Harnessing ferroptosis for cancer therapy: Mechanisms and therapeutic strategies (Review)

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Abstract. Ferroptosis is a type of programmed cell death characterized by accumulation of free iron, reactive oxygen species generation and lipid peroxidation and is distinct from other types of regulated cell deaths such as apoptosis, necrosis and autophagy. Ferroptosis is distinct from other programmed cell deaths for its iron dependence and its significant role in tumor suppression. Therefore, harnessing ferroptosis may offer promising avenues for cancer therapy. In the present review, the different pathways that lead to ferroptosis, the genes and transcription factors involved in both iron and lipid metabolism, as well as the impact of small-molecule alterations on the regulation of ferroptotic cell death, were discussed. Furthermore, the emergence of combination therapies with ferroptosis-inducing molecules that overcome resistance to conventional chemotherapy, particularly in solid tumors, were highlighted.

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Abbreviations: AA, arachidonic acid; ABCC5, ATP-binding cassette subfamily C member 5; ACSL4, acyl-CoA synthetase long-chain family member 4; AdA, adrenic acid; AML, acute myeloid leukemia; ATF4, activating transcription factor 4; BCAT2, enzyme branched-chain amino acid transferase 2; BH4, tetrahydrobiopterin; CD36, cluster of differentiation 36 or fatty acid translocase; circRNA, circular RNA; CoQ10, Coenzyme Q10; COX, cyclooxygenase; DHODH, dihydroorotate dehydrogenase; DMT1, divalent metal transporter 1; FATP, fatty acid transporter; FSP1, ferroptosis suppressor protein 1; FTH1, ferritin heavy chain 1; GCH1, guanosine-5'-triphosphate cyclohydrolase-1; GCL, glutamate-cysteine ligase; GSH, reduced glutathione; GSSG, oxidized glutathione; GSTZ1, glutathione S-tranferase zeta 1; HCC, hepatocellular carcinoma; HIC1, HIC ZBTB transcriptional repressor 1; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HNF4α, hepatocyte nuclear factor 4α; HO-1, heme oxygenase 1; HSC, hematopoietic stem cell; HSPA5, heat shock protein family A (Hsp70) member 5; LD, lipid droplets; lncRNA, long-non-coding RNA; LOX, lipoxygenase; LPCAT3, lysophosphatidylcholine acyl-transferase 3; LPO, lipid peroxidation; MDA, malondialdehyde; miRNA, microRNA; NCOA4, nuclear receptor coactivator 4; ncRNA, non-coding RNA; NRF2, nuclear factor erythroid 2-related factor 2; NSCLC, non-small cell lung cancer; OTUB1, OTU deubiquitinase; POR, cytochrome P450 oxidoreductase; PSAT1, phosphoserine aminotransferase 1; PSTK, phosphor-seryl-tRNA kinase; PUFAs, polyunsaturated fatty acids; Rb, retinoblastoma; ROS, reactive oxygen species; SAS, sulfasalazine; Sec, selenocysteine; TFR1, transferrin receptor 1; TNBC, triple-negative breast cancer

Key words: ferroptosis, iron metabolism, lipid peroxidation, GPX4/GSH/System Xc^- axis, ROS accumulation, chemoresistance, cancer therapy

Contents

1. Introduction

Cancer therapies that rely on the induction of apoptosis have long faced significant challenges due to one of the defining hallmarks of cancer cells; their inherent ability to evade apoptotic cell death (1). Traditionally, cell death has been considered to occur following two main pathways: The physiological process of apoptosis and the pathological process of necrosis. Previously, new forms of programmed cell deaths have been discovered, one of which being ferroptosis. In 2012, Dixon *et al* (2) coined the term 'ferroptosis' after discovering a form of cell death induced by an increase in reactive oxygen species (ROS) and lipid peroxidation (LPO) (2). The Nomenclature Committee on Cell Death later classified ferroptosis as a form of non-apoptotic cell death, based on its unique morphological and biochemical features (3). This type of cell death differs from apoptosis as it does not involve cell shrinkage, and from necrosis as it does not result in cell swelling. Additionally, it occurs independently of caspase activation (4).

The standard treatment for malignant tumors commonly includes chemotherapy, often combined with other approaches such as radiotherapy and surgical resection. Both

chemotherapy and radiotherapy are intended to target rapidly dividing cancer cells but may also affect normal proliferating cells (5). In certain cancers, such as hepatocellular carcinoma (HCC), resistance to chemotherapy can develop secondary to the expression of resistance-associated genes, thereby lowering the effectiveness of conventional therapeutics (6).

The activation of ferroptosis has emerged as a promising cancer therapeutic strategy. Inducing this non-apoptotic form of regulated cell death has shown effectiveness across various cancer types, offering new avenues for overcoming chemoresistance and improving outcomes. In the present review, the molecular mechanisms underlying ferroptosis were first explored, then the findings specific to different cancer types were examined, and finally the potential of ferroptosis-based therapeutic approaches were assessed.

2. Mechanisms of ferroptosis

Understanding the intricacies of this cell death pathway requires a closer look at the molecular regulators of iron homeostasis, antioxidant defense and lipid metabolism.

Iron metabolism. Tumor cells often exhibit iron overload, making them prone to ferroptotic cell death. Key iron metabolism-associated proteins such as transferrin, transferrin receptor 1 (TFR1), ferroportin, ferritin and divalent metal transporter 1 (DMT1) are frequently dysregulated during carcinogenesis. The regulatory role of iron metabolism in ferroptosis is illustrated in Fig. 1.

Transferrin is a glycoprotein that transports iron through the bloodstream in a controlled, non-toxic form (7). It plays an indirect yet significant role in regulating ferroptosis by modulating the cellular iron pool. Iron is delivered to cells via the interaction between transferrin and TFR1 on the cell surface. TFR1 expression is tightly linked to iron availability: It is upregulated under conditions of low intracellular iron to enhance uptake, and downregulated when iron is abundant to prevent overload (8). As such, TFR1 is a key regulator of cellular iron homeostasis and plays a pivotal role in balancing a cell's vulnerability or resistance to ferroptosis. Once internalized, iron binds to ferritin, an intracellular iron-storage protein. Accumulation of free Fe^{2+} in the cell, resulting either from iron overload or from insufficient expression or excessive degradation of ferritin, leads to the conversion of hydrogen peroxide to hydroxyl radicals, through the Fenton reaction, resulting in production of ROS. If cellular ROS accumulates secondary to disruptions in the cell's antioxidant system, it will lead to LPO, the hallmark of ferroptosis, and subsequent cell death (9).

Ferritin is an intracellular iron-storage protein that plays a central role in iron homeostasis by sequestering excess iron and releasing it when needed (10). Structurally, ferritin consists of 24 subunits comprising heavy (H) and light (L) chains, which together can store thousands of iron atoms (11). This prevents iron from participating in Fenton reactions and minimizes oxidative stress (12). Similarly to TFR1, ferritin expression is also linked to iron availability, as well as the presence of certain hormonal regulators such as hepcidin (13). Elevated ferritin levels reduce the pool of free iron and suppress ferroptosis. Conversely, low ferritin expression increases labile iron levels, promoting Fenton chemistry, LPO and ultimately, ferroptosis. In the context of carcinogenesis, ferritin regulation is often disrupted. Tumor cells frequently upregulate ferritin expression to buffer against iron-induced oxidative stress, thereby enhancing resistance to ferroptosis and promoting survival under iron-rich conditions (14).

Ferroportin, a transmembrane protein that exports iron from cells into the bloodstream to re-enter circulation, recycles transferrin back into the bloodstream, regulating systemic iron homeostasis. Hepcidin, a hormone synthesized by the liver, tightly regulates ferroportin by inducing its degradation to maintain iron homeostasis (15). Elevated hepcidin levels lead to ferroportin internalization and subsequent degradation resulting in reduced iron efflux and ultimately increased ferroptosis. However, when hepcidin levels are low, ferroportin is found more abundantly on the cell surface, increasing iron efflux, and most importantly, decreasing the cell's susceptibility to iron-induced stress and ferroptosis (16). Often, ferroportin is downregulated in several types of cancer, leading to iron accumulation, and rendering them more susceptible to ferroptosis (17). It has been reported that taking advantage of this downregulation may provide an alternative therapeutic strategy, leading to ferroptotic cell death in several tumors. However, targeting ferroportin expression must be conducted carefully as it could be a double-edged sword, potentially both protecting and eliminating cancer cells (18).

DMT1, also known as natural resistance-associated macrophage protein 2, is a transmembrane protein involved in the uptake of dietary iron from the small intestine, the absorption of iron by proliferating red blood cells, and the ejection of iron from endosomes in numerous cell types (19). The expression of DMT1 is inversely regulated by iron availability. Elevated iron levels lead to the downregulation of DMT1, while low iron levels lead to its upregulation (20). Cellular sensitivity to ferroptosis increases when DMT1 is overexpressed. DMT1 expression varies across tumor types with tumors having a high demand for iron often showing DMT1 upregulation, whereas others downregulate DMT1 as an anti-ferroptotic defense mechanism against iron accumulation. It has been revealed that overactivation of DMT1 can promote ferroptosis in several cancers, highlighting its potential as a therapeutic target (21).

It is now well established that ferroptosis occurs in cells with dysregulated iron metabolism or impaired antioxidant defense. Malfunction, mutation or dysregulation of any of the key proteins involved in these processes can either reduce or enhance cellular vulnerability to ferroptosis.

GSH/GPX4/System Xc^- axis

GSH and GPX4 as central antioxidant defenses. The GSH/GPX4/System Xc^- axis serves as the primary defense mechanism against ferroptosis by suppressing the accumulation of lipid peroxides. At its core, the key regulatory enzyme glutathione peroxidase 4 (GPX4) utilizes reduced glutathione (GSH) to reduce lipid peroxides into non-toxic lipid alcohols, thereby inhibiting ferroptosis (22). GSH is then regenerated from its oxidized form (GSSG) by glutathione reductase. Therefore, maintaining adequate intracellular GSH levels is vital for sustaining GPX4 activity and blocking this cell death pathway (23,24).

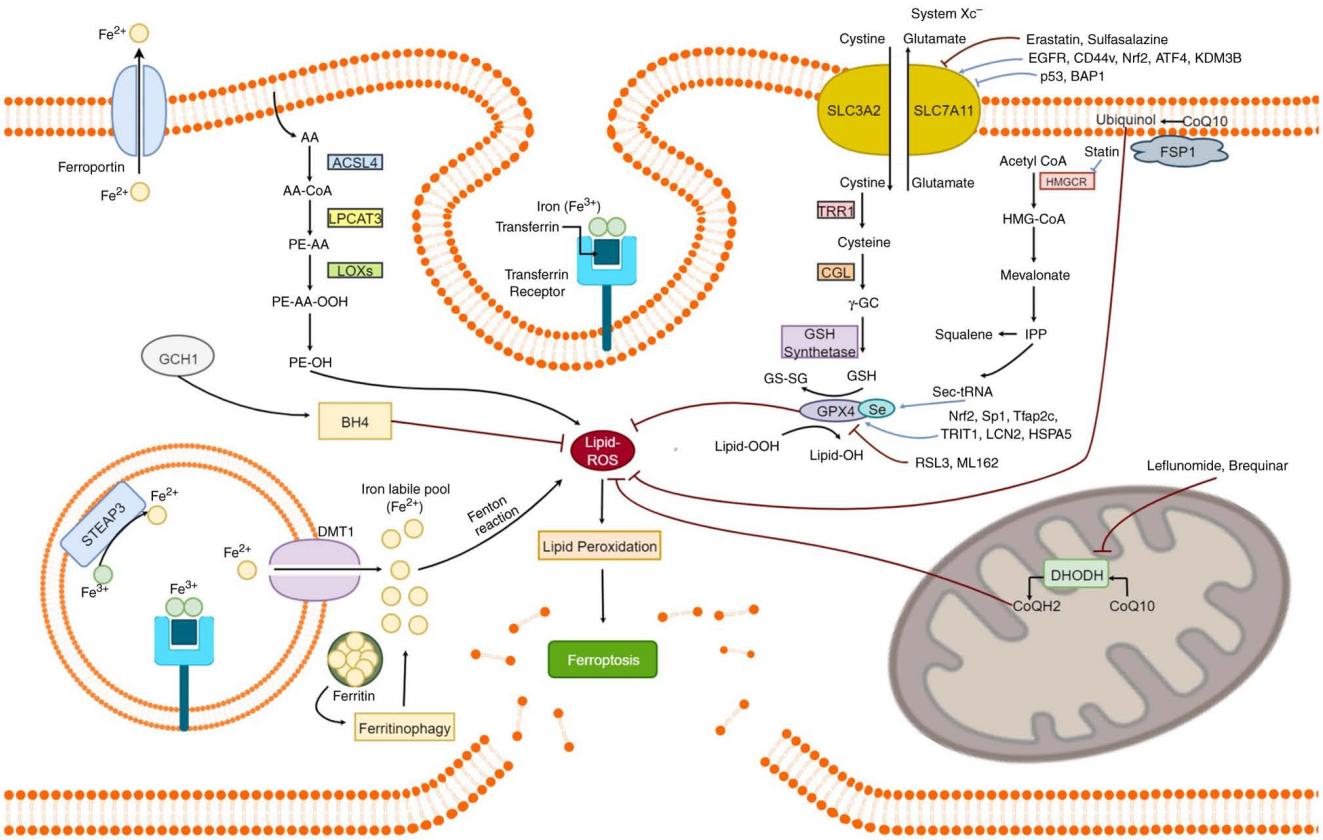

Figure 1. Overview of key pathways and molecular regulators involved in ferroptosis, an iron dependent form of regulated cell death marked by the accumulation of ROS. Iron metabolism increases the labile iron pool (Fe^{2+}), which drives LPO through Fenton reactions. The System Xc^- antiporter, composed of SLC7A11 and SLC3A2, imports cystine in exchange for glutamate, enabling the synthesis of GSH, a crucial antioxidant that supports GPX4 function. GPX4 protects cells from ferroptosis by converting toxic lipid hydroperoxides (Lipid-OOH) into non-toxic lipid-alcohols (Lipid-OH). Enzymes such as ACSL4, LPCAT3 and LOXs facilitate phospholipid peroxidation, enhancing ferroptosis. Ferritin degradation (ferritinophagy) releases free iron, enhancing sensitivity to ferroptotic cell death. In mitochondria, DHODH reduces CoQ to CoQH2, providing an additional defense against lipid peroxidation, particularly when GPX4 activity is impaired. In the cytosol, the GCH1/BH4 axis offers a GPX4-independent antioxidant pathway, where BH4 synthesis helps suppress lipid peroxidation and ferroptosis. Small molecules (for example, erastin and RSL3) and regulatory proteins (for example, FSP1, NRF2 and p53) modulate ferroptotic signaling through various mechanisms, including GSH depletion and GPX4 inhibition. ROS, reactive oxygen species; LPO, lipid peroxidation; GSH, reduced glutathione; GPX4, glutathione peroxidase 4; LOX, lipoxygenase; DHODH, dihydroorotate dehydrogenase; CoQ10, Coenzyme Q10; COX, cyclooxygenase.

System Xc⁻. GSH biosynthesis is dependent on cystine uptake mediated by the System Xc^- amino acid antiporter, which is expressed in various cell types, including hepatocytes, fibroblasts and macrophages (25). This transporter consists of two subunits, SLC3A2 and SLC7A11, and exchanges intracellular L-glutamate for extracellular L-cystine. Upon entry into the cell, the L-cystine molecule is reduced to L-cysteine by thioredoxin reductase 1 (26). L-cysteine then combines with glutamate to form γ-glutamyl cysteine, in a reaction catalyzed by glutamate-cysteine-ligase (GCL). The subsequent addition of glycine to the γ-glutamyl cysteine, catalyzed by the enzyme GSH synthetase, generates the potent antioxidant GSH.

SLC7A11 regulation. The activity of the System Xc-antiporter is primarily determined by the expression of its SLC7A11 subunit. Elevated SLC7A11 expression promotes cystine uptake, facilitating GSH synthesis promoting cell survival by suppressing ferroptosis. Conversely, reduced SLC7A11 expression impairs this antioxidant defense pathway, inducing ferroptotic cell death (27). Therefore, regulation of SLC7A11 is critical in ferroptosis resistance (28).

Transcriptionally, transcription factors such as activating factor 4 (ATF4) and nuclear factor erythroid 2-related factor (NRF2) induce SLC7A11 expression under oxidative and nutrient stress (cysteine deprivation) respectively, while in cancer, ATF4 additionally supports tumor growth, proliferation and angiogenesis (29-31).

Epigenetically, repressors including nuclear deubiquitinase, anti-oncogene BRCA1-associated protein 1 and tumor suppressor protein p53 have been shown to interact with the SCL7A11 gene promoter and repress its expression, reducing L-cysteine uptake and increasing sensitivity to ferroptosis (32,33). By contrast, the histone lysine demethylase 3B enzyme enhances SLC7A11 expression by demethylating of histone 3 on lysine 9, enhancing L-cystine uptake and resistance to ferroptosis (34).

Post-translationally, factors such as epidermal growth factor receptor, adhesion molecule CD44v (expressed in cancer stem cells) and deubiquitinases, stabilize SLC7A1, protecting it from degradation and sustaining cystine uptake, thus decreasing sensitivity to ferroptosis (35,36). By contrast, small molecule inhibitors such as Erastin block SLC7A11 function to induce this cell death pathway, highlighting its potential as a therapeutic target (37).

Beyond SLC7A11, GSH synthesis is regulated by the enzyme GCL. Inhibition of GCL with sulfonamide or disruption of its stability reduces GSH production and sensitizes cells to ferroptosis (38-40). Moreover, pharmacological depletion of cysteine, such as with engineered cyst(e)inase, selectively induces cancer cell death by reducing GSH and elevating ROS (41). Furthermore, salvage pathways like trans-sulfuration can maintain cysteine and GSH pools independently of System Xc^-, representing an alternative route to ferroptosis resistance (42,43).

GPX4 regulation. Finally, the selenoprotein GPX4 itself is a key regulatory node in ferroptosis (44). Its expression is dependent on selenium metabolism and the mevalonate pathway, which generates the isopentenyl pyrophosphate required for the maturation of the selenocysteine tRNA essential for the incorporation of Sec into its catalytic site (45-47). Blocking the mevalonate pathway with statins, cholesterol-lowering drugs, has been shown to impair GPX4 translation and maturation, thereby increasing cell sensitivity to ferroptosis (47). At the transcriptional level, GPX4 is regulated by the transcription factors such as NRF2, Sp1 and Tfap2c and mTORC, LCN2 upregulates both SLC7A11 and GPX4 to block ferroptosis (48-51).

Post-translationally, GPX4 and its stability is primarily regulated by three major protein modifications: Succination (fumarate binding), alkylation (RSL3, ML162, withaferin A) and ubiquitination, which can target it for degradation (52-56).

Epigenetically, chaperones such as heat shock protein A5 (HSPA5) can directly bind to GPX4, shielding it from proteasomal degradation and thereby stabilizing the protein (57). Similarly, lipoxygenases contribute to GPX4 inactivation by catalyzing the oxidation of its Sec residue, inactivating its catalytic site (58).

Moreover, some aggressive and chemo-resistant cancers, such as HCC, have been shown to exhibit increased sensitivity to LPO. This supports the idea that combining ferroptosis inducers that target the GSH/System Xc^- and GPX4 axis with conventional chemotherapeutic agents may offer a novel and effective clinical strategy for cancer treatment (59). The regulatory role of the GSH/GPX4/System Xc^- axis in ferroptosis is illustrated in Fig. 1.

LPO and metabolism. Ferroptosis is triggered by the accumulation of lipid peroxides. It has been previously demonstrated that phosphatidylethanolamines containing polyunsaturated fatty acids (PUFAs) such as Arachidonic acid (AA) or adrenac acid (AdA), which are embedded in the cell membrane, are susceptible to LPO (60). Chemical modifications of these acids, particularly acylation, can alter their properties and significantly influence the regulation of ferroptosis. The acylation of AA/AdA is performed by two enzymes: Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lyso-phosphatidyl-choline acyltransferase 3 (LPCAT3) (61). Inhibition of either enzyme reduces LPO and, thus, may suppress ferroptosis. Additionally, the ferroptosis suppressor protein 1 (FSP1) plays a vital role in protecting cells from ferroptosis due to decreased GPX4 levels. FSP1 catalyzes the regeneration of coenzyme Q10 (CoQ10, also known as ubiquinone) using NADPH. The reduced form of CoQ10, ubiquinol traps lipid peroxyl radicals, effectively limiting LPO and preventing ferroptotic cell death (62).

Among the numerous metabolic alterations observed in cancer cells, compared with normal; cells, are changes in lipid metabolism, which have significant implications for ferroptotic cell death (63). Lipid metabolism includes fatty acid synthesis and transport, mevalonate and cholesterol synthesis pathways, as well as several other essential signaling cascades (64). AA and AdA are major substrates for LPO and require the activity of two enzymes: Elongation of very long-chain fatty acid protein 5 and fatty acid desaturase 1, both of which are highly expressed in certain tumors such as gastric cancer cells (65). Upregulation of these enzymes has been shown to increase resistance to ferroptosis in these cells. On the contrary, epigenetic silencing of these enzymes through DNA methylation of their respective promoter regions downregulates their expression, restoring ferroptosis sensitivity (66).

During lipid synthesis, excess glucose is funneled into the *de novo* lipogenesis pathway, which enables cells to synthesize most of their necessary fatty acids, except for a few essential PUFAs that depend on dietary intake, namely alpha-linoleic acid and linoleic acid (67,68). Compared with a healthy cell, cancer cells divert glucose for anabolic processes instead of using it for oxidative energy production (69). In fact, nearly all fatty acids in tumor cells are derived from endogenous synthesis (70). This metabolic shift suggests that cancer cells may evade ferroptosis by upregulating *de novo* lipogenesis, ensuring a continuous supply of fatty acids.

Moreover, one of the products of this pathway, triacylglycerol, contributes to the formation of lipid droplets (LDs), which are energy storage units implicated in cancer cell metabolism and proliferation (71). Certain cyclooxygenase (COX) enzymes, necessary for LPO, have been localized within LDs and shown to enhance angiogenesis, suggesting that elevated LD levels may play a critical role in ferroptosis resistance (72).

In case the *de novo* lipid synthesis pathway is impaired, cancer cells compensate by increasing lipid uptake. This is mediated by the increased expression of fatty acid transporter (FATP), fatty acid translocase (FAT/Cluster of differentiation 36 or CD36) and fatty acid-binding proteins, which facilitate the import of extracellular fatty acids. These transporters are not only highly expressed in cancer cells but are also associated with increased tumor metastasis (73). Notably, studies have shown that the inhibition of CD36 and FATP2 has been shown to suppress tumor growth and promote ferroptosis, highlighting their potential as therapeutic targets (74,75).

The mevalonate pathway, responsible for cholesterol biosynthesis, is tightly linked to the regulation of ferroptosis and the activity of the GPX4 selenoprotein (76). Within this pathway, the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) catalyzes the conversion of HMG-CoA to mevalonate. HMGCR is frequently upregulated in cancer cells, where it promotes their proliferation and migration. However, inhibiting this enzyme has been shown to increase vulnerability to ferroptosis, largely due to its disruptive effect on the overall pathway and the subsequent impairment of GPX4 maturation and function (77). Moreover, the use of statins inhibits HMGCR, leading to inactivation of GPX4 and the increase in ferroptosis occurrence overall (59). The contribution of LPO to ferroptosis is illustrated in Fig. 1.

GPX4-independent regulation of ferroptosis

DHODH/CoqH2 axis. Recent studies have explored the role of dihydroorotate dehydrogenase (DHODH) in the

context of ferroptosis regulation. DHODH is a mitochondrial inner-membrane enzyme capable of reducing CoQ to regenerate CoqH2, thus mitigating LPO and ultimately suppressing ferroptotic activity. This axis serves as the main mitochondrial defense against LPO (78). In addition, loss of GPX4 function is significantly compensated by enhanced production of DHODH-mediated CoQH2, especially in cancer cells (79). DHODH inhibitors such as leflunomide and Brequinar have shown promising results in cancers such as HCC where GPX4 is lowly expressed, significantly enhancing cell sensitivity to ferroptosis and boosting therapeutic approaches (80,81).

GCH1/BH4 axis. While the DHODH/CoqH2 axis is localized in the mitochondria, the GCH1/BH4 axis is primarily a cytosolic pathway, recently identified as a GPX4-independent ferroptotic regulatory system (82). Guanosine-5'-triphoshpate cyclohydrolase-1 (GCH1) catalyzes the biosynthesis of tetrahydrobiopterin (BH4), a prominent antioxidant similar in function to CoQ10. A direct link between GCH1 expression levels and cell resistance to ferroptosis has been reported. Indeed, inhibition of GCH1 leads to low levels of BH4 and thus drives cells towards accumulation of LPO and eventually, ferroptotic death (83). By contrast, upregulation of this axis protects cells from ferroptosis, and emerging data highlights specific pathways, such as the RAS pathway in oncogenic signaling, capable of enhancing GCH1 transcription and suppressing ferroptosis (84).

Altogether, the DHODH/CoQH2 axis as well as the GCH1/BH4 axis are both GPX4-independent regulatory systems of ferroptosis, localized within the mitochondria and the cytosol, respectively. Emerging research focuses on their vulnerability and targetability in cancer therapy (85).

3. Ferroptosis across cancers

The molecular framework of ferroptosis manifests differently across cancer types, with distinct patterns of iron regulation, antioxidant capacity and lipid metabolism shaping each tumor's response to ferroptotic stress. In the present review, cancers where ferroptosis has been more extensively investigated (for example, HCC, lung, breast, bladder and gastrointestinal cancers) were prioritized, while noting that studies in ovarian, cervical and thyroid cancers remain comparatively limited. To provide a focused and comprehensive overview rather than an exhaustive survey, HCC and bladder cancer were selected as representative examples. HCC was chosen given the extensive body of research available, whereas bladder cancer was included to highlight a tumor type in which ferroptosis is less well explored. Together, these examples capture both established and emerging perspectives on ferroptosis-related vulnerabilities.

Bladder cancer. Mazdak *et al* (86) reported that patients with bladder cancer had significantly lower serum iron levels compared with healthy controls, suggesting that reduced free and serum iron may play a role in promoting bladder cancer development. Indeed, reduced levels of free iron have been shown to markedly promote the growth of bladder cancer cells (87). However, treatment with baicalin, a bioactive flavonoid compound, has been shown to elevate intracellular chelated iron and generate ROS, promoting ferroptosis *in vitro* and *in vivo*. To further elucidate the underlying mechanisms, the expression of iron regulatory protein and DNA damage-related proteins was assessed using western blotting. Results showed increased transferrin, phosphorylated histone H2AX, p53 and tumor suppressor p53 binding protein 1 levels, alongside a notable decrease in ferritin heavy chain 1 (FTH1) levels in baicalin-treated bladder cancer cell lines 5637 and KU-19-19. Interestingly, the use of ferroptosis inhibitors reversed this effect, confirming that this is the predominant cell death pathway (88).

Proteins that regulate ferroptosis, such as GPX4 and SLC7A11, also play important roles in tumor-related signaling pathways, particularly in bladder cancer development. SLC7A11 appears to be controlled by the deubiquinating enzyme OTUB1, which is overexpressed in human bladder cancer and contributes to ferroptosis resistance (36). *In vivo* and *in vitro* experimental studies revealed that deleting OTUB1 lowers SLC7A11 levels, decreases cystine uptake, and induces ferroptosis, indicating that targeting SLC7A11 may contribute to inhibition of bladder cancer progression (87,89).

Furthermore, ferroptosis in bladder cancer cells can also occur due to a collapse of the antioxidant defense system and ROS accumulation. Following treatment with erianin, elevated levels of ROS and reduced GSH levels were reported. Additionally, malondialdehyde (MDA) levels increased, and ferrous iron accumulated in the bladder cancer cells, all of which drive ferroptosis (90). Western blot analysis further revealed that erianin significantly downregulated several key ferroptosis-associated proteins, including NRF2, FTH1, GPX4, heme oxygenase 1 (HO-1), glutaminase and xCT/SLC7A11 in KU-19-19 and RT4 bladder cancer cells (91). Collectively, the downregulation of these specific proteins impairs the cell's ability to maintain a redox balance resulting in ferroptotic death.

Finally, recent research explores the crosstalk between autophagy and ferroptosis in bladder cancer. FIN56, a potent ferroptosis inducer through the degradation of GPX4 and ferritin, was found to be enhanced when combined with Torin 2, an autophagy activator. Interestingly, FIN56-induced ferroptosis was suppressed by bafilomycin A1 and SAR405, both of which attenuated LPO (92). These findings confirm that ferroptosis may also occur dependent on autophagy, specifically ferritin (ferritinophagy). A summary of key-ferroptosis related vulnerabilities and therapeutic approaches in this type of cancer is presented in Table I.

HCC. The primary therapeutic approach for inducing ferroptosis in HCC cells involves targeting the system Xc^- antiporter and the GPX4 selenoprotein (93). Sorafenib, a multikinase inhibitor, is commonly used as a first-line treatment for advanced HCC and has been shown to stimulate ferroptosis (94). However, due to the chemorefractory nature of HCC, the emergence of resistance-related genes limits its efficacy. Upon treatment with sorafenib, dysregulation of several transcription factors such as NRF2, retinoblastoma (Rb) protein, hepatocyte nuclear factor 4α (HNF4α), HIC ZBTB Transcriptional Repressor 1 (HIC1), as well as components of the Hippo pathway, can be observed. A well-documented link exists between sorafenib and the NRF2 signaling axis. By inhibiting system Xc^-, sorafenib depletes intracellular

Table I. Cancer type-specific ferroptosis vulnerabilities and therapeutic strategies.

Cancer type	Key vulnerabilities	Ferroptosis inducers	Major molecular changes	Sensitization strategies
Bladder	GSH/GPX4 depletion, autophagy-dependence, iron/ROS imbalance	Baicalin, Erianin, FIN56, RSL3	↓Serum iron; ↑ROS/Fe^{2+}/MDA; ↑Tf/p53/p-H2AX/p53BP1; ↓FTH1/GPX4/SLC7A11/NRF2/HO-1/GLS; OTUB1-mediated ↑SLC7A11	GSH/GPX4 depletion; SLC7A11/OTUB1 suppression; autophagy-dependent ferritinophagy
HCC	GSTZ1-NRF2-GPX4 axis, PSAT1 regulation	Sorafenib, Trigonelline, Punicallin	↓GSTZ1, ↑SLC7A11/PSAT1 (context-dependent)	NRF2 targeting, PSAT1/SLC7A11 inhibition, cysteine salvage blocking
NSCLC	High SLC7A11 and GPX4 expression	Erastin, Sorafenib, Cisplatin (combos)	↑SLC7A11 (RBMS1-driven), GPX4 (mTORC1-mediated)	RBMS1 knockout, mTORC1 inhibition, cisplatin combos
TNBC	Selenocysteine biosynthesis (GPX4/SLC7A11)	RSL3, Sulfasalazine	↑GPX4 and SLC7A11 (selenocysteine-rich)	miR-5096 overexpression to target SLC7A11
Gastric/ Colorectal	GPX4/SLC7A11 overexpression	Erastin	GPX4/SLC7A11 overexpression	CDO1 silencing to sensitize cells
PDAC	Nrf2-mediated GPX4/GSH, apoptosis resistance	Gemcitabine + Erastin (with LONP1)	Gemcitabine ↑Nrf2/GPX4; LONP1 inhibits Nrf2/GPX4	LONP1 + Erastin to block GPX4
Leukemia	Iron/ROS overload, GSH/GPX4 and SLC7A11 dependence, lipid ROS stress	RSL3, FIN56, ML385, BL-8040, Erastin (±BV6)	↑Iron/ROS, ↑GSH/GPX4/SLC7A11/ NRF2/FSP1; LPO; immune suppression	GSH/GPX4 and SLC7A11 suppression; NRF2 inhibition; cysteine salvage disruption; lipid ROS exploitation

↑, Increased/Upregulated; ↓, Decreased/Downregulated; GSH, glutathione; GPX4, glutathione peroxidase 4; ROS, reactive oxygen species; MDA, malondialdehyde; Fe^{2+}, iron ions; NRF2, nuclear factor erythroid 2-related factor 2; FTH1, ferritin heavy chain 1; Tf, transferrin; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; PDAC, pancreatic ductal adenocarcinoma; SLC7A11, solute carrier family 7 member 11 (xCT subunit); RBMS1, RNA binding motif single stranded interacting protein 1; mTORC1, mechanistic target of rapamycin complex 1; CDO1, cysteine dioxygenase type 1; LONP1, Lon peptidase 1; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; FSP1, Ferroptosis suppressor protein 1; LPO, lipid peroxidation; HO-1, heme oxygenase 1; GLS, glutaminase; p-H2AX, phosphorylated histone H2AX; p53BP1, tumor suppressor p53 binding protein 1; OTUB1, OTU deubiquitinase, ubiquitin aldehyde binding 1.

GSH, prompting compensatory activation of the NRF2 pathway. Moreover, using trigonelline to inhibit this pathway appears to enhance the antitumor effect of sorafenib (95). Additionally, NRF2 upregulates the expression of several iron metabolism-related genes such as HO-1, Metallothioenin-1G and Sigma-1 receptor, all of which contribute to suppression of ferroptosis (96-98). Previous studies have also elucidated the role of glutathione S-transferase zeta 1 (GSTZ1), an enzyme involved in the phenylalanine catabolism, which is markedly downregulated in HCC cells (99). GSTZ1 does suppress the NRF2 pathway, resulting in decreased GPX4 expression and increased sensitivity of HCC cells to ferroptosis (100).

The tumor suppressor proteins Rb, HNF4α and HIC1 all influence ferroptotic sensitivity via the regulation of the phosphoserine aminotransferase 1 (PSAT1) gene, which plays a critical role in GSH metabolism. Louandre *et al* (101) revealed that when Rb is inhibited, cells are more susceptible to ferroptosis. Similarly, HNF4α and HIC1 regulate PSAT1 in opposing ways, affecting redox homeostasis and are therefore interesting targets for overcoming sorafenib resistance (102). Additionally, metabolic regulators such as c-Jun have also been associated with higher levels of expression of PSAT1, thus conferring resistance to sorafenib (103,104). Finally, dysregulation of the Hippo pathway has been associated with the overexpression of SCL7A11 subunit of system Xc^-, promoting the activity of ATF4 and further increasing resistance to ferroptosis (105).

Beyond these transcription factors, other mechanisms present a clinical challenge to treatment of liver cancer. For instance, the enzyme branched-chain amino acid transferase 2 (BCAT2) suppresses ferroptosis by maintaining intracellular GSH levels (106). Similarly, ATP-Binding Cassette Subfamily C Member 5 (ABCC5) is overexpressed in HCC cells and may function analogously to BCAT2 by stabilizing the expression of SLC7A11 (107). On the other hand, inhibition of ABCC5 leads to GSH depletion and marked reduction in sorafenib resistance (108). Additionally, RNA-binding proteins such as DAZ-Associated protein 1 are upregulated in HCC cells and contribute to ferroptosis resistance by enhancing SCL7A11 stability at the transcriptional level. Besides that, micropinocytosis of cysteine and trans-sulfuration pathways replenish intracellular cysteine and contribute to GSH synthesis even in the presence of system Xc^- inhibitors, rendering cells resistant to sorafenib-induced ferroptosis (109). A previous study has discussed the protective role of the trans-sulfuration pathway that maintains primary hepatocytes viability for several days, despite the absence of cystine/cysteine in the medium (110).

Novel therapeutic approaches focus on targeting proteins involved in these resistance pathways. Recently, a study by Y. Chen *et al* (111) elucidated the correlation of GPX4 with the phosphor-seryl-tRNA kinase (PSTK) in HCC. Inhibition of PSTK was shown to reduce GSH metabolism, thereby decreasing GPX4 activity and sensitizing HCC cells to ferroptosis inducers such as erastin. Furthermore, inhibition of the *PSTK* gene with punicalin, an agent used to treat hepatitis B virus, a major risk factor for HCC development, and Geraniin, a plant-derived therapeutic compound, resulted in cytotoxic effects on HCC cells. Additionally, combination therapy involving punicalin or geraniin with ferroptosis inducers like sorafenib and erastin exhibited a synergistic effect, enhancing cancer cell death without causing damage to surrounding organs such as the kidney, intestine or lung in mouse models. These findings underscore the therapeutic potential of concurrently targeting the GPX4/GSH/System Xc^- axis alongside conventional chemotherapeutics as a strategy for overcoming drug-resistant HCC. The major ferroptosis-related vulnerabilities mechanisms and therapeutic strategies in this cancer are highlighted in Table I.

Other solid tumors. While ferroptosis offers a promising approach for the treatment of liver and bladder cancer, it is also important to highlight its potential in other malignancies such as lung, gastrointestinal and breast cancers. In non-small cell lung cancer (NSCLC), SLC7A11 subunit of the system Xc^- antiporter is highly expressed, promoting metastasis and reducing ROS levels by facilitating cysteine uptake (112). This overexpression is attributed to RNA-binding protein RBMS1 that directly enhances transcription by stabilizing SLC7A11 mRNA. Knockout of this protein led to a reduction in cysteine uptake and promoted ferroptosis (113). In parallel, the discovery of novel microRNAs (miRNAs) has gained attention for therapeutic targeting. These small RNAs bind to the 3'-untranslated region of mRNAs, leading to its degradation. Notably, inhibition of miR-27a-3p enhances the sensitivity of NSCLC cells to ferroptosis inducers such as erastin (114). Alongside SLC7A11, GPX4 also appears to be highly expressed due to enhanced activation of the mTORC1 signaling pathway (115). Inhibition of this pathway leads to downregulation of GPX4 as well as increased sensitivity to lapatinib, a tyrosine kinase inhibitor that potentiates oxidative stress and leads to ferroptosis (116). Although cisplatin is commonly used as a first-line therapy, NSCLC cells quickly develop resistance. Consequently, combination strategies involving low doses of ciplastin with sorafenib or erastin have shown promise. These combinations suppress the NRF2/SLC7A11 pathway, amplifying the anticancer efficacy of cisplatin (117).

Similarly, in triple-negative breast cancer (TNBC), both GPX4 and SLC7A11 are overexpressed, largely due to the selenophilic nature of most breast cancer cells, which increases Selenocysteine (Sec) biosynthesis and thus protects cells against ferroptosis (118). Ferroptosis resistance in TNBC is usually overcome by inhibiting GPX4 activity with treatment of RSL3 or sulfasalazine (SAS) (119) or by overexpression miR-5096 which specifically targets SLC7A11 transcription (120). Gastric and colorectal cancer also exhibit similar levels of GPX4 and SLC7A11 overexpression (121,122) and thus high levels of ferroptosis resistance. In gastric cancer, it has been shown that silencing of the CD01 gene strengthens the adaptation of cancer cells to oxidative stress, conferring resistance to erastin and promoting proliferation (123). On the other hand, poor pancreatic ductal adenocarcinoma prognosis is often attributed to the lack of early diagnosis and resistance to apoptosis-inducers, namely gemcitabine (124). Upon treatment with gemcitabine, NRF2-mediated GPX expression increases and intracellular GSH levels are elevated, which can subsequently be targeted by ferroptosis-inducers for improved therapeutic outcomes (125). Previously, it has been reported that mitochondrial protease Lon peptidase 1 is capable of inhibiting NRF2-mediated GPX4 expression, thus promoting induced ferroptosis when used in conjunction with erastin (126). In summary, the GSH/GPX4/System Xc^- axis

plays a crucial role in ferroptosis across numerous cancer types, presenting itself as a target for ferroptosis-based therapies aimed at overcoming drug resistance in cancer cells (127). Key ferroptosis-associated vulnerabilities and sensitization strategies across these cancer types are summarized in Table I.

Leukemia. Beyond solid tumors, leukemic cells display dysregulated iron metabolism, leading to iron overload and increased ROS production, which in turn disrupt normal hematopoietic stem cell (HSC) functions like self-renewal, differentiation and quiescence (128,129). Excess ROS drive further cell apoptosis and reduce tumorigenic potential, while iron accumulation reshapes the tumor microenvironment in ways that trigger ferroptosis in cancer cells (130,131). However, leukemia cells take advantage of iron overload to fuel their rapid proliferations by relying on iron-dependent ribonucleotide reductase, an enzyme required for DNA synthesis (132-134). In addition, iron buildup induced apoptosis in nearby $CD4^+$ T cells, $CD8^+$ T cells and natural killer cells, while expanding regulatory T cell populations, thereby enabling leukemic cells to escape immune surveillance (135,136). Moreover, unlike solid tumors, patients with hematological malignancies often undergo repeated blood transfusions due to chemotherapy and impaired erythropoiesis, resulting in elevated iron and ROS levels. This, in turn, can promote the tumorigenic transformation of HSCs by exhausting NADPH oxidase and GSH (130). Together, these findings highlight iron metabolism as a double-edged sword in leukemia, as modulating iron homeostasis alters vulnerability of leukemic cells to ferroptosis, while disease progression further exacerbates iron overload in patients (137).

Furthermore, leukemia cells exhibit abnormally high levels of GSH and GPX4, both of which are key suppressors of ferroptosis (138). Moreover, increased GPX4 expression has been associated with a poor prognosis in patients with acute myeloid leukemia (AML) (139,140). Studies have shown that modulation of GSH and GPX4 is critical for controlling cell death and proliferation across leukemia subtypes (141). Indeed, GPX4 inhibitors (FIN56 or RSL3) combined with the NRF2 inhibitor ML385 synergistically trigger ferroptosis in AML cells (142). Similarly, blocking GSH synthesis by BL-8040 has been shown to induce ferroptosis in T-cell acute lymphoblastic leukemia (ALL) cells by promoting oxidative stress (143). Conversely, supplementing chronic lymphocytic leukemia cells with GSH or its precursor N-acetylcysteine markedly improved cell viability, highlighting the role of GSH in regulating leukemia cell proliferation through ferroptosis (144). Collectively, these findings underscore the role of GSH and GPX4 as key regulators of ferroptosis in across leukemia subtypes, highlighting the therapeutic potential of targeting the GSH/GPX4 axis to resistance to conventional treatments (138).

SLC7A11 has been found to be frequently overexpressed in leukemia and regulate cell proliferation by regulating ferroptosis (138,145). Inhibiting SLC7A11, genetically or chemically, leads to cysteine deprivation and reduces AML cell viability and self-renewal by promoting ferroptosis, while upregulation of SLC7A11 by the small molecule drug APR-246 enhances cystine uptake and detoxifies lipid peroxides, protecting cells from ferroptotic death (146,147). Nevertheless, leukemia cells can bypass system Xc^- inhibition via the trans-sulfuration pathway to maintain cysteine and GSH levels, which highlights a key metabolic resistance mechanism to ferroptosis (138).

In addition, dysregulated lipid metabolism and oxidative stress in leukemic cells promotes lipid ROS accumulation (148), which leads to LPO, a hallmark of ferroptosis and a biomarker in patients with leukemia (149). In ALL cells, ferroptosis-mediated inhibition of leukemia growth by the combining RSL3 and BV6 depends on lipid ROS and is preventable with the LPO inhibitor Fer-1 (150). By contrast, leukemic cells counteract this stress by activating antioxidant defenses such as NRF2, SLC7A11 and FSP1, which neutralize lipid ROS and shield cells from ferroptosis (138). Together, these findings underscore ferroptosis as a critical vulnerability in leukemia, with iron metabolism, antioxidant defenses and lipid ROS influencing disease progression and presenting potential therapeutic targets.

4. Therapeutic strategies

Exploiting cancer-specific vulnerabilities to ferroptosis has inspired the development of therapies that harness this cell death pathway, from targeting metabolism to small molecule inducers and combination treatments.

Monotherapy approaches

Targeting metabolic pathways

Iron metabolism modulation. Iron metabolism is frequently dysregulated in various cancers, including breast cancer, pancreatic cancer, lymphoma and HCC, making iron metabolism-related genes critical targets for stimulating ferroptosis (151). The use of artesunate, an antimalarial drug, has been shown to increase lysosomal activity and iron concentration in cells (152). Additionally, artesunate has been shown to influence the transcriptional regulation of iron-related genes (153). One of the upregulated genes is the nuclear receptor coactivator 4 (NCOA4) gene, a selective cargo receptor that mediates degradation of ferritin by autophagy, in a process termed ferritinophagy, and thus increases cellular iron concentration and induces ferroptosis (154). Cisplatin, another chemotherapeutic agent, targets ferritin degradation in a similar fashion by upregulating NCOA4 and contributing to GSH depletion, leading to an increase in intracellular iron concentration and reduced GPX4 activity, ultimately triggering ferroptosis (155). In addition to classical chemotherapeutics, natural products such as Baicalin, derived from the traditional Chinese medicinal herb *Scutellaria baicalensis* has also been shown to influence iron metabolism and promote ferroptosis. Baicalin facilitates iron buildup and LPO, both critical for triggering ferroptosis. Treatment of osteosarcoma cells with this natural compound has been shown to enhance iron accumulation, ROS generation and MDA production, while decreasing the ratio of GSH to GSSG (156).

However, different cancer types may respond differently to modulators of iron metabolism. For example, some tumors may develop resistance to iron overload caused by cisplatin by upregulating ferroportin or activating NRF2 to strengthen antioxidant defenses. Additionally, off-target ferroptosis

in cells with naturally high levels of iron may also occur, causing undesirable systemic oxidative stress and posing a significant clinical challenge. The role of iron modulation in ferroptosis-based therapy is outlined in Fig. 2.

Activation of LPO. LPO may occur in two distinct pathways. The non-enzymatic pathway involves the Fenton Reaction, where hydrogen peroxide reacts with ferrous ions (Fe^{2+}) to generate hydroxyl radicals, contributing to oxidative damage and ferroptosis (157). Alternatively, the enzymatic pathway engages lipoxygenases (LOX), cytochrome p450 oxidoreductase (POR) and COX enzymes, all of which trigger ferroptosis by facilitating ROS production (158). LOX enzymes catalyze the oxidation of PUFAs in membrane phospholipids and may be transcriptionally regulated by p53 to promote ferroptosis (159). Furthermore, POR donates electrons from NADPH to downstream effectors such as cytochrome p450, reducing them in the process and allowing the peroxidation of membrane-bound PUFAs, which may eventually trigger ferroptotic cell death (160).

Certain ferroptosis inducers, such as FIN56, act through dual mechanisms: Promoting GPX4 degradation and activating squalene synthase, which exhausts levels of CoQ10, a coenzyme involved in the mevalonate pathway, thereby sensitizing cells to ferroptosis (89). Alternatively, pharmacological inhibition of this pathway through statins, which block HMGCR, has also shown potential anticancer therapies by impairing antioxidant defenses and enhancing ferroptotic susceptibility (161).

Therapeutic strategies may also involve targeting lipid metabolism in cancer cells. Specifically, modulating LPO through enzymes such as COX, LOX and cytochrome POR presents a promising avenue for inducing ferroptosis. Gemcitabine, an antimetabolite that disrupts DNA replication and is commonly used in treating pancreatic cancers, causes ROS accumulation and stimulates ferroptosis (162). Interestingly, the anticancer effect of gemcitabine is enhanced when HSPA5 is unable to bind to and stabilize GPX4, leading to its degradation and eventual ferroptosis (57).

Furthermore, erianin, a bioactive compound extracted from *Dendrobium chrysotoxum* Lindl, has been reported to trigger ferroptosis by iron-dependent LPO in multiple cancer cell types. It has been shown to facilitate the buildup of harmful lipid-based ROS and deplete GSH, a key cellular antioxidant, thereby inducing oxidative stress and cell death, which are hallmarks of ferroptosis (91,163-165). Moreover, it has been shown to elevate intracellular Fe^{2+} concentrations, which catalyze ROS generation via the Fenton reaction, further enhancing LPO and ferroptotic cell death. It has also been reported to suppress the expression of ferroptosis-protective proteins, including GPX4 and SLC7A11. Since GPX4 plays a critical role in detoxifying lipid peroxides, its downregulation results in the accumulation of toxic lipid peroxides (163-165). The role of LPO activation in ferroptosis-based therapy in cancer is summarized in Fig. 2.

Nonetheless, a major limitation of this approach lies in the complexity and heterogeneity of lipid metabolism across different tumor types. Some cancers may evade ferroptosis by enriching their membranes with monounsaturated fatty acids instead of PUFAs, reducing LPO susceptibility. Furthermore, the frequent mutation of p53 in cancer cells can impair its ability to activate pro-ferroptotic axis pathways, further complicating treatment efforts.

Direct ferroptosis inducers

System Xc^- inhibitors. Erastin is a small molecule compound capable of inducing ferroptotic cell death by binding to and irreversibly inhibiting the SLC7A11 subunit of System Xc^- antiporter. This inhibition reduces cystine uptake, resulting in diminished GSH biosynthesis. Without GSH, GPX4 becomes non-functional, allowing toxic lipid ROS to accumulate within the cell, causing oxidative stress and ultimately, ferroptosis. Additionally, erastin has been shown to interact with voltage-dependent anion channels on the outer membrane of mitochondria, further contributing to ROS production (166). In various cancer types, including HCC, erastin sensitizes cells to ferroptosis and shows promise as a potent anticancer therapeutic. However, its clinical utility is limited to poor solubility, metabolic instability and potential toxicity to healthy tissues, particularly the kidneys (167). To address these challenges, researchers are developing erastin analogs and exploring advanced delivery systems, such as nanotechnology and exosome-based encapsulation (168).

SAS, another ferroptosis inducer, similarly blocks cystine uptake and inhibits GPX4. Nevertheless, its use in cancer therapy is constrained by significant off-target effects, including inhibition of the NF-KB signaling pathway and alterations in immune cell function, which may raise concerns about safety and specificity. These mechanisms of action are summarized in Fig. 2.

GPX4 inhibitors. When cancer cells develop resistance to System Xc^- inhibitors, targeting downstream effectors such as GPX4 becomes a valuable alternative. RSL3 and ML162 are small molecule inhibitors that directly bind to the Sec active site of GPX4, blocking its lipid peroxide-reducing activity. As a result, PUFAs undergo unchecked peroxidation, ultimately stimulating ferroptosis (169). Although structurally distinct, RSL3 and ML162 function in a similar fashion and thus share similar limitations, including chemical instability and broad off-target effects that may hinder regular cell function, especially in neurons and kidneys. Much like the System Xc^- inhibitors, GPX4 inhibitors also suffer from low solubility and rapid inactivation. Additionally, cancer cells may develop resistance by altering membrane lipid composition to reduce PUFA content and limit the effects of both RSL3 and ML162, or by upregulating ferroptosis-suppressing proteins. One such protein is FSP1, which is overexpressed in some cancers. FSP1 acts as an oxidoreductase that generates reduced CoQ10, thereby preventing LPO through a pathway parallel to the GSH/GPX4 axis. In a mouse model using ferroptosis-resistant H460 lung cancer cell xenografts, FSP1 inhibition leads to significant tumor suppression in both GPX4 knockout and GPX4 KO/FSP1 groups (170). The aforementioned therapeutic mechanisms are summarized in Fig. 2.

Regulatory RNAs: miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). Non-coding RNAs (ncRNA) are an increasingly interesting topic for researchers as they have recently been shown to regulate ferroptosis in cancer cells, having both stimulating and inhibitory effects depending

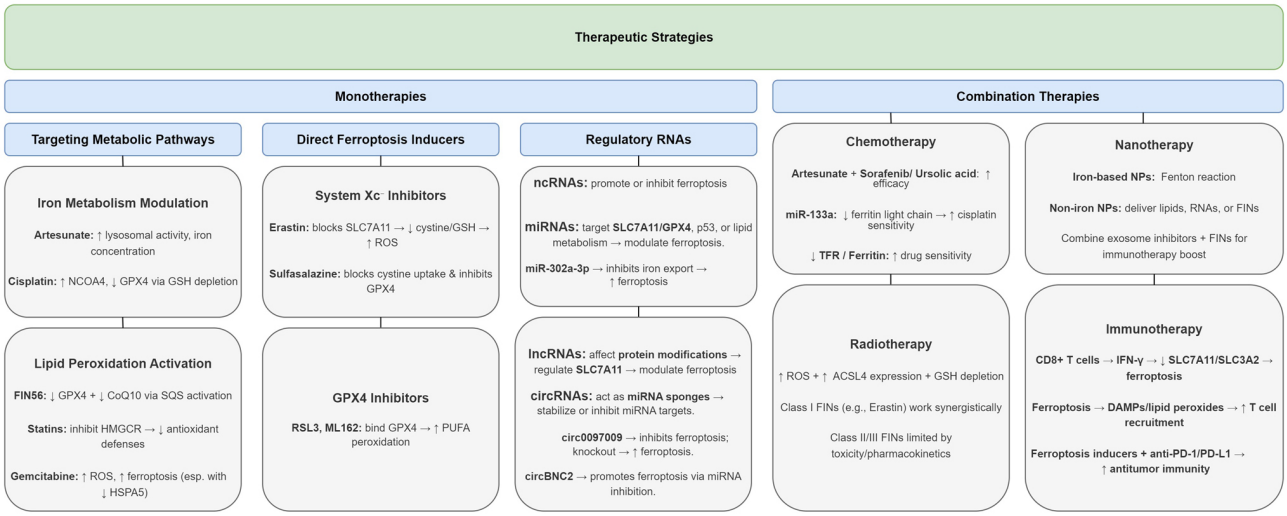

Figure 2. Key therapeutic approaches to induce ferroptosis in cancer cells can be classified into two main categories: monotherapies and combination therapies. Monotherapies can be further categorized as: i) targeting metabolic pathways, including modulation of iron metabolism and activation of LPO; ii) using direct ferroptosis inducers, such as inhibitors of System Xc^- or GPX4; and iii) employing regulatory RNAs, such as miRNAs, lncRNAs and circRNAs. Combination therapies include strategies that synergize with chemotherapy, radiotherapy, immunotherapy, or nanotechnology-based approaches. LPO, lipid peroxidation; GPX4, glutathione peroxidase 4; miRNAs or miRs, microRNAs; lncRNAs, long non-coding RNAs; circRNAs, circular RNAs; ROS, reactive oxygen species; GSH, reduced glutathione; NCOA4, nuclear receptor coactivator 4; CoQ10, Coenzyme Q10; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HSPA5, heat shock protein family A (Hsp70) member 5.

on the nature of the ncRNA. For instance, miRNAs have been identified to target either SLC7A11 or GPX4 and enhance or suppress ferroptosis (171). Other miRNAs may target the p53 signaling pathway or even regulate lipid metabolism and are capable of greatly enhancing cell sensitivity to ferroptosis. It has been recently reported that miR-302a-3p interacts with the 3'-untranslated region of FPN 1 and directly enhances ferroptosis in NSCLC by inhibiting cellular iron export (172). Furthermore, lncRNAs also regulate post-translational modifications of RNA-binding proteins through numerous various mechanisms: Ubiquitination, acetylation and phosphorylation. These modifications both directly and indirectly modulate ferroptosis by affecting levels of specific protein expression and degradation, notably the SLC7A11 protein (173). Finally, circRNAs may also play a pivotal role in modulating ferroptotic sensitivity, as they often act as sponges for miRNAs, stabilizing them and keeping them from reaching their targets (174). In a previous study, a specific circRNA, circ0097009, was found to be overexpressed in HCC serving as a sponge for miR-1261, whose target is the SLC7A11 subunit. Knockout of circ0097009 lead to decreased expression of SLC7A11, inactivation of GPX4 and a decrease in GSH/GSSG ratio, all of which result in increased sensitivity to ferroptosis (175). Additionally, some circRNA may sponge miRNA that would normally inhibit ferroptosis. A recent study reported that exogenous delivery of circBNC2 lead to increased LPO and ROS levels in prostate cancer, greatly increasing cell sensitivity to ferroptosis by inhibiting microRNA-4298 (176).

Combination therapy approaches

Synergy with chemotherapy. Currently, several effective strategies have been identified to reverse tumor resistance, primarily by targeting iron and lipid metabolism, two key regulators to ferroptosis (64). A major contributing factor to drug resistance is the suppression of ferroptosis-related genes and signaling pathways in tumor cells (177). For instance, clinical agents such as artesunate have been shown to act synergistically with sorafenib, enhancing its antitumor efficacy (178). Likewise, co-administration of ursolic acid with sorafenib enhances its therapeutic effect (179).

In the context of iron metabolism, a correlation between tumor drug resistance and TFR expression has been recently suggested, with evidence indicating that the downregulation of TFR can help overcome resistance (180). In multiple myeloma cells, elevated ferritin levels are considered to be associated to bortezomib resistance, while iron supplementation promotes cell death. By contrast, a reduction in ferritin has been shown to sensitize tumor cells to bortezomib (181). Additionally, miR-133a has been found to downregulate the ferritin light chain subunit in cisplatin- and doxorubicin-resistant breast cancer cells, increasing their sensitivity to the drugs (182). A summary of these mechanisms is provided in Fig. 2.

In terms of lipid metabolism, cells with high GSH expression levels and upregulation of the SCL7A11 light chain subunit of System Xc^- have been linked to resistance to both radiation and chemotherapy (183). Moreover, numerous cancer cells develop a dependency on the GPX4 enzyme, which contributes massively to its acquired drug resistance. Loss of GPX4 function renders cells more susceptible to ferroptosis and has been shown to prevent tumor relapse in mouse models (184).

Synergy with radiation therapy. Radiation therapy may induce ferroptosis by promoting oxidase activity via the production of highly reactive hydroxyl radicals (185). It triggers ferroptosis through three primary mechanisms: Producing excess ROS that drive LPO, upregulating ACSL4 expression to enhance polyunsaturated phospholipid biosynthesis, and depleting GSH, thereby inhibits the protective effects of GPX4 against LPO (61,186).

Tumor sensitivity to radiation therapy can be increased by combining radiation therapy with ferroptosis inducers. For

example, class I FINs such as erastin and SAS inhibit cystine uptake, while class II FINs like RSL3 and ML162 directly inhibit GPX4. Class III FIN, such as FIN56, degrade GPX4 and deplete CoQ10 (64). Research indicates that the combination of radiation therapy with ferroptosis inducers significantly increases the radiosensitivity of NSCLC, yielding improved outcomes than radiotherapy alone (187). Among the different classes of FINs, class I FINs show the most promising synergistic effect with radiotherapy, particularly through targeting SLC7A11. By contrast, class II and III FINs face limitations due to poor pharmacokinetics and higher cytotoxicity, which reduce their overall therapeutic benefit in combination treatments (185). A summary is illustrated in Fig. 2.

Synergy with immunotherapy. Emerging research suggests potential therapeutic interplay between ferroptosis and immunotherapy. $CD8^+$ T cells secrete interferon-γ which in turn inhibits expression of both the SLC7A11 and SLC3A2 subunits of the System Xc-, sensitizing the cell to ferroptotic death (188). In turn, the lysed tumor cells release damage-associated molecular patterns as well as LPO products, enhancing recruitment of T-cells in a positive-feedback manner to amplify antitumor immunity (189). Furthermore, with the rise of immune checkpoint inhibitors as a viable therapeutic avenue, combining both ferroptosis inducers with anti-PD-1/PD-L1 therapies greatly enhance the antitumor response by reversing immune suppression within the tumor microenvironment (190). In a recent study, mefloquine, an antimalarial, was revealed to not only induce ferroptosis in melanoma and lung cancer cells, but also sensitize them to both ferroptosis and anti-PD-1 immunotherapy when combined with T-cell-derived interferon-γ. Mefloquine was reported to significantly upregulate LPCAT3, a key gene in LPO-associated ferroptosis, highlighting how LPO can also boost the efficacy of checkpoint blockade immunotherapy (191). The combined effective delivery of both ferroptosis inducers as well as immune checkpoint inhibitors remains a significant hurdle, as much of recent research focuses on optimizing efficient delivery to maximize antitumor effects (192,193).

Synergy with nanotherapy. Ferroptosis-based nanotherapies are currently under development as a promising approach in cancer treatment. Nanomaterials used in this context are generally categorized as either iron-based or non-iron based (64). Iron-based nanoparticulate materials can induce ferroptosis by releasing iron at the tumor site, where it catalyzes the Fenton reaction to generate ROS (194). These nanoparticles can also be engineered to carry ferroptosis inducers or chemotherapeutic agents, such as erastin, to circumvent its poor solubility and off-target effects (168,195).

Iron free or non-iron based nanotherapies operate through alternative mechanisms, such as delivering lipids, non-coding RNAs, or ferroptosis-inducing compounds (196). For instance, nanoparticle formulations can supplement PUFAs, modulating LPO and promoting ferroptosis in tumor cells (197). Additionally, tumor cells release exosomal PD-L1, which suppresses T-cell activity, blocking immune checkpoint responses, and contributing to therapy resistance (198). By combining exosome inhibitors with ferroptosis inducers into a single nanotherapeutic unit, researchers aim to harness both immune activation and ferroptotic cell death. This strategy represents a novel and promising direction in immunotherapy (187). Despite their potential, ferroptosis-based nanotherapies remain largely experimental. Further research, optimization and clinical validation are needed to fully realize their therapeutic potential in cancer treatment. A summary of these strategies is presented in Fig. 2.

5. Discussion

Accumulation of ROS and LPO, resulting from an imbalance in the cellular redox system, can trigger ferroptosis, a form of programmed cell death. Over time, different tumor types have become more aggressive and resistant to conventional therapies such as surgical resection and chemotherapy, leading to poor prognosis. Given the uncontrolled proliferation of cancer cells, it is expected that, over the course of repeated treatment, some will acquire mutations that confer resistance, mirroring the principles of natural selection, where the fittest variants survive.

The emergence of drug-resistant tumors remains a major challenge in oncology. However, since the initial discovery of ferroptosis, mounting evidence has supported its potential as an effective antitumor mechanism. Inhibition of key components of the GPX4/GSH/System Xc^- axis, along with related pathways such as the mevalonate and trans-sulfuration pathways, has demonstrated the ability to induce ferroptosis in various cancer models.

Although clinical data on ferroptosis induction remain limited, they are steadily increasing. For example, SAS, which inhibits system Xc^-, is currently being tested against solid tumors and glioblastoma in clinical trials (NCT04205357). Moreover, carbon nanoparticle-loaded iron [CNSI-Fe(II)] is under clinical investigation as a ferroptosis-inducing therapy for patients with advanced solid tumors (NCT06048367).

Despite these promising findings, translating preclinical results into clinical practice has been hindered by challenges such as poor pharmacokinetics and significant side effects observed with classical inducers. For instance, erastin exhibits poor solubility and metabolic stability as observed in a mouse liver microsome assay and, upon intraperitoneal administration in mice, induces ferroptosis-associated alterations in multiple organs, indicating potential toxicity to normal tissues (167). Moreover, RSL3 at tumoricidal doses is cytotoxic to normal cells such as neurons (199), fibroblasts (200) and nephrocytes (201) and shows poor selectivity and pharmacokinetics due to covalent binding to GPX4 via a reactive alkyl chloride moiety (202).

Therefore, future studies should focus on enhancing drug distribution, reducing systemic toxicity, and improving the pharmacokinetics of currently used ferroptosis inducers. Moreover, just as tumors evolve resistance to chemotherapy, they may also adapt to evade ferroptosis. For example, prolonged treatment with sorafenib has been associated with the overexpression of resistance-related genes (203), highlighting the need to understand the mechanisms underlying acquired ferroptosis resistance and tumor heterogeneity.

To address these challenges, efforts are ongoing to develop combination therapies, ranging from nanotechnology-based approaches that improve drug solubility and reduce resistance (204), to co-treatment with traditional compounds such as artesunate alongside ferroptosis inducers targeting the

GPX4/GSH/System Xc^- axis. Additional strategies involve disrupting aberrant iron or lipid metabolism in tumor cells to indirectly destabilize redox balance and promote ferroptotic cell death.

Looking ahead, future research should prioritize establishing rational combination regimens that optimize efficacy and identifying predictive biomarkers to stratify patients most likely to respond to ferroptosis-based therapies. Ultimately, translating this promising strategy from bench to bedside will require the development of next generation ferroptosis inducers with enhanced selectivity and safety profiles, alongside longitudinal clinical investigations to evaluate long-term outcomes.

Recently, ferroptosis has been the focus of numerous reviews, spanning both broad and disease-specific perspectives. Broad overviews, such as those by Singh *et al* (205), Ojo *et al* (206) and Ubellacker *et al* (207) survey the underlying mechanisms and general therapeutic potential of ferroptosis. By contrast, disease-focused reviews include Hino *et al* (208) on liver disease and HCC, Meng *et al* (209) on melanoma, Hsu *et al* (210) on exosomal ncRNAs in lung cancer, and Chen *et al* (211) on digestive cancers and therapy resistance. While collectively informative, these reviews are either mechanistic surveys at a broad level or limited to single cancer contexts, leaving a gap for integrative perspectives that explicitly connect ferroptosis mechanisms to therapeutic resistance across multiple malignancies.

By contrast, the present review employs a focused yet comparative approach. In particular, HCC was selected, a cancer well-characterized in ferroptosis research, and bladder cancer, where ferroptosis is comparatively understudied, as representative models. This dual focus enables us to merge well-established and emerging findings, highlight research gaps and outline directions for future research. In addition, rather than examining molecular regulators in isolation as previous reviews have, our approach associates iron metabolism, antioxidant defenses and LPO with drug resistance, presenting a translational framework that bridges molecular insights with clinical applications. Finally, the present review evaluates therapeutic strategies, including monotherapies such as ferroptosis inducers and regulatory RNAs, and synergistic combinations with chemotherapy, radiotherapy, immunotherapy and nanotherapy. Collectively, these points underscore the novel insights and distinctive contribution of our manuscript relative to prior reviews.

In conclusion, the present review highlights the promising potential of combination therapies aimed at inducing ferroptosis as a novel approach for cancer treatment, particularly in drug-resistant tumors. Combining ferroptosis inducers with existing treatments such as chemotherapy, radiotherapy and more recently, nanotherapy, has shown encouraging results. Nonetheless, further research is necessary given that most studies to date are relatively recent and primarily conducted in xenograft models. In summary, current findings suggest that targeting pathways involved in iron metabolism, lipid metabolism and the GPX4/GSH/System Xc^- axis holds significant therapeutic promise. As research in this field progresses, ferroptosis-based combination strategies continue to emerge as a compelling new avenue for cancer therapy.

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NM drafted the initial manuscript. NEJ restructured the manuscript's organization and ideas, created the figures and table, and performed proofreading. RAH and MES wrote the final draft and edited the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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