUFA, Polyunsaturated fatty acid; LPCAT, Lysophosphatidylcholine acyltransferase; ACSL, Acyl-CoA synthetase long-chain family member; PL, Phospholipid; ALOXS, Arachidonate lipoxygenase; POR, NADPH-cytochrome P450 reductase; GPX, Glutathione peroxidase; FIN, Ferroptosis inducer.

and CTLA4, on the surface of tumor cells (135). In conclusion, combining immunotherapy with ferroptosis is a promising strategy for LC management. Continued investigation into ferroptosis-based immunotherapies, along with the development of innovative combination therapies, may offer benefits in future medical treatments (Fig. 4).

Nanomedical strategies to treat ferroptosis in LC. Recent advances in nanomedicine and tumor diagnostic technologies have led to progress in the detection and treatment of LC (136,137). The use of nanodrugs in LC therapy may enhance the efficacy of conventional radiation and chemotherapy while decreasing cancer cell resistance. Numerous nanomaterials, including iron-based nanoparticles, leverage the Fenton reaction as their core mechanism. An approach to cancer treatment has been developed (138) through the creation of a multifunctional CO/thermo/chemotherapy nanoparticle, triiron dodecacarbonyl-doxorubicin@mesoporous carbon nanoparticles (FeCO-DOX@MCN). This nanoparticle converts near-infrared light into heat, triggering the release of doxorubicin within the TME (138). Key anticancer mechanisms include iron loading, increased ROS levels, glutathione depletion and GPX4 inactivation (138). Additionally, CO

molecules produced by the nanoparticle enhance tumor responsiveness to chemotherapeutics by activating ferroptosis (138). Photoacoustic imaging has demonstrated the effectiveness of the FeCO-DOX@MCN nanoplatfrom in both laboratory and nude mice models when combined with chemotherapy, photothermal treatment and gas therapy (138). This versatile platform holds promise for precision cancer treatment (138).

Nanomedicine exploits iron through various mechanisms to induce cell death, including enhancing the Fenton reaction, reducing glutathione levels, modulating lipid peroxidation and integrating multiple therapeutic approaches. This strategy minimizes the adverse effects of drugs and allows precise targeting of cancer cells. In a study by Wei *et al* (139) calcium carbonate nanoparticles were synthesized using a platinum (IV) catalyst. Surface modifications with 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-Polyethylene Glycol, MW ~2,000 Da (PEG2000)-Biotin improved the water solubility and tumor-specific distribution (139). The researchers also developed a novel Janus nanoparticle, Fe₃O₄-TA-GOD/anti-LILRB4&Sor@MSN-DMMA (FTG/L&SMD), which, once inside tumor cells, uses glucose oxidase to convert glucose into hydrogen

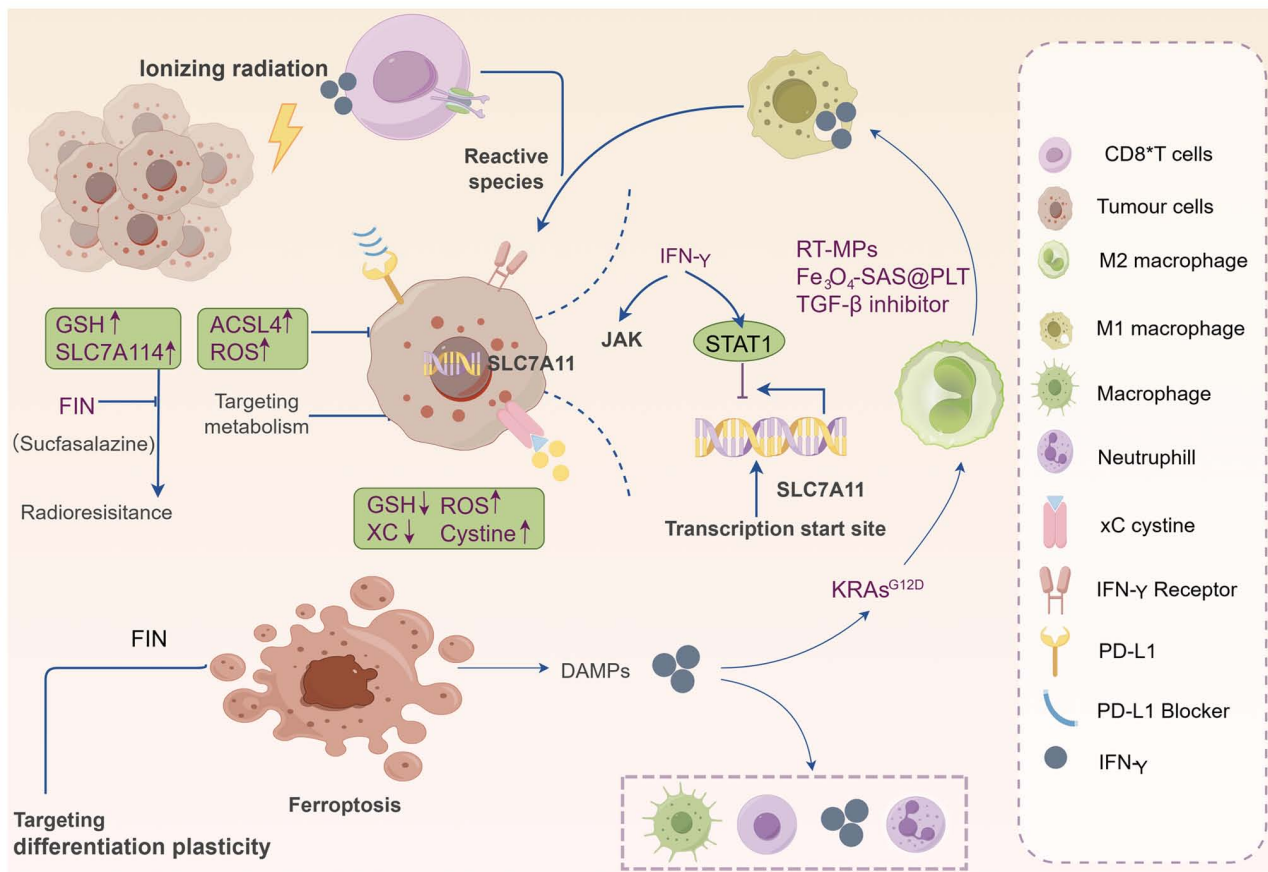


Figure 4. Ferroptosis and immunotherapy. Ionizing radiation generates reactive species, which can induce ferroptosis in tumor cells. FINs (e.g., Sucfasalazine) target key metabolic pathways, such as increasing glutathione (GSH) depletion (via SLC7A11 inhibition) and enhancing reactive oxygen species (ROS) production (via ACSL4 activation). This leads to lipid peroxidation and ferroptosis. Ferroptosis is characterized by decreased GSH, increased ROS, decreased cystine uptake (via system XC-inhibition), and subsequent cell death. Ferroptotic tumor cells release DAMPs, which act as 'find-me' and 'eat-me' signals to recruit and activate immune cells (e.g., CD8+ T cells, M1 macrophages). This creates an immunogenic microenvironment. Immunotherapy Synergy: Combining FINs with immunotherapies like PD-L1 blockers enhances anti-tumor immunity. For example, radiotherapy-modified platelets (RT-MPs) loaded with ferroptosis nanoagents (Fe₃O₄-SAS@PLT) and TGF-β inhibitors can further boost immune responses by promoting interferon-gamma (IFN-γ) production and STAT1 signaling. Targeting Differentiation Plasticity: Ferroptosis can also influence the differentiation plasticity of immune cells (e.g., macrophages), shifting them toward a pro-inflammatory (M1) phenotype, which supports tumor clearance. GSH, Glutathione; SLC7A11, Solute carrier family 7 member 11; ROS, Reactive oxygen species; FIN, Ferroptosis inducer; ACSL, Acyl-CoA synthetase long-chain family member; XC, System Xc-(cystine/glutamate antiporter); RT-MP, Radiotherapy-modified platelet; SAS@PLT, Sucfasalazine-loaded platelet; DAMP, Damage-associated molecular pattern; PD-L, Programmed death-ligand.

peroxide. This leads to ferroptosis via lipid peroxidation and the generation of hydroxyl radicals by the interaction of hydrogen peroxide with iron (140). Notably, these nanoparticles cause minimal damage to healthy cells, highlighting their potential for treating NSCLC.

Novel strategies have been developed to integrate nanomedicines with conventional treatment. Wang *et al* (141) synthesized a metal-organic supramolecular compound (nano p53-activator peptide @CeO₂) capable of restoring TP53 expression and enhancing the efficacy of ferroptosis. This compound significantly inhibits LC progression in a syngeneic transplantation model (141). Additionally, its good biocompatibility makes it a promising therapeutic candidate for cancer treatment (141). A pH-responsive superparamagnetic iron oxide nanoparticle cluster has demonstrated both diagnostic and therapeutic properties (142). Researchers have used chemodynamic therapy and radiation to further enhance local ferroptosis (142). The careful engineering of nanoparticles to complement traditional treatments represents a promising strategy for improving LC therapy, enabling more effective

integration of diagnosis and treatment. Nanomedicine holds potential in LC detection and treatment, offering the ability to enhance ferroptosis, increase treatment responsiveness in combination with conventional therapy, decrease drug resistance and provide precise treatments with decreased toxicity.

However, the direct application of nanomedicine to induce ferroptosis in LC is still in its early stages. Future research should focus on developing nanomedicines that specifically target ferroptosis regulators in LC cells and assess their therapeutic potential in preclinical models. Moreover, exploring the combination of nanomedicine with other therapeutic modalities may enhance synergistic effects and improve treatment outcomes.

Biomarkers to predict cancer cell responsiveness to ferroptosis induction therapy. The tumor suppressor p53 regulates ferroptosis in a context-dependent manner. In certain cancer cells, wild-type p53 delays the onset of ferroptosis in response to cystine deprivation. This requires the p53 transcriptional target cyclin-dependent kinase inhibitor

1A (encoding p21) and is associated with slower depletion of intracellular glutathione and decrease accumulation of toxic lipid-ROS (143). However, in other contexts such as iron metabolism regulation, antioxidant modulation, and tumor microenvironment, p53 may promote ferroptosis by regulating genes involved in iron metabolism and antioxidant defense (144). The Nrf2/KEAP1 signaling pathway serves a key role in maintaining redox homeostasis. In cancer cells, activation of this pathway leads to the upregulation of antioxidant defense genes such as SLC7A11 and GPX4, making the cells more resistant to ferroptosis (145). For example, in glioma cells, overexpression of Nrf2 or knockdown of Keap1 accelerates proliferation and confers resistance to ferroptosis (146). Conversely, inhibiting the Nrf2/KEAP1 pathway, such as by targeting Keap1, can sensitize cancer cells to ferroptosis-inducing agents (147).

Alterations in the regulatory mechanisms of ferroptosis may serve as biomarkers for predicting cancer cell sensitivity to ferroptosis induction. For example, the expression of key regulators such as GPX4 and SLC7A11 can indicate how susceptible cancer cells are to ferroptosis. circRNA ST6GALNAC6 (circST6GALNAC6) enhance the sensitivity of bladder cancer cells to erastin-induced ferroptosis. Mechanistically, circST6GALNAC6 binds to the N-terminus of small HSPB1, preventing its phosphorylation at the Ser-15 site, which is involved in the protective response to ferroptosis stress (148). In LC, the expression of genes associated with the Nrf2/KEAP1 pathway may also serve as biomarkers. High Nrf2 expression or low Keap1 expression may indicate resistance to ferroptosis-based therapies, while the reverse may suggest increased sensitivity (149). Understanding these biomarker-based predictions may facilitate the development of personalized treatment strategies, optimizing the use of ferroptosis-inducing agents in cancer therapy.

4. Conclusion

In summary, the present review outlined the dual role of ferroptosis in LC, highlighting both its detrimental and therapeutic effects, and biological agents that target ferroptosis as potential therapies for LC, with certain compounds inducing ferroptosis and decreasing tumor cell resistance. These findings suggest that further study of ferroptosis may lead to significant breakthroughs in cancer treatment. The therapeutic potential of nanomedicine has been demonstrated through promising outcomes from nanotechnology-based treatment for malignant disorders. The present review also provided an overview of nanomedicine delivery methods that have promise in cancer therapy. The effectiveness of ferroptosis in tumor treatment is enhanced when these nanocarriers, with distinct physical and chemical properties, deliver drugs directly to the target site, minimizing loss and blockage.

Despite progress in ferroptosis research, several issues remain. These include the unique characteristics of ROS in ferroptosis and the precise role of ferroptosis in immunotherapy. Cancer cells are highly susceptible to ferroptosis in numerous types of cancer, yet the study of its dynamic regulatory mechanisms is still limited (150,151). As ferroptosis is typically characterized by lipid peroxidation and membrane damage, it remains unclear whether lipid peroxides harm

healthy cells or result in other potential adverse effects (152). Additionally, tissue-specific susceptibility to ferroptosis varies, and the efficacy of FINs is inconsistent between individuals (153-155). A limitation of current research is that most studies focus on NSCLC, with limited investigations into other types of LC (156,157). *In vivo*, distinguishing ferroptosis from other forms of PCD is challenging due to the presence of lipid peroxidation in various PCD pathways (158). DNA and protein alterations resembling those seen in ferroptosis may also occur in ROS-induced cell death (159). Currently, ferroptosis cannot be identified by a single marker *in vivo* (160,161).

Future research should investigate the association between ferroptosis and the immune response in LC. Ferroptosis is induced by various agents, including cisplatin, sulfasalazine, sorafenib and zalcitabine (162). However, the development of highly specific ferroptotic drugs with low cytotoxicity is key, as current drugs have the potential to induce other types of renal cell disease (162). Investigating novel FINs may deepen understanding of ferroptosis-associated disorders and improve the accuracy of LC diagnosis and treatment. Identifying biological markers to predict susceptibility or resistance to ferroptosis in cells and patients is key. Furthermore, evaluating the safety and toxicity of small-molecule drugs or nanomaterials that induce ferroptosis is key. As a groundbreaking cancer therapy approach, ferroptosis offers promising solutions to the challenges faced by current LC treatment. Multidisciplinary collaboration is key to investigate the dual effects of targeted ferroptosis, identify novel therapeutic agents and assess their potential applications in LC treatment.

Acknowledgements

Not applicable.

Funding

The present study was supported by National Natural Science Foundation of China (grant no. 82370253), Jiangsu Provincial Research Hospital (grant no. YJXY202204) and Innovation Team Project of Affiliated Hospital of Nantong University (grant no. XNBHCX31773).

Availability of data and materials

Not applicable.

Authors' contributions

AW, YN and JS wrote and edited the manuscript. AW and YZ performed the literature review. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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