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Review Article

Targeting ferroptosis in lung cancer: pharmacological regulation, nanomedicine-based delivery, and AI-enabled translational strategies

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Abstract: The problem of lung cancer poses a great threat to the health of people all over the world. This threat is mainly associated with resistance to treatment. There is evidence that shows that ferroptosis fails to take place in lung cancer. There is a high degree of suppression in those that have become resistant to treatment. There seems to be a link between resistance to treatment and suppression of ferroptosis. This led to the development of a strategy to induce ferroptosis. In this review, the mechanisms of ferroptosis in drug-resistant non-small lung cancer cells will be discussed, along with a synopsis of recent studies analyzing combination therapies that involve the pharmacological induction of ferroptosis, thus further validating the notion that the prevention of ferroptosis plays an important role in drug resistance. Based on these principles, we will assess the inadequacies in current ferroptosis-inducing agents regarding their use in the treatment of lung cancer, focusing mainly on the suboptimal targeting of cancer cells and drug delivery efficiency. Conversely, these inadequacies have triggered new approaches in cancer therapy, which include using nanomedicine for improved drug delivery, functional nanomaterials for directly triggering ferroptosis, among others. In addition, we evaluate the validity of nanomaterials for precision medicine in cancer therapy, in addition to utilizing bioactive compounds. Lastly, we discuss the integration with artificial intelligence in single-cell sequence analysis for the development of modeling systems for ferroptosis control.

Keywords: Ferroptosis, lung cancer, cancer pharmacology, drug resistance

Introduction

However, pulmonary adenocarcinoma remains one of the leading causes of death worldwide. According to international reports, approximately 2.48 million new cases were diagnosed in 2022, with pulmonary adenocarcinoma responsible for 1.82 million deaths [1]. A significant problem in treatment is that responses are frequently undermined by acquired resistance [2, 3]. According to data, cisplatin treatment inevitably fails in more than 60% of patients, leading to tumor recurrence and poor outcomes [4]. Patients with epidermal growth factor receptor (EGFR) mutations also suffer from the same problems, with more than half of the patients experiencing resistance between 9 and 14 months after the treatment has been administered [5-7]. Immunotherapy involving the programmed death protein 1 (PD-1) pathway also suffers from limitations; acquired resistance was observed in more than 60% among 1,201 cases [8].

It is increasingly being seen that there is a common factor for these treatment resistances. This is the suppression of ferroptosis, which is a common feature of chemotherapy or radiotherapy-resistant lung cancer cells. Ferroptosis is an iron-dependent form of lipid peroxidation-mediated cell death. There is an increasing body of evidence that has implicated this process in the responsiveness of cancers to therapies [9]. In the case of resistant lung cancers, there is a significant decrease in the expression of ferroptosis, which is due to a variety of fac-

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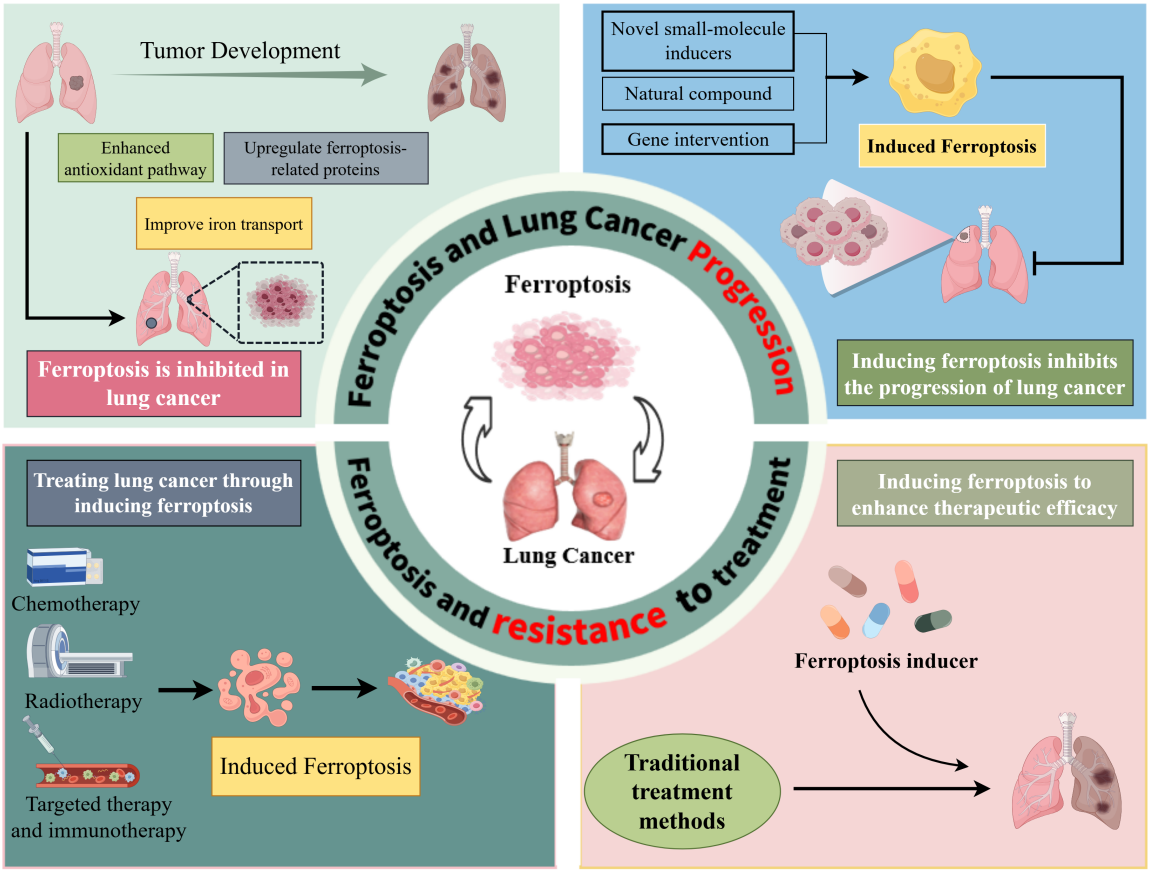

Figure 1. Overview of ferroptosis in lung cancer progression, therapy resistance, and therapeutic targeting. This schematic summarizes the main themes of the present review. The central panel highlights the dynamic relationship between ferroptosis and lung cancer. The upper-left section illustrates how suppression of ferroptosis contributes to tumor development through enhanced antioxidant pathways, altered iron transport, and upregulation of ferroptosis-related protective proteins. The lower-left section shows that inhibition of ferroptosis is a common feature of resistant lung cancer and may contribute to reduced sensitivity to chemotherapy, radiotherapy, targeted therapy, and immunotherapy, whereas ferroptosis induction may help overcome resistance. The upper-right section summarizes current strategies for inducing ferroptosis, including novel small-molecule inducers, natural compounds, and gene intervention approaches, which may suppress lung cancer progression. The lower-right section outlines ferroptosis-based therapeutic strategies aimed at improving treatment efficacy, and highlights emerging precision tools, including optimized delivery platforms and artificial intelligence-based models, as well as natural bioactive compounds with ferroptosis-modulating potential.

tors rather than the effect of a single pathway. This is achieved by a higher ability of resistant cells to counteract lipid peroxides, iron levels, and factors that oppose ferroptosis [10]. Induction of ferroptosis could provide a way to counteract this issue. Clinical trials have shown that ferroptosis inducer agents increase the effectiveness of traditional chemotherapy and radiation therapy [11, 12], which further supports the use of ferroptosis in lung cancer resistance. However, precise regulation of ferroptosis is difficult, and the goal is to regulate ferroptosis in TME without impairing normal tissues.

Figure 1 summarizes the framework of this review from four interrelated perspectives. First, it shows how suppression of ferroptosis may facilitate lung cancer progression by strengthening antioxidant defenses, disrupting iron homeostasis, and upregulating proteins that protect against ferroptotic death. Second, it links reduced ferroptotic activity to resistance to chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Third, it outlines current strategies to induce ferroptosis, including small molecules, natural compounds, and gene-based approaches. Finally, it highlights emerging efforts to improve the precision of

ferroptosis-targeted therapy, such as advanced drug delivery platforms, artificial intelligence-based predictive models, and naturally derived bioactive agents with ferroptosis-modulating potential. Together, these components provide an integrated view of the role of ferroptosis in lung cancer biology and therapeutic response.

Alterations of ferroptosis in lung cancer

Among major forms of cell death, ferroptosis is uniquely defined by iron-dependent phospholipid peroxidation rather than caspase activation, gasdermin pore formation, lysosomal self-digestion, or nonspecific membrane breakdown. Its most distinctive morphological hallmark is mitochondrial shrinkage with increased membrane density and loss of cristae, while the nucleus usually remains free of the prominent chromatin condensation seen in apoptosis. In contrast, apoptosis shows cell shrinkage, nuclear fragmentation, and apoptotic bodies with intact plasma membranes; pyroptosis is characterized by inflammasome-driven membrane pores, cell swelling, and lytic rupture; autophagy features double-membrane autophagosomes and autolysosomes; and necrosis presents with generalized swelling, membrane disruption, and organelle collapse. These features make ferroptosis a mechanistically and morphologically distinct death program, with particular relevance to overcoming apoptosis resistance in cancer.

In lung cancer, ferroptosis can be understood to be a series of events that are triggered by iron overload, which specifically targets phospholipids bound to polyunsaturated fatty acids, referred to as polyunsaturated fatty acid-containing phospholipids (PUFA-PLs). This series of events culminates in the breakdown of the antioxidant defense system. Dysregulated iron metabolism acts as a key trigger that propels the series of events. Acyl-CoA synthetase long chain family member 4 (ACSL4) has emerged as a key effector molecule that promotes lipid damage, whereas the glutathione peroxidase 4 (GPX4) and ferroptosis suppressor protein 1 (FSP1) belong to the key defense mechanisms that protect against cell death [13]. It is pertinent to note that treatment-resistant lung cancer cells often rewire these pathways to reprogram iron and lipid metabolism pathways and further improve their own protective mechanisms against cell death.

Previous studies have largely interpreted ferroptosis in lung cancer through three interdependent modules: iron homeostasis, lipid peroxidation, and antioxidant defense. **Figure 2** further illustrates how these modules converge to suppress ferroptosis during lung cancer progression. Altered iron handling, involving TFR, FPN, and FTH1, reshapes the labile iron pool and restricts iron-dependent oxidative damage. At the same time, ACSL4-driven lipid remodeling channels arachidonic acid into peroxidation-prone intermediates, leading to the accumulation of reactive aldehydes such as MDA and 4-HNE. Counteracting these events, the SLC7A11/SLC3A2-GSH-GPX4 axis reinforces antioxidant capacity and prevents the propagation of lethal lipid peroxidation. In addition, ferroptosis-related gene expression is further tuned by non-coding RNA networks, including circRNAs, lncRNAs, and miRNAs. Taken together, these pathways explain how ferroptosis is restrained in lung cancer and why its suppression favors tumor survival and resistance to therapy.

Dysregulated iron metabolism: a critical switch for ferroptosis

The regulation of iron homeostasis is a complex process that requires the coordination of uptake, transport, storage, and efflux. These cellular processes function collectively to modulate the size of the labile iron pool (LIP), which defines the iron state of cells and their consequent sensitivity to ferroptosis. The uptake of iron is mediated by the transferrin receptor 1 (TFR1) that ingests iron-bound transferrin (Fe^{3+}) for internalization. The iron is released at the acidic cellular compartment and reduced to Fe^{2+}, which represents the labile iron pool. There is evidence that the expression of TFR1 in cells defines their sensitivity to ferroptic cell death [14]. Ferritin is the iron-storage complex that is composed of ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), and FTH1 has iron oxidation activity that converts labile iron to a form that can be stored, thus protecting the cell membrane from iron-induced damage [15]. Efflux of iron for storing and other purposes is mediated by ferroportin (FPN), which is tightly controlled by the peptide hormone hepcidin [16]. The cellular consequences of disorganized regulation of iron homeostasis at any of the steps listed can result in iron overload, which causes the accumulation of free iron that

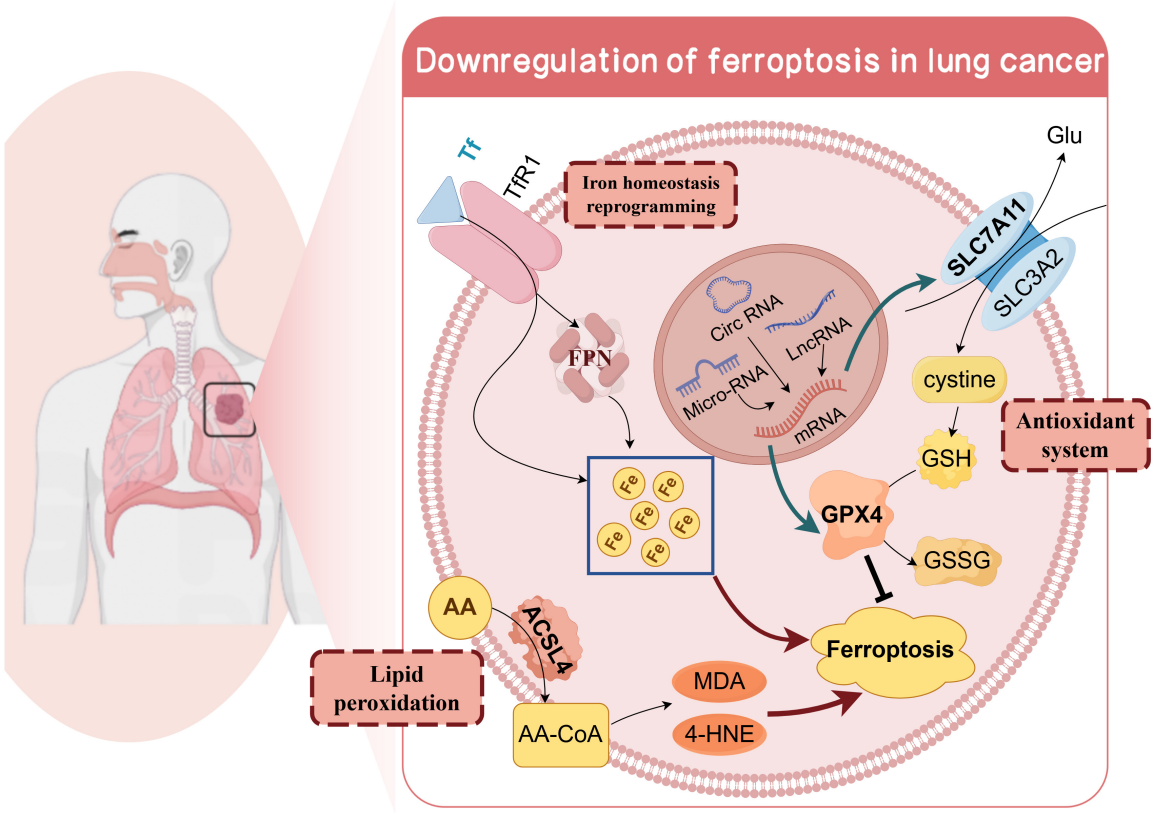

Figure 2. Downregulation of ferroptosis in lung cancer. This schematic illustrates the major mechanisms contributing to ferroptosis downregulation in lung cancer. The left panel indicates the anatomical location of the lung tumor, whereas the enlarged panel on the right summarizes the intracellular regulatory network in a lung cancer cell. Overall, the figure shows that reprogrammed iron homeostasis, RNA-mediated regulation, activation of the antioxidant system, and suppression of lipid peroxidation collectively promote ferroptosis resistance. In the upper-left region of the enlarged panel, iron metabolism is represented by Tf-mediated iron transport. Tf interacts with TFR to facilitate iron uptake, while FPN mediates iron export. Altered iron trafficking contributes to iron homeostasis reprogramming and may reshape ferroptosis sensitivity in lung cancer cells. The central region depicts multiple RNA regulatory layers, including circRNA, miRNA, lncRNA, and mRNA. These RNA networks converge on ferroptosis-related pathways and influence downstream regulators involved in redox balance and cell survival. On the right side, the antioxidant defense system is centered on the SLC7A11/SLC3A2 antiporter complex (system Xc^-), which imports cystine and exports Glu. This process supports GSH synthesis and sustains the activity of GPX4. GPX4 detoxifies lipid peroxides while converting GSH into GSSG, thereby limiting ferroptotic damage. In the lower part of the figure, the lipid peroxidation pathway is shown. AA is converted by ACSL4 into AA-CoA, which contributes to the formation of peroxidizable lipids. Reduced lipid peroxidation decreases the accumulation of toxic end products, including MDA and 4-HNE, thereby suppressing ferroptosis. Arrows indicate molecular transport, metabolic conversion, or regulatory direction. Together, these alterations create an intracellular environment characterized by enhanced antioxidant capacity, altered iron handling, and reduced lipid peroxidation, ultimately leading to ferroptosis downregulation in lung cancer. Abbreviations: Tf, transferrin; TFR, transferrin receptor; FPN, ferroportin; circRNA, circular RNA; miRNA, microRNA; lncRNA, long non-coding RNA; mRNA, messenger RNA; NRF2, nuclear factor erythroid 2-related factor 2; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; Glu, glutamate; GSH, glutathione; GSSG, oxidized glutathione; GPX4, glutathione peroxidase 4; AA, arachidonic acid; ACSL4, acyl-CoA synthetase long-chain family member 4; AA-CoA, arachidonoyl-CoA; MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal.

can trigger the generation of ROS and lipid peroxide formation.

It has recently been found that the iron-resistant lung cancer cells display a sophisticated strategy, not only for downregulating iron uptake. They organize iron storage and export to ideally maintain the iron pool levels to sustain proliferation and keep them low enough to avoid ferroptosis.

Amplification of lipid peroxidation

The key amplification reaction that leads to oxidative stress-induced cell death through iron overload and ROS overproduction is lipid per-

oxidation. Essentially, this reaction involves the massive synthesis and oxidation of PUFA-PLs within the cell membranes. The reaction begins with the activation of polyunsaturated fatty acids to acyl-coenzyme A by ACSL4, which results in the generation of acyl-coenzyme A that can be used to incorporate polyunsaturated fatty acids into membrane phospholipids. The reaction is then catalyzed by lysophosphatidylcholine acyltransferase 3 (LPCAT3), which incorporates polyunsaturated fatty acids derived from acyl-coenzyme A to synthesize PUFA-containing membrane lipids that can be directly used for lipid peroxidation reactions. The polyunsaturated fatty acid-containing phospholipids are then catalyzed by arachidonate lipoxygenases (ALOXs), which results in the generation of phospholipid hydroperoxide (PLOOH) that directly stimulates the lipid peroxidation reaction cascade. The Fenton reaction, which is catalyzed by iron, leads to the generation of reactive species that produce lipid peroxidation products; thus, low membrane fluidity, high membrane permeability, as well as membrane rupture, eventually lead to ferroptotic cell death [17]. During the entire process, the antioxidant machinery mediated by GPX4 works to inhibit unchecked lipid peroxidation, thus playing a key role as an essential protector against ferroptosis.

Antioxidant defense and its failure: the SLC7A11-GSH-GPX4 axis

To counter ferroptosis, cells activate various antioxidant response pathways focused on reducing lipid peroxides and maintaining redox balance. At the forefront of this process is the solute carrier family 7 member 11 (SLC7A11) Glutathione (GSH) GPX4 system, which is considered the main antioxidant system safeguarding cells from ferroptotic cell death. The main role of this system is lipid peroxide detoxification, which is associated with maintaining the redox balance of lipid membranes. The System Xc^-, which uses SLC7A11 as its catalytic unit, is responsible for cystine uptake via glutamate secretion. The internalized cystine is rapidly reduced to cysteine, a limiting substrate for GSH biosynthesis. GSH, acting as a GPX4 reducing equivalent, is pivotal in GPX4-mediated reduction of phospholipid hydroperoxides to their respective alcohols, thus inhibiting lipid peroxidation-mediated ferroptosis. Genetic or pharmacologic knocking down SLC7A11 or GPX4 inhibits cells from dealing with PLOOHs and makes cells highly susceptible to ferroptosis [18].

GPX4 is not the only barrier to ferroptosis. Tumor cells can also suppress lipid peroxidation through the FSP1/CoQ10/NAD(P)H axis and the GCH1/BH4/VKORC1L1/vitamin K pathway, two major GPX4-independent antioxidant systems.

FSP1 reduces CoQ10 to ubiquinol in an NAD(P)H-dependent manner, providing a membrane-associated defense against lipid peroxidation [19]. In NSCLC, FSP1 is upregulated downstream of KEAP1/NRF2 and has been associated with sorafenib resistance, immunosuppressive TAM infiltration, and poor outcome [20, 21]. GCH1 confers a similar protective effect by driving BH4 synthesis and VKORC1L1-dependent production of reduced vitamin K, which traps phospholipid peroxyl radicals [22].

Because both pathways generate lipophilic radical-trapping antioxidants, they can buffer ferroptotic stress when GPX4 activity is limited. Their compensatory activation in sorafenib- or lenvatinib-resistant NSCLC further supports this view and suggests that co-targeting FSP1 and GCH1 may be a practical way to enhance ferroptosis and counter drug resistance.

Treatment resistance in lung cancer

Accumulating evidence suggests that ferroptosis is increasingly recognized as a tumor-suppressive mechanism distinct from apoptosis, pyroptosis, and autophagy. In lung cancer, several standard treatments, including chemotherapy and radiotherapy, appear to derive part of their antitumor efficacy from engaging ferroptosis-related pathways. This also implies that evasion of ferroptosis may represent a shared route to treatment failure.

As summarized in **Table 1**, drug-resistant lung cancer cells frequently exhibit metabolic adaptations that blunt ferroptotic signaling. Iron handling is remodeled in ways that reduce the labile iron pool (LIP); coordinated changes in TFR1 and FPN can limit Fe^{2+}-driven lipid peroxidation and increase the threshold for ferroptosis initiation. Lipid remodeling further constrains this process: downregulation of

Table 1. Downregulation of ferroptosis-related proteins in drug-resistant lung cancer cells

Module	Change in resistant cells	Main mechanism	Pathway	Ref
Activate the antioxidant system	GPX4↑	GSH↑→LPO↓→Ferroptosis inhibition	Post-transcriptional control Non-coding RNA axis: circ_0082374/miR-491-5p circPVT1/miR-338-3p; m6A RNA: METTL16/GPX4 mRNAs Classic signaling pathway: Notch, HIF-1α/Hippo-YAP, APOC1/NRF2/HO-1 Protein Interactions: TMRM154/ATG5, RRM2/PRDX6, TMRM154	[23-30]
	SLC7A11↑	Imports cystine→GSH↑→Activates GPX4→Ferroptosis inhibition	Transcriptional Regulation Transcription factor: SOX2/AhR Epigenetic modifications: HDAC10/miR-223-5p post-transcriptional control Non-coding RNA axis: circ_0070440/miR-485-5p, circPDSS1/miR-137, Uc.339/pri-miR-339, SLC7A11AR/miR-150-5p, miR-27a-3p RNA binding protein: ROR1-AS1/IGF2BP1/LAPTM4B translational control: RBMS1/eIF3d	[31-40]
	FSP1↑	Regenerates $CoQH_2$→LPO↓→Ferroptosis inhibition	miR-4443/METTL3 cooperatively regulate FSP1 expression through an m6A-dependent mechanism.	[28]
Remodel iron metabolism	TFR1↓	Iron uptake↓→LIP↓→Fenton reaction↓→Ferroptosis inhibition	METTL3 decreases iron uptake by destabilizing TFRC mRNA and reducing TFR1 expression, while upregulating the anti-ferroptosis iron-storage proteins FTH1 and FTL.	[41]
	FTH1↑ FTL↑	Iron storage↑→LIP↓→Fenton reaction↓		
	FPN↑	Iron efflux↑→LIP↓→Fenton reaction↓	USP35 binds to FPN, directly preventing its ubiquitination and maintaining FPN stability.	[42]
Remodel lipid metabolism	ACSL4↓	PUFA↓→LPO↓→Ferroptosis inhibition	Post-transcriptional control circ_0002638/SENP1, circSCN8A/miR-1290, NEAT1 (lncRNA) Post-translational modification Ubiquitination: HERC1 SUMOylation/Destabilization: SUMO2-K111, SENP1 Metabolic signal: HMOX1 pathway	[42-47]

Table 2. FRPs-based predictive model for lung cancer

Cancer	Type	Standard	prognosis	Enrichment pathway	TME	Treatment sensitivity	Reference
SCLC	S1	Main related protein Low	medium	/	/	/	[48]
	S2	RGS4↑ SLC12A2↑ GPX2↑ GCH1↑	Worst	MYC↑ ASCL1↑	Immune exhaustion	Platinum-resistant	
	S3	Main related protein High	Best	NOTCH↑ CDH2↑ FN1↑ POU2F3↑ YAP1↑	Immune-enriched	theophylline sensitivity	
NSCLC	FP1	RPL8↑ SAT1↑ CYP4B1↑	medium	Cytochrome P450 metabolism abnormal	neutrophile granulocyte↑	Glutathione inhibitor (BSO)	[49]
	FP2	GPX4↑ PEBP1↑ SQLE↑	Worst	MYC expression abnormal	$CD8^+$ T cell↓	GPX4 inhibitor (RSL3)	
	FP3	AKR1C3↑ NQO1↑ SLC7A11↑	Best	GSH expression abnormal	M1 macrophage activation	Cisplatin and radiotherapy	

enzymes such as ACSL4 decreases peroxidation-prone PUFA-containing phospholipids. Antioxidant capacity is reinforced in parallel. Upregulation of the GPX4-SLC7A11 axis supports glutathione (GSH) production and detoxification of lipid hydroperoxides, while auxiliary defenses such as FSP1 provide additional buffering. Collectively, these features connect ferroptosis tolerance with broader therapy resistance and highlight ferroptosis induction as a potential strategy to resensitize lung cancer to treatment.

Table 2 further summarizes the currently available evidence showing that lung cancer cells derived from different subtypes display distinct expression patterns of ferroptosis-related proteins. These subtype-specific differences are associated with prognosis and may also affect therapeutic sensitivity. At present, the evidence is more extensive for non-small cell lung cancer (NSCLC), and therefore the following discussion mainly focuses on NSCLC.

Figure 3 outlines the role of ferroptosis in the response and resistance to major lung cancer therapies. In cisplatin treatment, ferroptosis is driven mainly by ROS accumulation, while resistant cells suppress this response through NRF2/HO-1-mediated antioxidant defense and GPX4 activity. In radiotherapy, ferroptosis is controlled by regulators including p53, SLC7A11, PHKG2, NRF2, FSP1, ACSL4, ALOX15, and several stress-responsive RNA-associated pathways, and disruption of this network promotes radioresistance. In targeted therapy, especially in EGFR-mutant lung cancer, ferroptosis is linked to lipid peroxidation, xCT/SLC7A11, GSH, GPX4, and iron metabolism, whereas resistance is shaped by additional signaling circuits involving SREBP-1, HDAC, Wnt, DDR1, and multiple non-coding RNAs. Overall, the figure highlights ferroptosis as a key regulator of treatment response across distinct therapeutic settings.

Ferroptosis-related mechanisms underlying chemotherapy resistance in lung cancer

Platinum-based chemochemotherapy has remained a cornerstone in NSCLC and is considered a crucial therapeutic approach for around 85% of lung carcinoma patients [50]. At the molecular level, cisplatin is assumed to possess anti-tumor activities through the induction of reactive oxygen species (ROS) and lipid peroxidation related to ferroptosis pathways [50]. Still, around 60% of leukaemic patients exhibiting resistance to cisplatin provide suboptimal clinical outcomes and promote relapse

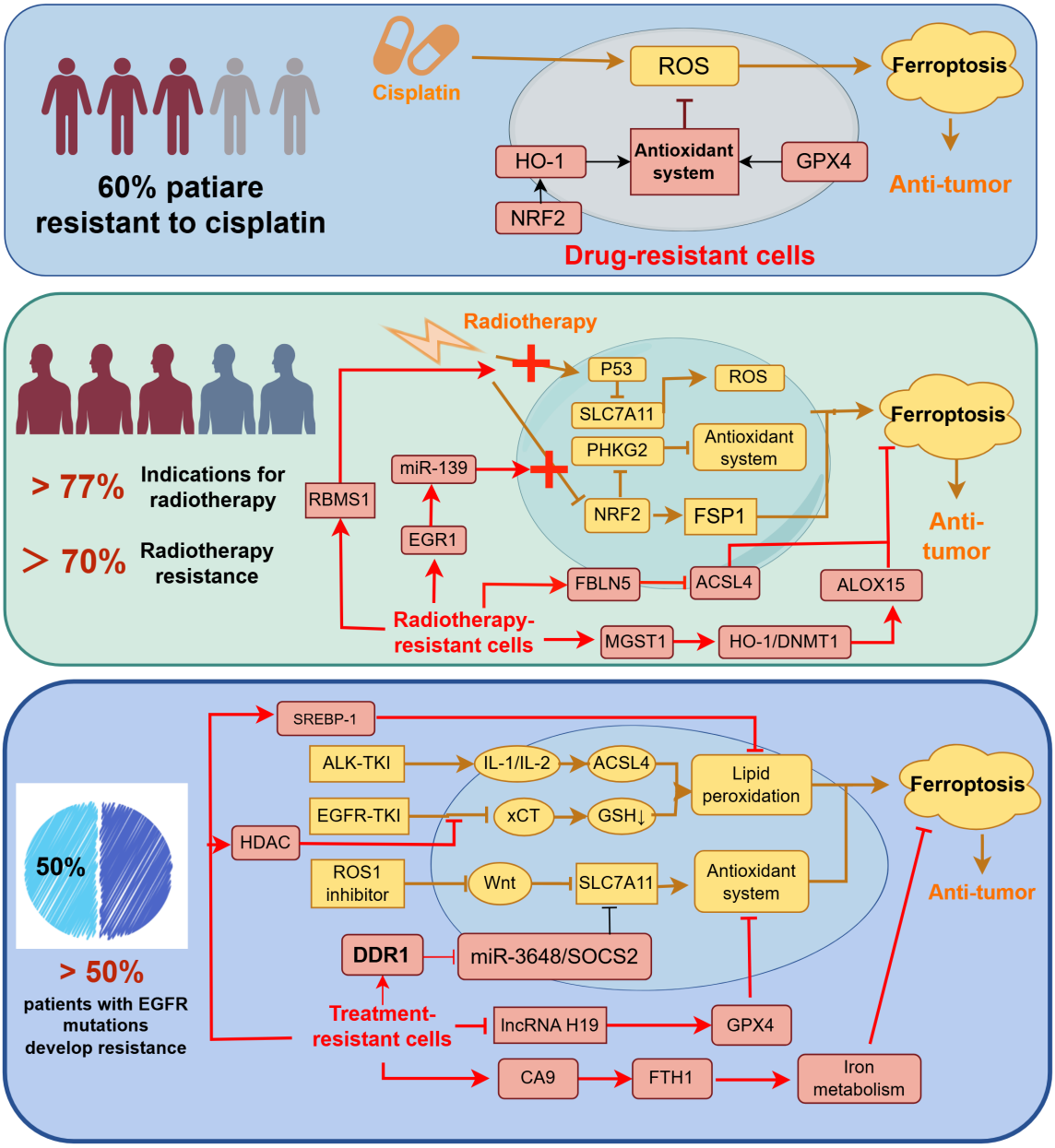

Figure 3. Roles of ferroptosis in therapy-resistant lung cancer: implications for cisplatin resistance, radioresistance, and targeted therapy resistance. This schematic summarizes the involvement of ferroptosis-related pathways in treatment resistance in lung cancer and how their modulation may influence antitumor responses. The figure is divided into three horizontal panels representing cisplatin-resistant cells, radiotherapy-resistant cells and targeted therapy-resistant cells. In all panels, the cloud-shaped symbol labeled "Ferroptosis" denotes the terminal cell death process associated with antitumor activity. Boxes indicate molecular regulators or signaling components, and arrows indicate regulatory, metabolic, or signaling relationships. In the top panel, approximately 60% of patients are indicated to develop cisplatin resistance. In cisplatin-resistant cells, ferroptosis is mainly regulated by the NRF2/HO-1-associated antioxidant pathway and the GPX4 axis. ROS act as upstream oxidative signals linked to ferroptosis, whereas the antioxidant system and GPX4 counteract oxidative lipid damage and limit ferroptotic cell death. This panel highlights the balance between ROS accumulation and antioxidant defense during cisplatin resistance. In the middle panel, the relationship between ferroptosis and radioresistance is illustrated. The left side indicates the broad clinical use of radiotherapy and the substantial frequency of radiotherapy resistance. In radiotherapy-resistant cells, the regulatory network includes RBMS1, miR-139, EGR1, FBLN5, and MGST1, together with established ferroptosis regulators such as p53, SLC7A11, PHKG2, NRF2, FSP1, ACSL4, ALOX15, and HO-1/DNMT1. These factors converge on ROS production, antioxidant defense, and lipid peroxidation-related pathways, thereby modulating ferroptosis sensitivity during radiotherapy response. In the bottom panel, the figure focuses on targeted therapy

resistance, indicating that more than 50% of patients with EGFR mutations may eventually develop resistance. The illustrated resistant-cell network involves EGFR-TKI-, ALK-TKI-, and ROS1 inhibitor-related settings. Key regulators include HDAC, DDR1, SREBP-1, IL-1β/IL-6, Wnt, xCT/SLC7A11, GSH, ACSL4, GPX4, iron metabolism, FTH1, CA9, lncRNA H19, and the miR-3648/SOCS2 axis. Together, these factors influence lipid peroxidation, antioxidant capacity, and iron handling, thereby shaping ferroptosis susceptibility in targeted therapy-resistant cells. Overall, the figure indicates that therapy-resistant lung cancer cells often acquire a ferroptosis-resistant phenotype through enhanced antioxidant defense, altered iron metabolism, and reduced lipid peroxidation. Restoring ferroptotic vulnerability may therefore represent a potential antitumor strategy to overcome resistance to chemotherapy, radiotherapy, and targeted therapy. Abbreviations: ROS, reactive oxygen species; NRF2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase 1; GPX4, glutathione peroxidase 4; RBMS1, RNA-binding motif single-stranded interacting protein 1; miR-139, microRNA-139; EGR1, early growth response 1; FBLN5, fibulin 5; MGST1, microsomal glutathione S-transferase 1; p53, tumor protein p53; SLC7A11, solute carrier family 7 member 11; PHKG2, phosphorylase kinase catalytic subunit gamma 2; FSP1, ferroptosis suppressor protein 1; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX15, arachidonate 15-lipoxygenase; DNMT1, DNA methyltransferase 1; EGFR, epidermal growth factor receptor; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ALK-TKI, anaplastic lymphoma kinase tyrosine kinase inhibitor; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase; HDAC, histone deacetylase; DDR1, discoidin domain receptor 1; SREBP-1, sterol regulatory element-binding protein 1; IL-1β, interleukin-1 beta; IL-6, interleukin-6; Wnt, Wingless/Integrated signaling pathway; xCT, cystine/glutamate antiporter light chain, also known as SLC7A11; GSH, glutathione; FTH1, ferritin heavy chain 1; CA9, carbonic anhydrase 9; lncRNA, long noncoding RNA; H19, H19 imprinted maternally expressed transcript; SOCS2, suppressor of cytokine signaling 2.

[50]. Consistent with this, cisplatin-resistant lung carcinoma cells, relative to their parent cells A549, present a conspicuous reduction in GPX4 and NRF2/HO-1 levels [51, 52].

On the basis of these mechanism studies, targeting the antioxidant protection machinery in drug-resistant cells has been proposed and deemed viable. It was found that cotreatment with cisplatin and agents targeting ROS homeostasis could significantly increase antitumor efficacy in drug-resistant cell models and restore partial cisplatin sensitivity [53]. PRLX-93936, which is a structural analog of the drug erastin, could effectively downregulate GPX4 expression; in addition, cotreatment with cisplatin could efficiently decrease GPX4 expression in cisplatin-resistant lung cancer cells, thereby inducing ferroptosis and showing synergistic antitumor efficacy [54]. These functional results clearly verify that “chemotherapy + ferroptosis induction” could break the GPX4-A BR in drug-resistant cells, providing new hopes for the treatment of chemotherapy-resistant lung cancer.

Meanwhile, recent research has confirmed that the canonical ferroptosis inducers erastin and RSL3 can induce ferroptosis through the suppression of glutathione (GSH) biosynthesis and GPX4 inhibition, and thus reverse the resistance of A549 cells to docetaxel. In addition, the pharmacodynamic models provided the capacity to discover the three non-covalent GPX4 inhibitors named I14, I20, and I22. This result indicates that the cisplatin resistance is not limited to the escape from the cytotoxicity associated with the DNA damage response but rather indicates ferroptosis-resistance, including the strengthened GPX4 antioxidant defense system, and thus provides an even more systematic explanation for the treatment of tumor drug resistance via attacking ferroptosis [55].

Ferroptosis-associated mechanisms underlying radiotherapy resistance in lung cancer

Radiotherapy is a major therapeutic approach for patients with early and loco-regionally advanced non-small cell lung cancer (NSCLC) and is particularly indicated for those who cannot undergo surgery [56]. Evidently, radiotherapy significantly inhibits cancer cells in patients with a clinical response rate of approximately 77% among those with NSCLC [57]. It is hypothesized that radiotherapy exerts its anticancer activity in part by inhibiting the antioxidant system represented by FSP1, inducing ROS, and triggering ferroptosis in non-small cell lung carcinoma cells [58-60]. Nonetheless, during this process, radiotherapy’s sensitivity tends to reduce over time, leading to more than 70% acquisition of radioresistance in patients [4].

Recently, studies have increasingly found connections between radioresistance and decreased sensitivity to ferroptosis in non-small lung cancer cells. The suppression of ferroptosis in radioresistant NSCLC is not caused by a single pathway but is instead a cumulative result of several different pathways involving various

molecules. Moreover, in particular, in radioresistant NSCLC, it has been found that the inhibitory effects of radiation therapy on NRF2/FSP1 and p53/SLC7A11 pathways are considerably reduced, and as a consequence, it has been noted that there is a reduced activation of antioxidant responses and an impaired uptake of ROS in cells, thereby causing decreased induction of ferroptosis initiation for both pathways. At the same time, enzymatic activity in lipid oxidation pathways, for example, those involving ACSL4 proteins, has been reduced and made limited, thereby causing decreased lipid peroxide accumulation and further decreased induction of ferroptosis execution for lipid pathways, reflecting a type of FT-suppressing reprogramming exhibited in therapy-resistant NSCLC [61, 62].

In this regard, therapeutic approaches based on ferroptosis pathways to increase radiosensitization have appeared highly promising. It has been found that when combined with the conventional ferroptosis-inducing agent RSL3, radiotherapy can importantly enhance ferroptosis by increasing lipoxygenase activity and lipid peroxidation, thereby overcoming radioresistance in lung cancer models [63]. In addition, a Secreted Protein Acidic and Rich in Cysteine (SPARC) engineered by humans has been recently found to be a new ferroptosis-inducible agent that can decrease primary antioxidant regulator expression such as GPX4 and SLC7A11 and importantly improve the therapeutic sensitivity of radiotherapy for radioresistant tumors [64].

In conclusion, radioresistance induced by ferroptosis represents an adaptation towards reduced sensitivity to ferroptosis rather than an innate defect of radiotherapeutic cell death.

Ferroptosis and resistance to targeted therapy

Targeted therapy remains an invaluable treatment option for non-small cell lung cancer patients with specific oncogenic drivers. Recent data suggest that drugs targeting primary drivers like anaplastic lymphoma kinase and epidermal growth factor receptor can potentially increase antitumor effectivity through the induction of ferroptosis, either via the enhancement of lipid peroxidation pathways like ACSL4 [65] or through the inhibition of glutathione-based antioxidant pathways [66].

Notably, the therapeutic effects of targeted therapy are hampered by acquired resistance to a considerable extent. In EGFR-targeted therapy, over 50% of cases acquire resistance to therapy within 9-14 months, and this is closely related to the reduced sensitivity of cancer cells to ferroptosis. In terms of molecular mechanisms, Manoalide has been shown to trigger ferroptosis by concurrently suppressing the NRF2-SLC7A11 signaling pathway and an FTH1-associated pathway involving mitochondrial Ca^{2+} overload, thus greatly improving the sensitivity of osimertinib-resistant non-small lung cancer cells to osimertinib [67]. These observations emphasize the fundamental role played by resistance to ferroptosis in driving resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). Moreover, RAD001, an mTOR inhibitor, induces ferroptosis by regulating the expression levels of FTH1 and GPX4. In non-small lung cancer cells with resistance mutations in EGFR, the therapeutic effect of RAD001 is additive to erastin, thus augmenting its therapeutic effects on these cells further. Taken together, resistance to EGFR tyrosine kinase inhibitors signifies that resistance to ferroptosis is another important node that could enable cancer cells to evade therapy in driver-mutant non-small lung cancer [68]. Significantly, despite the fact that chemotherapy, radiation therapy, and targeted therapy all initiate different types of lethal signals, acquired resistance to these therapies often involves inhibition or attenuation of ferroptosis.

Ferroptosis and resistance to immunotherapy

Ferroptosis in lung cancer is not solely a cell-autonomous event. It is strongly influenced by the cellular composition and signaling context of the tumor microenvironment. In particular, immune cells, including $CD8^+$ T cells, macrophages, regulatory T cells, natural killer cells, and dendritic cells, can promote ferroptosis in tumor cells by reshaping iron handling and lipid metabolic pathways [69-71]. A well-established example is interferon-γ released by $CD8^+$ T cells, which induces ferroptosis by suppressing SLC7A11-dependent cystine uptake. This crosstalk is often bidirectional. Ferroptotic tumor cells release damage-associated molecular patterns and neoantigens that further enhance $CD8^+$ T-cell surveillance, thereby forming a positive feedback loop between antitumor

immunity and ferroptosis. In addition, metabolites generated during ferroptosis can remodel the tumor microenvironment by affecting macrophage polarization and cytokine signaling networks.

Within this context, immunotherapy has reshaped the treatment landscape of lung cancer and has produced durable clinical benefit in a subset of patients. Available evidence indicates that immune checkpoint blockade, particularly anti-PD-1 therapy, promotes interferon-γ production by effector T cells. This, in turn, enhances ACSL4-dependent lipid peroxidation in tumor cells [72] and weakens GPX4-mediated antioxidant defenses [73], thereby increasing ferroptosis sensitivity and strengthening the antitumor efficacy of immunotherapy.

Despite these advances, the overall response rate to immunotherapy in lung cancer remains limited to approximately 20% to 30%. Notably, SLC7A11 and GSH are often highly expressed in tumor cells from PD-L1-positive patients [74], suggesting intrinsic plasticity in the regulation of ferroptosis and providing a theoretical basis for combining ferroptosis inducers with anti-PD-1 antibodies. Further studies have shown that the erastin derivative IKE, when used in combination with PD-L1 antibodies, can markedly suppress the GSH-GPX4 antioxidant system, promote ferroptosis, and effectively inhibit the growth and progression of both subcutaneous and metastatic lung tumors in mouse models [75].

Overall, current evidence suggests that ferroptosis is tightly linked to the antitumor activity of immunotherapy in lung cancer. As shown in **Figure 4**, immune checkpoint blockade enhances T-cell-derived IFN-γ signaling, which activates the IFNR-STAT1-IRF1 cascade in tumor cells and shifts ferroptosis-related metabolism toward increased lipid peroxidation and impaired antioxidant defense. Key mediators in this process include ACSL4, LPCAT3, and GPX4. Meanwhile, ferroptotic tumor cells release HMGB1 and ATP, which can stimulate the cGAS-STING pathway and strengthen immune activation. The figure further illustrates that ferroptosis inducers such as erastin and RSL3 may cooperate with checkpoint inhibitors, supporting combination strategies to improve the response to immunotherapy in lung cancer.

However, despite the increasing body of evidence in various therapeutic contexts indicating that targeted induction of ferroptosis can be used to break treatment resistance, it is still difficult to apply this strategy to clinical practice on the basis of experimental models. Such limitations have caused increased consideration of the safety, predictability, and delivery methods of interventions based on ferroptosis.

Current challenges and emerging strategies for clinical translation

Notwithstanding the strong rationale for using ferroptosis inducers in drug-resistant non-small-cell lung cancer, the translation of this strategy in a clinical setting is made difficult by some challenges. First, a marked degree of intra-tumor and inter-tumor heterogeneity is a characteristic that is present in various malignancies, including lung cancer, where, in the same lesion, pathways linked to iron metabolism as well as levels, activity, or both, among key modulator regulators SLC7A11, GPX4, or FSP1, can be highly disparate. Second, ferroptosis is not cell-lineage specific. That is, in addition to cancer cells, ferroptosis can affect 'normal cells', thus setting limitations in the dose range. Furthermore, conventional ferroptosis-inducer drugs tend to have poor in vivo transfer efficacy or specificity for targeting cancer, which may reduce ferroptosis in cancer cells, while potentially inducing non-specific cytotoxic damage in 'normal cells'; thus, this increases the probability or risk for drug-induced toxicities. In sum, these challenges represent major bottlenecks for the development of ferroptosis-inducer therapy in the clinical setting, as these in essence reflect, in a fundamental sense, 'therapy-induced diversification' in ferroptotic sensitivity, as well as 'reinforcement' of 'anti-ferroptotic protective mechanisms'; thus, ferroptotic-inducer therapy 'monotherapy' is unlikely in the clinical setting.

In response to such limitations, there is an increasing trend in research towards focusing on approaches besides FINs only. Notably, targeted delivery mediated by nanomaterials, AI-assisted ferroptosis efficacy prediction models based on single-cell sequencing data, as well as the design of new agents particularly NACs, have recently received considerable attention. In general, such approaches are ex-

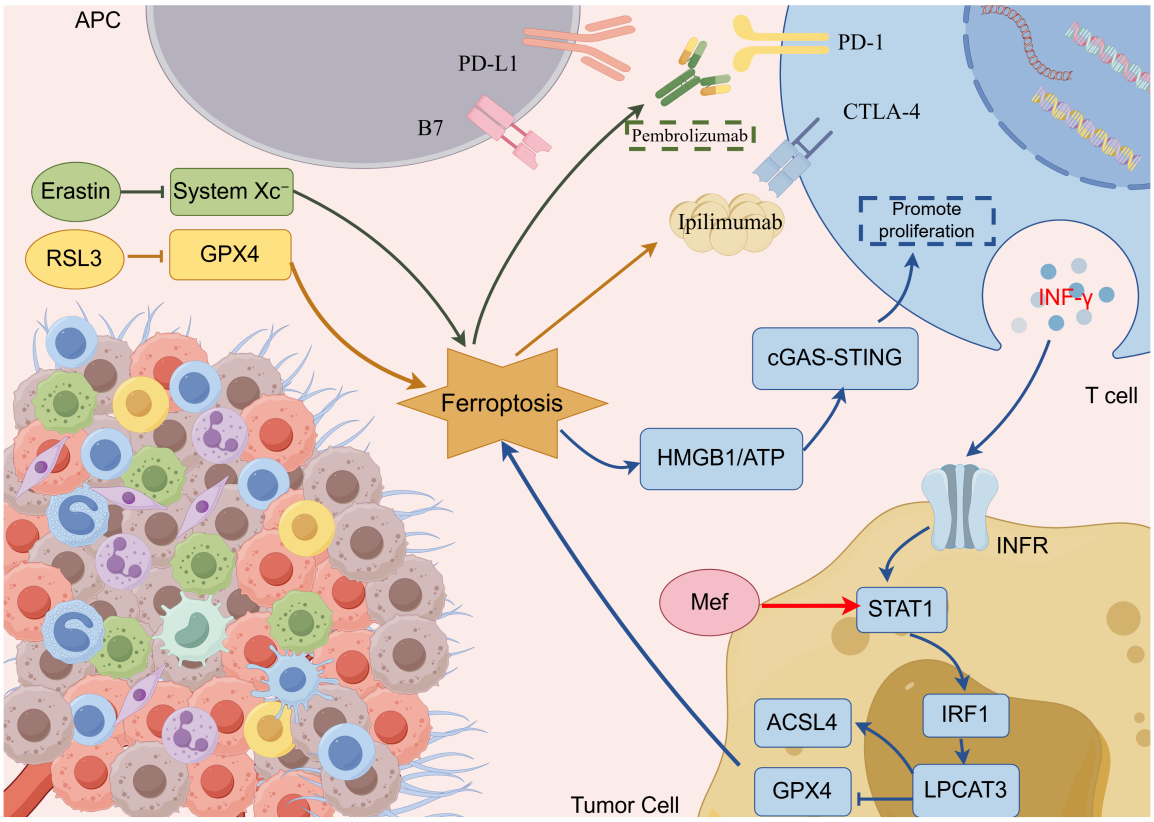

Figure 4. Interplay between ferroptosis and immunotherapy in lung cancer. This schematic illustrates the reciprocal interactions between ferroptosis and antitumor immune responses in the lung cancer microenvironment. On the left, ferroptosis in tumor cells is induced by the system Xc^- inhibitor erastin and the GPX4 inhibitor RSL3. In the center, ferroptosis is shown as a key event linking tumor cell death to immune activation. The upper part depicts APCs, T cells, and immune checkpoint molecules, whereas the lower-right part highlights ferroptosis-related signaling events within tumor cells. Immune checkpoint blockade is represented by pembrolizumab targeting the PD-1/PD-L1 axis and ipilimumab targeting CTLA-4. These interventions enhance T-cell activity and promote antitumor immunity. Activated T cells release IFN-γ, which acts on tumor cells through the IFN-γR and downstream STAT1 signaling. STAT1 activation induces IRF1 and contributes to the regulation of ferroptosis-related metabolic pathways, including ACSL4, GPX4, and LPCAT3, thereby influencing ferroptosis sensitivity in tumor cells. The figure also shows that ferroptotic tumor cells release damage-associated molecular patterns, including HMGB1 and ATP, which activate the cGAS-STING pathway and further support immune activation. Through these mechanisms, ferroptosis may enhance inflammatory signaling and facilitate antitumor immune responses. Conversely, immune activation may increase the susceptibility of tumor cells to ferroptosis, indicating a bidirectional relationship between ferroptosis and cancer immunity. Arrows indicate regulatory, signaling, or functional direction. Overall, the figure suggests that ferroptosis not only contributes directly to tumor cell death but also cooperates with immune checkpoint blockade and IFN-γ-mediated signaling to strengthen antitumor effects in lung cancer. Abbreviations: APC, antigen-presenting cell; system Xc^-, cystine/glutamate antiporter; GPX4, glutathione peroxidase 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IFN-γ, interferon gamma; IFN-γR, interferon-gamma receptor; STAT1, signal transducer and activator of transcription 1; IRF1, interferon regulatory factor 1; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; HMGB1, high mobility group box 1; ATP, adenosine triphosphate; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes.

pected to improve the stability, safety, and practicality of ferroptosis-targeting therapies.

Nanomaterial-based targeted induction of ferroptosis

However, the clinical translation of ferroptosis-inducing agents still faces substantial challenges, including poor pharmacokinetics and systemic toxicity. To overcome these barriers, a variety of nanotechnology platforms have been developed to deliver these agents with high precision and spatiotemporal control. Based on their design principles and therapeutic mechanisms, these nanomedicines can be classified

Table 3. Nanomaterial-induced ferroptosis for overcoming therapy resistance in lung cancer

Therapy	Category	Name	Target mechanism	Reference
Chemotherapy resistance: cisplatin	Metal-based Nano-modulation Systems	ExoFeRTF	SLC7A11↓; GPX4↓; Fe^{2+}↑	[76]
		HSA@Pt(IV)	Fe↑; GSH↓; ROS↑	[77]
		Pt(IV)SS@ CaCO3@Biotin	GSH↓; ROS↑	[78]
		Ir-rhod	ACSL4↑, GPX4↓	[79]
		RuBTB	GSH↓GPX4↓	[80]
	Catalytic/Responsive Nano-systems	FP@SFN	GPX4↓; ROS↑; Ferritin Autophagy↑	[81]
	Bionic/Targeted Delivery Nano-system	FP@SLCDH	GPX4↓; GSH↓; Ferritin Autophagy↑; ROS↑	[82]
		ZnO@BBC	GSH↓; ROS↑	[83]
Chemotherapy resistance: Paclitaxel	Catalytic/Responsive Nano-systems	CACuPDA	GSH↓; GPX4↓; ROS↑	[84]
Radiotherapy Resistance	Bionic/Targeted Delivery Nano-systems	N-7DHC-lipos	GPX4↓; SLC7A11↓; ACSL4↑	[85]
	Metal-based Nanomodulation Systems	SPIONCs	Fenton reaction↑; SLC7A11↓; GPX4↓	[86]
	Metal-Based Nano-Modulation Systems	CeO_2@ZIF-8-HA	GSH↓; ROS↑	[57]
targeted therapy resistance: Gefitinib	Metal-based Nano-modulation Systems	FePt NPs	lipid peroxidation↑; ROS↑; GSH↓	[87]
targeted therapy resistance: Osimertinib	Catalytic/Responsive Nano-systems	VF/S/A@CaP	Fenton reaction↑; GSH↓; GPX4↓	[88]
	Bionic/Targeted Delivery Nano-systems	124I/Cy5.5-sO@ FCLs	cGAS-STING-ROS pathway↑ GPX4↓	[89]
Immunotherapy resistance	Metal-based Nano-modulation Systems	ZVI-NPs	NRF2↓; AMPK/mTOR↑	[90]

into three major categories, as summarized in **Table 3**.

Firstly, metal-based nanomodulation systems primarily trigger ferroptosis by introducing exogenous metal ions to catalyze oxidative stress. Iron-based nanoparticles, such as SPIONCs and FePt-NPs, directly expand the intracellular labile iron pool, fueling Fenton reactions to generate lethal lipid peroxides. These platforms often achieve therapeutic synergy by simultaneously downregulating GPX4 and upregulating ACSL4, thereby reversing resistance to cisplatin and gefitinib in lung cancer models.

Beyond direct metal catalysis, catalytic/responsive nano-systems are designed to activate specifically within the tumor microenvironment. Systems like RuBTB or CACuPDA respond to local acidity or high GSH levels, acting as potent GSH depletors to trigger GPX4 inactivation. By integrating such catalytic elements, these responsive nanocarriers can sensitize tumor cells to radiotherapy-induced oxidative damage while minimizing off-target toxicity to normal tissues.

At the same time, bionic/targeted delivery nano-systems, which utilize cell membrane coatings or specific ligands to enhance tumor-homing efficiency. Platforms such as ExoFeRTF and N-7DHC-lipos bypass biological barriers to deliver inhibitors targeting SLC7A11 or GPX4 directly into resistant cells. Concurrently, these carriers can activate secondary pathways, such as the cGAS-STING axis, to amplify ferroptotic signals. By ensuring robust intracellular accumulation and precise molecular targeting, these bionic platforms effectively restore drug sensitivity in paclitaxel- or osimertinib-resistant phenotypes. Together, these engineered nanostructures transform the therapeutic index of ferroptosis induction, offering a versatile toolkit to overcome various forms of therapy resistance in lung cancer.

Table 4. Nanomaterial-based precision therapy induces ferroptosis for antitumor activity

Therapy	Mechanism	Advantages	Nanomaterials for limitation compensation	Related materials
PDT	ROS generation upon light stimulation, primarily via the Fenton reaction cascade.	1. High targeting specificity 2. Ability to overcome therapeutic resistance 3. Synergistic enhancement of multiple therapeutic strategies	Precise regulation and efficient delivery Enhanced iron ion supply to promote ferroptotic reactions	1. CoFeOQDs [91] 2. Bithiophene-functionalized Ru(II)/Os(II)/Ir(III) [92] 3. TBPPN [93]
PTT				1. CuMnO@Fe3O4 (CMF) [94] 2. Bi2Se3-Fe3O4/Au [95]
SDT		1. Suitable for deep-seated tumors 2. Minimal invasiveness		1. cyclic arginine-glycine-aspartic acid to the αvβ3 receptor (cRGD-GIPG) [96] 2. DHA-DDF [97] 3. bowl-shaped COF nanosensitizers accumulate [98]

Precision medicine strategies based on nanomaterial-induced ferroptosis

The accumulating evidence has shown that nanomaterials not only can act as carriers for ferroptosis inducer delivery but also can act as endogenous ferroptosis inducers, which originate from their unique physicochemical properties.

Therefore, this strategy has enabled research to move into a stage of precision amplification, in which nanomaterials with intrinsic ferroptosis-regulating properties, together with controllable external physical energy, can synergistically enhance nanomaterial-induced ferroptosis within defined spatiotemporal regions. Consequently, a range of nanoplatform-based photodynamic therapy, photothermal therapy, and sonodynamic therapy strategies have emerged to cooperate with nanomaterial-triggered ferroptosis by increasing ROS production, disrupting membrane lipid metabolism, and impairing the antioxidant system. These approaches show stronger antitumor effects in drug-resistant lung cancer models and may provide alternative options for the treatment of drug-resistant and recurrent disease, as summarized in **Table 4**.

Moreover, ferroptosis-inducing chemodynamic therapy (CDT), which involves TME-specific activation of the Fenton reaction to produce hydroxyl radicals, has gained much attention recently. In contrast to traditional treatment approaches that lack specificity for cancer cells, CDT has high specificity for cancer tissues and can selectively kill cancer cells without damaging normal cells [99]. However, the poor cancer-targeting ability of CDT catalysts and low catalysis sustainability in the TME are the key limitations to improving CDT efficacy [100].

Further experimental studies have revealed that rationally engineered nanoplatforms might be able to overcome those limitations through maintaining catalytic activity and successfully inducing ferroptosis, leading to improved therapeutic efficacy for CDT and confirming its application potential for treating various pulmonary cancer with multi-drug-resistant characteristics. For example, A@P/uLDH can simultaneously maintain Fenton reactions and deplete GSH, thereby avoiding inevitable catalytic activity limitations and achieving improved antitumor effects in pulmonary cancer models [101]. Correspondingly, DHA@MIL-101 can load DHA, a ferroptosis inducer, to enhance ROS accumulation on nanomaterial platforms to overcome kinetic barriers existing in traditional single modality-based chemodynamic approaches and has exhibited strong therapeutic efficacy [102].

Together, the nanoplatforms with the capability to regulate ferroptosis could improve accumulation effectivity, spatiotemporal controllability, as well as multi-target-induced ferroptosis, so as to improve consistency and safety for drug-resistant lung cancer Fin-based approaches. Additionally, the nanoplatforms offer engineered solutions for pivotal translational obstacles of PDT, PTT, SDT, or CDT in solid tumors.

Single-cell RNA sequencing (scRNA-seq)-based AI model for monitoring ferroptosis progression

While nanomaterial-based approaches aimed at inducing ferroptosis show considerable

Table 5. Single-cell profiling of ferroptosis-related proteins in drug-resistant lung cancer

relationship	Name	Function	Ref.
Ferroptosis-suppressing factor	GPX4	Promotes radioresistance	[103]
	SLC7A11	Drives multidrug resistance	
	miR-6077	Enhances CDKN1A/KEAP1 signaling and chemoresistance	
	HNRNPA2B1/HDGF/PTN	Mediates radioresistance	[104]
	SPP1	Increases sensitivity to CEP-9722	[105]
	ADH1C	Acts as a protective biomarker	
	GLS	Contributes to radioresistance	[106]
	SREBP1-GPX4-ACSL4 axis	Induces resistance to ALK-targeted therapy	[107]
Ferroptosis-promoting factor	TFRC	Correlates with PD-L1, CTLA4 expression and immunotherapy response	[103]
	ACSL4	Indicates chemoresistance and poor prognosis	
	SLC7A5	Marker of poor prognosis	[108]
	CYBB		

promise for overcoming therapeutic resistance in lung cancer, treatment outcomes still vary substantially across different lung cancer subtypes, resistance patterns, and cellular populations within tumors. In this context, single-cell analysis provides an effective approach to characterize intercellular differences in molecular features related to ferroptosis and thus offers essential information for predicting the therapeutic response to nanomaterials. Single-cell-level analyses have revealed marked heterogeneity in the regulation of ferroptosis-related genes such as GPX4 and SLC7A11 in lung cancer, and this heterogeneity is closely associated with patient survival, as summarized in **Table 5**.

Nevertheless, despite the observation made by single-cell analysis that a notable heterogeneity exists in ferroptosis-related pathways, the high-dimensional and multi-modal characteristics of such datasets significantly complicate the process of analyzing and interpreting them. Nonetheless, AI models, which can be trained with ferroptosis-related single-cell molecular profiles, as well as resistance phenotypes and treatment response, can serve a technological role in developing a ferroptosis state predictor and designing optimized nanomaterial approaches for therapy. Significantly, with its application focused upon a translational aspect, rather than expanding a network, its main utility is to translate a highly dynamic and cell-state-dependent process, such as ferroptosis, into a predictable and traceable event.

In recent years, AI models of ferroptosis were used on single-cell sequencing data for the prognosis and discovery of key regulatory networks for various cancers and respiratory disorders, such as esophageal carcinoma and chronic obstructive pulmonary disease [109, 110]. Such studies offer proof of concept for using a similar approach for the study of lung cancer.

For lung cancer, Ji et al. analyzed the scRNA-seq dataset GSE131907 from the GEO and carried out cross-validation with a total of eight machine-learning algorithms, and core genes HLF, HPCAL1, and NUPR1 were determined through this exercise, which are believed to modulate macrophage polarization through iron metabolism and oxidative stress. A prognostic model for LUAD was established using macrophage ferroptosis-related genes, and this work unraveled the relationship between immune modulation and ferroptosis in the tumor microenvironment and offered a strategy for tracking the ferroptosis-associated status. It is important to note that this work suggests a possible perspective where ferroptosis-associated AI models could go beyond the present prognosis and provide valuable clues regarding the transition from a inhibited to an active ferroptotic status in the tumor-immune microenvironment for guiding decisions regarding subsequent therapies [111].

From the GSE131907 dataset, a heme metabolism-related AI prognostic model (HMRS) was

identified that defined ABCC2, SLC2A1, and SMOX as key genes and utilized a deep neural network to categorize cells based on risk. The high-risk group was characterized by enhanced ferroptosis inhibitory pathways and reduced platinum sensitivity, indicating that ferroptosis inhibition could be a contributing factor to platinum resistance and a prognostic marker for poor outcomes in lung cancer [112].

More recent evidence also shows that glutaminase (GLS) has the ability to affect radiosensitivity in LUAD by regulating ferroptosis. The GLS-DSBr model designed using deep learning has been adopted as a benchmark model for ferroptosis dynamics analysis as well as predicting the radiosensitivity of lung cancer cells to radiotherapy and immunotherapy [106].

In contrast to traditional risk-stratification models, these more recent and complex models are more focused on dynamic models of prediction responses and on the role of ferroptosis-related changes in metabolic pathways as potential biomarkers in dynamics monitoring in multimodal therapy approaches.

Taken together, AI models derived from single-cell sequencing are rapidly shifting the paradigm on ferroptosis, from the challenging and measurable cell death approach to the interpretable cell state approacheable and measurable treatment outcomes. Its applications could explain heterogeneity in ferroptosis-related resistance to lung cancer treatment and offer tools for time-optimizing nano-therapeutic approaches on the data level.

Therapeutic potential of natural bioactive compounds

N-Acetylcactors (NACs), which include alkaloids, flavonoids, polyphenols, and saponins, and originate from traditional Chinese medicines, have attracted considerable attention based on their assumed anticancer effects. Compared to ferroptosis inducers that have been designed using chemical synthesis methods, these compounds often entail relatively lower production costs and can potentially resist the induction of acquired resistance, which can pose adverse effects to the cells. Emerging research has suggested that the spectrum of NACs is vast and can induce ferroptosis, which appears to offer a diverse resource for the development of ferroptosis-based therapy for the treatment of lung cancer.

The growing body of data points to the fact that NACs control ferroptosis through several mechanisms. Specifically, they regulate ferroptosis-related iron processing and antioxidant protection in lung cancer by four main pathways: the SLC7A11-GSH-GPX4 system [113-116]; NCOA4-dependent ferritinolysis [117]; the Nrf2-GPX4 pathway [118]; and the Nrf2/HO-1 signaling axis [119-121].

In these respects, these mechanisms suggest that NACs could modulate the ferroptosis threshold instead of acting as a single node for triggering cell death. Therefore, the use of NACs could alleviate systemic toxicity effectively and may be more appropriate for long-term treatment or a combination of therapies including chemotherapy, radiotherapy, and nanomaterial therapies.

Several NACs have been shown to cause ferroptosis by means of the reprogramming of iron metabolism and antioxidant pathways in lung cancer models, as well as to have sensitizing effects in drug-resistant cancer cells. This data offers a possible pharmacological rationale for improvement in the safety margin for targeting ferroptosis, as shown in **Table 6**.

Conclusion and discussion

Emerging evidence indicates that ferroptosis-resistance is an important player in the development of therapeutic tolerance in lung cancer cells. Combination therapy with ferroptosis inducers (FINS) has shown the potential for overcoming therapeutic tolerance and improved treatment response and outcomes. In an effort to cover the most critical shortcomings of FINS, namely inefficient tumor targeting, the inability to control inducible ferroptosis, and systemic toxicity, advances in nanotechnology, precision therapeutic strategies, machine-learning-assisted monitoring, and nutraceuticals based on traditional Chinese medicines (NACs) are currently explored and investigated with great expectations across the following dimensions for overcoming the translational hurdles associated with FINS.

What is significant is that there is a gradual migration of NAC-based herbal medications

Table 6. Natural bioactive compounds for overcoming therapy resistance in lung cancer

Natural Active Ingredient	Source	Resistance Type	Key Targets/ Pathways	Ferroptosis Mechanism	Reference
Artemisia santolinifolia	Artemisias	Chemotherapy: Docetaxel	STAT3/Survivin↓	GPX4↓; ROS↑	[122]
Dihydroisotanshinone I	Salvia miltiorrhiza Bunge	Chemotherapy: cisplatin	PI3K/MDM2/ P53↓	GPX4↓; SLC7A11↓	[123]
d-Borneol	Borneol		NCOA4↑; PRNP↑; PCBP2↓	ROS↑; GSH↓	[124]
Heterosaponin VII	Rhizoma Paridis		ACSL4↑; NADPH oxidase 4↑	ROS↑	[125]
gallic acid	nutgall	Radiotherapy	Nrf2↓	SLC7A11; GPX4↓; ACSL4↑	[126]
β-Elemene	Curcuma Rhizoma	Targeted therapy: Erlotinib	TFEB↑	GPX4↓	[127]
betulin	Birch tree	Targeted therapy: Gefitinib	HO-1↑	ROS↑; GPX4/ SLC7A11/FTH1↓	[128]

into the clinic. For example, β-elemene has been found to trigger ferroptosis in NSCLC cells mediated via the GPX4/SLC7A11 pathway, and its injectable form (National Medical Products Administration approval no. H10960114) led to higher objective response rates during phase III trials, especially against therapy-resistant cells, by increasing sensitivity to ferroptosis. In addition, combinations containing β-elemene were found to make it possible for chemotherapy dose reduction in some patients with reduced adverse effects. In China, β-elemene injectable formulations are already used as part of combination therapies for treating NSCLC.

At the same time, the clinical trial NCT-06048367 assessed the nano-iron ferroptosis inducer CNSI-Fe(II) for treating lung cancer in its advanced stages in a phase I clinical trial. The preliminary findings suggested a favorable safety profile, regular pharmacokinetics, and tolerable levels of toxicity. Most importantly, the study suggested that no maximum tolerable dose of the treatment existed even up to doses of 30 mg to 150 mg, which reached a dosing level of only 90 mg for which dose-limiting toxicities were documented, and only a few treatment-related severe adverse events were noted, suggesting a sufficiently wide therapeutic window for treatment. These preliminary clinical results suggest the first clinical validation of the concept that nanoparticle-based ferroptosis inducers can decrease systemic toxicity due to controlled and targeted drug delivery.

In the clinical setting, artificial intelligence is increasingly incorporated in various aspects of pulmonary cancer diagnosis and therapy, to enable the seamless integration of surrogate markers for ferroptosis into current practice. Furthermore, machine-learning algorithms that utilize radiological, histopathological, and clinical data have significantly improved the sensitivity, specificity, and positive predictive value of cancer typing, staging, and risk assessment. Future developments in this area will enable the use of ferroptosis-related biomarkers in current platforms for cancer therapy, in an attempt to transition from dose escalation to ferroptosis status-guided precise therapy. Currently, this is feasible because the integration allows for the non-invasive assessment of ferroptosis status, real-time feedback on the impact of therapy on the redox and iron homeostasis pathways, and the ability to make necessary adaptational changes in therapy strategies in real time [129, 130].

Despite progress, there remain three key issues to be solved. First, there has been a lack of clear explanation of mechanisms of dynamic transition between ferroptosis-suppressed and ferroptosis-permissive environments. Second, a high level of invasiveness of primary current models using AI, which depend mainly on single-cell sequencing, calls for development of noninvasive imaging systems to evaluate ferroptosis activity. Third, despite a positive role of multi-target actions of natural products on toxicity, there remain problems in developing over-

all quality control standards concerning ferroptosis induction.

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Disclosure of conflict of interest

None.

Abbreviations

4-HNE, 4-hydroxynonenal; AA, Arachidonic acid; AA-CoA, Arachidonoyl-coenzyme A; ACSL4, Acyl-CoA synthetase long-chain family member 4; ADH1C, Alcohol dehydrogenase 1C; ALK-TKI, Anaplastic lymphoma kinase tyrosine kinase inhibitor; AMPK, AMP-activated protein kinase; ANRIL, Antisense non-coding RNA in the INK4 locus; APC, Antigen-presenting cell; APOC1, Apolipoprotein C1; ALOX13, Arachidonate lipoxygenase 13; ALOX15, Arachidonate lipoxygenase 15; ATP, Adenosine triphosphate; B7, B7 family costimulatory molecule; CA9, Carbonic anhydrase 9; cGAS, Cyclic GMP-AMP synthase; circRNA, Circular RNA; CoQH2, reduced coenzyme Q10; COF, Covalent organic framework; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; CYBB, Cytochrome b-245 beta chain; CDKN1A, Cyclin-dependent kinase inhibitor 1A; cRGD, Cyclic Arg-Gly-Asp peptide; DDR1, Discoidin domain receptor 1; DHA, Dihydroartemisinin; DNMT1, DNA methyltransferase 1; eIF3d, Eukaryotic translation initiation factor 3 subunit d; EGR1, Early growth response 1; EGFR, Epidermal growth factor receptor; EGFR-TKI, Epidermal growth factor receptor tyrosine kinase inhibitor; FBLN5, Fibulin 5; FPN, Ferroportin; FSP1, Ferroptosis suppressor protein 1; FTH1, Ferritin heavy chain 1; FTL, Ferritin light chain; GSH, Reduced glutathione; GSSG, Oxidized glutathione; Glu, Glutamate; GLS, Glutaminase; GPX4, Glutathione peroxidase 4; HA, Hyaluronic acid; HERC1, HECT and RLD domain containing E3 ubiquitin protein ligase 1; HDAC, Histone deacetylase; HDAC10, Histone deacetylase 10; HDGF, Hepatoma-derived growth factor; HIF-1α, Hypoxia-inducible factor 1-alpha; HMGB1, High mobility group box 1; HMOX1/HO-1, Heme oxygenase 1; HNRNPA2B1, Heterogeneous nuclear ribonucleoprotein A2/B1; IFN-γ, Interferon gamma; IFNR, Interferon receptor; IL-1, Interleukin 1; IL-2, Interleukin 2; IRF1, Interferon regulatory factor 1; Ir, Iridium; K11, Lysine 11; KEAP1, Kelch-like ECH-associated protein 1; lncRNA, Long non-coding RNA; LPCAT3, Lysophosphatidylcholine acyltransferase 3; LIP, Labile iron pool; LPO, Lipid peroxidation; m6A, N6-methyladenosine; MDA, Malondialdehyde; MDM2, Mouse double minute 2 homolog; Mef, Mefloquine; METTL3, Methyltransferase-like 3; METTL16, Methyltransferase-like 16; MGST1, Microsomal glutathione S-transferase 1; miR, microRNA; mTOR, Mechanistic target of rapamycin; NCOA4, Nuclear receptor coactivator 4; NADPH, Nicotinamide adenine dinucleotide phosphate (reduced form); NEAT1, Nuclear paraspeckle assembly transcript 1; NRF2/Nrf2, Nuclear factor erythroid 2-related factor 2; Os(II), Osmium(II); p53, Tumor protein p53; PCBP2, Poly(rC)-binding protein 2; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; PDT, Photodynamic therapy; PHKG2, Phosphorylase kinase gamma 2; PI3K, Phosphoinositide 3-kinase; PRDX6, Peroxiredoxin 6; PRNP, Prion protein; PTN, Pleiotrophin; PTT, Photothermal therapy; PUFA, Polyunsaturated fatty acid; ROS, Reactive oxygen species; ROS1, ROS proto-oncogene 1; RSL3, Ras-selective lethal 3; Ru(II), Ruthenium(II); RBMS1, RNA-binding motif single-stranded interacting protein 1; SDT, Sonodynamic therapy; SENP1, SUMO-specific protease 1; SLC3A2, Solute carrier family 3 member 2; SLC7A11, Solute carrier family 7 member 11; SLC7A5, Solute carrier family 7 member 5; SOX2, SRY-box transcription factor 2; SOCS2, Suppressor of cytokine signaling 2; SPIONCs, Superparamagnetic iron oxide nanoclusters; SPP1, Secreted phosphoprotein 1 (osteopontin); SREBP1, Sterol regulatory element-binding protein 1; STING, Stimulator of interferon genes; STAT1, Signal transducer and activator of transcription 1; STAT3, Signal transducer and activator of transcription 3; SUMO, Small ubiquitin-like modifier; TFEB, Transcription factor EB; Tf, Transferrin; TFRC, Transferrin receptor; TFR1, Transferrin receptor 1; USP35, Ubiquitin specific peptidase 35; Wnt, Wnt signaling pathway; xCT/XCT, Cystine/glutamate antiporter light chain; YAP, Yes-associated protein; ZIF-8, Zeolitic imidazolate framework-8.

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