Ferroptosis regulatory networks as therapeutic sensitizers in combination therapy for hepatocellular carcinoma (Review)

MENGXIAO ZHU[1,2] and XIAOXIONG HU[1,3]

[1]Department of Infectious Diseases and Hepatology, Yichun People's Hospital, Yichun, Jiangxi 336000, P.R. China; [2]School of Pharmacy, Yichun University, Yichun, Jiangxi 336000 P.R. China; [3]Yichun Clinical Medical Research Center for Portal Hypertension, Yichun People's Hospital, Yichun, Jiangxi 336000, P.R. China

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Abstract. Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, and multidrug resistance remains a major barrier to effective treatment. Ferroptosis, an iron-dependent form of programmed cell death driven by lipid peroxide accumulation, has emerged as a potential therapeutic strategy for HCC because it may bypass apoptosis-related resistance mechanisms. The present narrative review summarizes current evidence on ferroptosis-mediated sensitization mechanisms in combination therapy for HCC, focusing on core regulatory networks, including glutathione peroxidase 4, System Xc^- and iron metabolism pathways, and their interactions with key signaling pathways, such as activating transcription factor 4/signal transducer and activator of transcription 3, p53 and Wnt/β-catenin. The current review also discusses the synergistic effects and molecular mechanisms of ferroptosis inducers combined with targeted therapy, chemotherapy and immunotherapy. Furthermore, the potential value of ferroptosis-related biomarkers for predicting treatment response and prognosis is evaluated, and unresolved mechanistic questions and barriers to clinical translation are highlighted. Finally, the present review outlines future research directions, including the development of targeted nanodelivery systems and biomarker-based clinical trials, to support more precise ferroptosis-based combination strategies for HCC.

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Correspondence to: Professor Xiaoxiong Hu, Department of Infectious Diseases and Hepatology, Yichun People's Hospital, 1061 Jinxiu Avenue, Yichun, Jiangxi 336000, P.R. China
E-mail: huxiaoxiong99@126.com

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1. Introduction

Primary liver cancer (PLC) is a common malignancy worldwide. According to the International Agency for Research on Cancer of the World Health Organization, there were ~866,000 new PLC cases and 759,000 PLC-related deaths globally in 2022, ranking the disease at sixth in terms of incidence and third in terms of mortality among all malignancies (1). In China, PLC is the fourth most common malignancy and the second leading cause of cancer-related death, and is thus considered a major public health burden (2). Hepatocellular carcinoma (HCC) accounts for 75-85% of PLC cases and is characterized by marked heterogeneity and frequent drug resistance (2-4). According to the International Classification of Diseases, 10th Revision, PLC is coded as C22, and HCC as C22.000 (5). Current treatment for advanced HCC includes tyrosine kinase inhibitors, such as sorafenib, and immune checkpoint inhibitors; however, limited efficacy and treatment resistance remain major challenges (6,7). Therefore, new therapeutic strategies that overcome treatment resistance in HCC are urgently needed.

Ferroptosis, first described in 2012, is an iron-dependent form of programmed cell death characterized by lipid peroxidation and oxidative stress (8). Unlike apoptosis, ferroptosis does not depend on caspase activation; instead, iron-mediated Fenton reactions generate reactive oxygen species (ROS), leading to membrane lipid peroxidation and cell death (9,10) Evidence suggests that ferroptosis contributes to tumor biology in several types of cancer, including HCC, and has therapeutic potential, particularly in apoptosis-resistant tumors (11,12) In HCC models, ferroptosis induction can enhance the efficacy of existing drugs and may help overcome drug resistance (13,14). Conversely, ferroptosis inhibitors have been investigated for their

therapeutic potential; for example, they have been shown to reduce the toxicity of celastrol, a natural pentacyclic triterpenoid isolated from *Tripterygium wilfordii* that has been reported to promote ferroptosis in HCC, while preserving its insulin-sensitizing effects in insulin-resistant HepG2 human liver cancer cells (15).

Ferroptosis also interacts with other forms of programmed cell death through complex cross-regulatory networks. Cross-talk between ferroptosis and apoptosis is particularly relevant: When tumor cells acquire apoptosis resistance through mechanisms such as Bcl-2 upregulation or caspase mutations, ferroptosis may function as an alternative cell-death pathway (16); conversely, inhibition of glutathione (GSH) peroxidase 4 (GPX4), a key ferroptosis regulator, may activate apoptotic signaling pathways (17). GPX4 inhibition has been shown to activate caspase-3-dependent apoptosis, and p53 regulates both apoptosis (by Bcl-2 modulation) and ferroptosis [by inhibiting solute carrier family 7 member 11 (SLC7A11)] (18-20). Autophagy also has a dual role in ferroptosis: Nuclear receptor coactivator 4-mediated ferritinophagy can release free iron by degrading ferritin, thereby promoting Fenton reactions and lipid peroxidation (21), whereas excessive autophagy may limit ferroptosis by clearing damaged mitochondria (22). Cuproptosis, a recently described copper-dependent form of programmed cell death, may interact with ferroptosis through shared links to metal metabolism and mitochondrial dysfunction; although no direct studies exist in HCC, to the best of our knowledge, both pathways share mitochondrial dysfunction and metal ion homeostasis (for example, ferredoxin 1 and lipoic acid synthetase), suggesting a potential basis for combined therapeutic strategies in HCC (23,24). Given these interactions, further investigation of ferroptosis regulation in HCC may therefore support the development of novel combination-treatment strategies.

The present narrative review summarizes the regulatory mechanisms and translational prospects of ferroptosis in HCC treatment, with particular emphasis on its potential synergy with targeted therapy, chemotherapy and immunotherapy. In addition, current limitations and future directions are discussed, with the aim of clarifying how ferroptosis-based strategies could inform future HCC management.

2. Core molecular mechanisms and regulatory networks of ferroptosis

Key molecular characteristics and metabolic basis of ferroptosis. Ferroptosis depends on intracellular iron metabolism, GSH depletion and dysregulated lipid metabolism (8). The molecular mechanisms of ferroptosis involve multiple metabolic pathways, among which the System Xc^-/GSH/GPX4 axis is a central regulatory pathway. The cystine/glutamate antiporter System Xc^- consists of SLC7A11 and solute carrier family 3 member 2, which mediate cystine uptake for GSH synthesis (25). GPX4 uses GSH to reduce lipid peroxides to non-toxic lipid alcohols, thereby inhibiting ferroptosis and preserving membrane integrity (26). Iron metabolism-related proteins, including transferrin receptor (TFRC), ferroportin and ferritin light chain, regulate intracellular iron levels and thereby influence susceptibility to ferroptosis (27,28).

These aforementioned molecules are frequently dysregulated in HCC cells. For example, *SLC7A11* is highly expressed in several HCC cell lines, and is positively associated with tumor proliferation and drug resistance (29); *GPX4* expression is markedly associated with prognosis in patients with HCC (30); and TFRC, a ferroptosis-associated marker, is highly expressed in HCC and promotes ferroptosis by mediating iron uptake (27). Excessive ROS production is another key molecular feature of ferroptosis, and this oxidative stress response is primarily mediated by iron-catalyzed Fenton reactions (28). Dysregulation of these molecules may contribute to HCC initiation and progression, and influence sensitivity to ferroptosis inducers. The core molecular mechanisms and metabolic basis of ferroptosis are illustrated in Fig. 1, which depicts the System Xc^-/GSH/GPX4 axis and iron metabolism pathways.

Induction pathways and regulatory factors of ferroptosis. Ferroptosis can be induced through several mechanisms, including: i) Inhibition of System Xc^- function, such as blockade of cystine uptake by erastin or sorafenib, leading to GSH depletion (29,31); ii) direct inhibition of GPX4 activity by agents such as RSL3 or ML162 (26); and iii) modulation of iron metabolism by iron chelators or iron carriers, thereby affecting ROS production (28). Zhang *et al* (31) showed that, in addition to its kinase-inhibitory activity, sorafenib can induce ferroptosis by inhibiting *SLC7A11*. Previous studies have identified additional ferroptosis regulatory factors, including ubiquitin-specific peptidase 22 (USP22), which inhibits sorafenib-induced ferroptosis by deubiquitinating CDK1 (32); PNO1, which inhibits autophagy-mediated ferroptosis by reprogramming GSH metabolism (7); and m6A modification, which influences ferroptosis sensitivity by regulating key molecules such as *GPX4* (33). Fig. 2 summarizes the three main ferroptosis induction pathways (System Xc^- inhibition, direct GPX4 inhibition and iron metabolism dysregulation) along with identified regulatory factors.

USP22 has been reported to inhibit sorafenib-induced ferroptosis by deubiquitinating CDK1 (32). By contrast, erastin-induced ferroptosis does not appear to be affected by USP22 in the same cellular context. This discrepancy may arise from: i) Cell-type heterogeneity, as different HCC cell lines have distinct genetic backgrounds (4,6,13,14). ii) Different mechanisms of ferroptosis inducers; for example, sorafenib is a multi-kinase inhibitor that induces additional cellular stress responses, such as autophagy, beyond GSH depletion (31,33), whereas erastin is a more selective System Xc^- inhibitor (34); consequently, the USP22-CDK1 axis may be engaged only under the broader metabolic perturbations caused by sorafenib. iii) Experimental conditions, such as iron concentration and oxidative stress baseline. Notably, RSL3 directly inhibits GPX4, thereby bypassing both System Xc^- and the USP22-CDK1 axis, which explains why USP22 does not affect RSL3-induced ferroptosis (35,36). Currently, most evidence is derived from *in vitro* work (37), whereas *in vivo* and clinical validation is lacking. Resolving these contradictions will require systematic side-by-side comparisons under standardized conditions. These observations regarding USP22 expand the ferroptosis regulatory network and identify potential targets for HCC treatment.

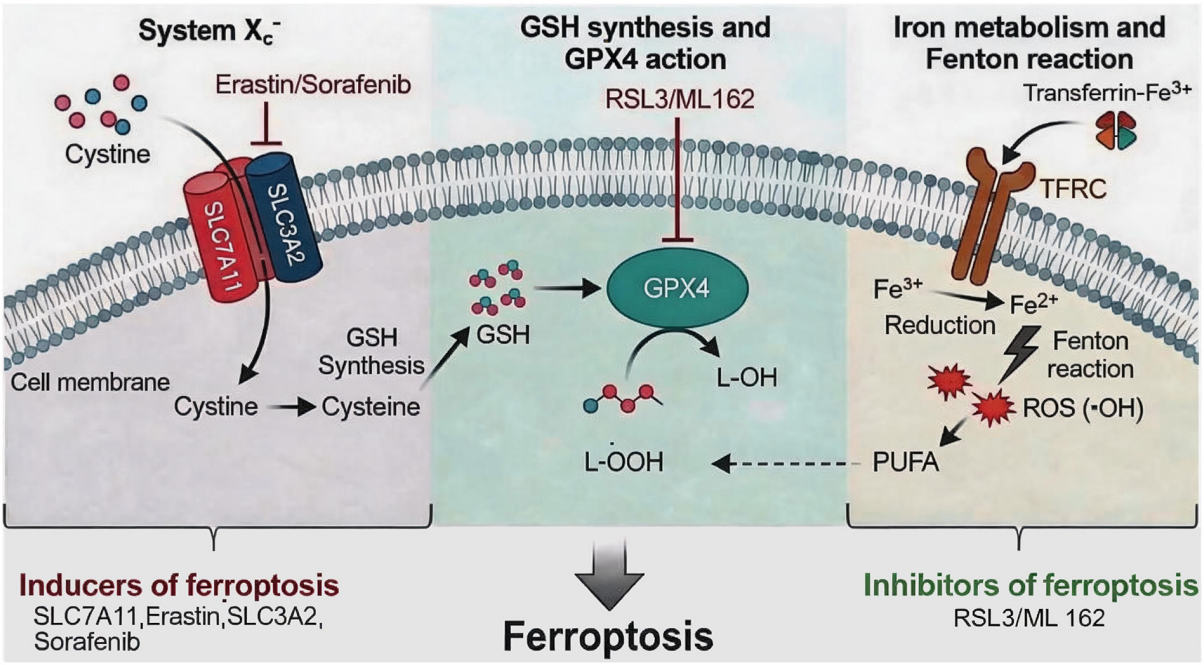

Figure 1. Core molecular mechanisms and metabolic regulation of ferroptosis. Ferroptosis is regulated mainly by the System Xc^-/GSH/GPX4 axis and iron metabolism. System Xc^-, composed of SLC7A11 and SLC3A2, mediates cystine uptake for GSH synthesis and can be inhibited by erastin or sorafenib. GPX4 uses GSH to reduce L-OOH to non-toxic L-OH, whereas GPX4 inhibitors such as RSL3 and ML162 promote lipid peroxide accumulation. TFRC-mediated uptake of transferrin-bound Fe^{3+} increases intracellular Fe^{2+}, which promotes ROS generation through the Fenton reaction and drives peroxidation of PUFAs, ultimately inducing ferroptosis. GPX, GSH peroxidase; GSH, glutathione; L-OH, lipid alcohols; L-OOH, lipid hydroperoxides; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; TFRC, transferrin receptor.

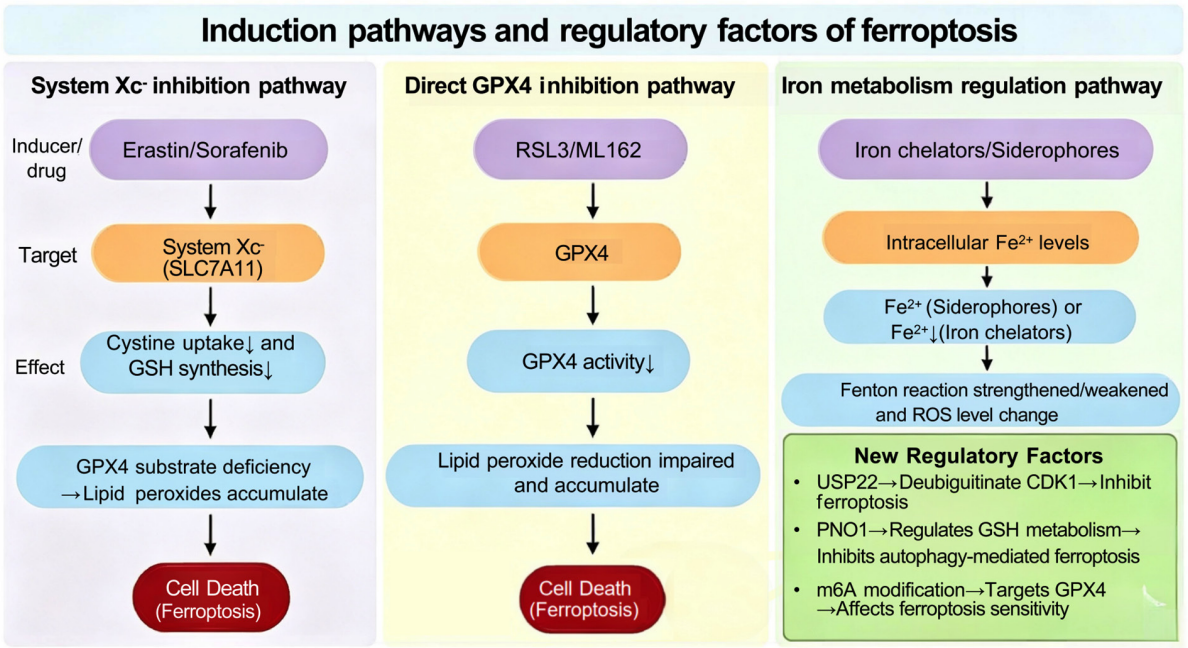

Figure 2. Induction pathways and regulatory factors of ferroptosis. Ferroptosis can be induced through three main pathways: i) Inhibition of System Xc^- (for example, via erastin or sorafenib), leading to GSH depletion; ii) direct inhibition of GPX4 (for example, by RSL3 or ML162), blocking lipid peroxide reduction; and iii) regulation of iron metabolism, affecting Fe^{2+} levels and the Fenton reaction. The lower right corner lists identified regulatory factors, including USP22, PNO1 and m6A modification, which regulate ferroptosis through post-translational modification, metabolic reprogramming or epigenetic mechanisms. GPX4, GSH peroxidase 4; GSH, glutathione; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; USP22, ubiquitin-specific peptidase 22.

Molecular determinants of ferroptosis sensitivity in HCC cells. HCC cells exhibit marked heterogeneity in ferroptosis sensitivity, which appears to be influenced by genetic background, microenvironmental factors and epigenetic modifications (38). For example, *p53* status can influence ferroptosis sensitivity: Wild-type *p53* promotes ferroptosis by

inhibiting *SLC7A11* expression, whereas mutant *p53* may exert the opposite effect (39). Additional regulatory factors, such as PNO1, have also been implicated in modulating ferroptosis sensitivity in HCC cells (7). Tumor microenvironmental factors, such as hypoxia and acidosis, can influence the expression of ferroptosis-related molecules by regulating signaling pathways such as hypoxia-inducible factor-1α and NF-κB (40). Sorafenib-resistant HCC cells often exhibit reduced sensitivity to ferroptosis, a process associated with *GPX4* activation and *SLC7A11* upregulation (29,41). Therefore, modulating these key molecules may help restore ferroptosis sensitivity and reverse treatment resistance in HCC.

The heterogeneity of HCC is reflected in diverse patterns of ferroptosis regulation. In hepatitis B virus (HBV)-associated HCC, HBV X protein (HBx) can suppress ferroptosis through the protein arginine methyltransferase 9/heat shock protein family A member 8/CD44 axis, thereby promoting disease onset and progression (42). Conversely, activation of protein inhibitor of activated STAT3 (PIAS3) promotes ferroptosis in HBV-positive HCC cells by activating TGF-β signaling and upregulating thioredoxin-interacting protein expression (43). The balance between HBx-mediated anti-ferroptotic signaling and PIAS3-mediated pro-ferroptotic signaling may influence the sensitivity of HBV-associated HCC to ferroptosis inducers. By contrast, non-alcoholic steatohepatitis (NASH)-associated HCC arises in the context of chronic lipid metabolic dysfunction and oxidative stress, with elevated lipid peroxidation and abnormal iron metabolism (44). Activating transcription factor (ATF)4 and SLC7A11 expression are markedly elevated in the livers of patients with NASH, suggesting that NASH-associated HCC may possess compensatory ferroptosis-defense mechanisms (45). Furthermore, ferroptosis mediated by long-chain acyl-CoA synthetase 4 (ACSL4) may have a dual role in non-alcoholic fatty liver disease (NAFLD)-associated HCC: It can promote cancer cell death (46), but may also indirectly promote carcinogenesis by exacerbating liver injury and fibrosis (47). Elucidating these subtype-specific mechanisms is important for designing personalized ferroptosis-targeted therapeutic strategies for patients with HCC arising from different etiological backgrounds.

3. Key pathways involved in ferroptosis-mediated sensitization in HCC therapy

Role of the ATF4/STAT3 signaling axis in ferroptosis regulation. ATF4 is a central transcription factor in the integrated stress response and has context-dependent effects on ferroptosis regulation. Mechanistically, this dual role appears to depend on stress intensity: Under mild oxidative stress, *ATF4* can upregulate *SLC7A11* expression through the PERK/eIF2 signaling axis, thereby enhancing antioxidant defenses and suppressing ferroptosis (45). Under sustained or intense ferroptosis-inducing stress, persistent high PERK/eIF2α phosphorylation and *ATF4* accumulation occur; ATF4 then induces pro-death mediators including C/EBP homologous protein (CHOP, also known as DNA damage-inducible transcript 3) and damage-regulated autophagy-modulating protein (DRAM). CHOP inhibits Bcl-2 and increases ROS production, whereas DRAM promotes autophagic ferroptosis. Together with GSH depletion and lipid peroxide accumulation, this shifts the cell towards ferroptotic death (48). This biphasic pattern suggests that *ATF4* initially supports cellular adaptation but may contribute to ferroptotic cell death when stress exceeds the compensatory capacity of the cell.

STAT3 may suppress ferroptosis by upregulating *SLC7A11* and *GPX4* expression, thereby supporting HCC cell survival (49). Preclinical studies have shown that *STAT3* antisense oligonucleotides can enhance sorafenib efficacy in HCC resistance models, suggesting that STAT3 inhibition may help overcome treatment resistance (50,51). Furthermore, *ATF4* and *STAT3* may interact to regulate ferroptosis sensitivity (52), although the mechanisms and clinical relevance of this interaction in HCC require further investigation. The stress intensity-dependent regulation of ferroptosis by *ATF4* and *STAT3* is summarized in Fig. 3.

Interaction between Wnt signaling and ferroptosis. The Wnt/β-catenin signaling pathway serves a crucial role in HCC development, progression and drug resistance. Recent studies have suggested an association between Wnt/β-catenin signaling and ferroptosis. Notably, the RNA helicase DEAD-box helicase 5 (DDX5) can prevent escape from sorafenib-induced ferroptosis by inhibiting Wnt/β-catenin signaling (53). In advanced HCC, DDX5 expression is positively associated with patient survival. Multikinase inhibitors such as sorafenib may reduce DDX5 expression, leading to activation of Wnt/β-catenin signaling and altered ferroptosis sensitivity (53,54). These findings suggest that targeting the Wnt/β-catenin-ferroptosis axis may improve therapeutic responses in HCC.

Mechanisms by which the p53 pathway regulates ferroptosis in HCC cells. p53 is a key tumor suppressor. In HCC cells, wild-type *p53* can directly inhibit *SLC7A11* transcription, thereby promoting lipid peroxidation (55); it can also enhance ferroptosis sensitivity through transcription-independent mechanisms, such as via interaction with spermidine/spermine N^1-acetyltransferase 1 (56). *p53*-mutant HCC cells are often associated with abnormal activation of the Wnt/β-catenin pathway (57). p53 restricts cystine/glutamate exchange (20), whereas Wnt signaling activation is typically associated with metabolic reprogramming in the tumor microenvironment (58). These pathways may converge at glutamine metabolism, which fuels GSH biosynthesis and maintains cellular redox homeostasis, thereby influence ferroptosis resistance in HCC cells (20,59).

Conversely, activation of the Wnt/β-catenin pathway upregulates *SLC7A11* expression, inhibiting ferroptosis (53,54). These two pathways converge on *SLC7A11* regulation in an antagonistic manner. Moreover, *p53*-mutant HCC frequently exhibits aberrant Wnt/β-catenin activation, which may cooperatively suppress ferroptosis and contribute to treatment resistance (20,57). The interplay between p53 and Wnt signaling in the context of ferroptosis represents a promising target for combination therapy, although the precise molecular mechanisms require further investigation.

Systemic regulation of ferroptosis by non-coding RNAs (ncRNAs). Previous studies have shown that long ncRNAs (lncRNAs) and circular RNAs (circRNAs) regulate ferroptosis

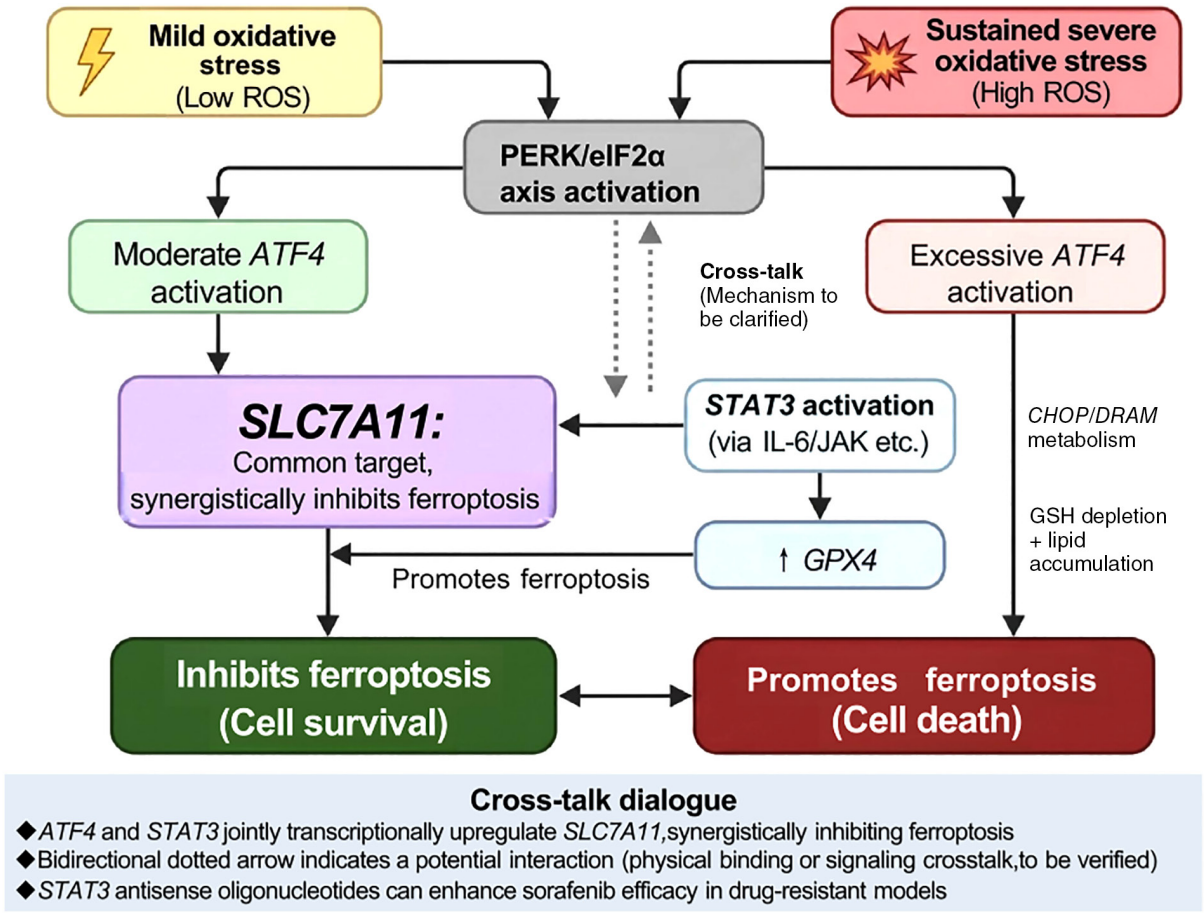

Figure 3. Mechanisms by which *ATF4* and *STAT3* signaling regulate ferroptosis. Under mild oxidative stress, moderate activation of the PERK/eIF2α-ATF4 pathway can upregulate *SLC7A11*, promote GSH synthesis and suppress ferroptosis. Under sustained or severe oxidative stress, excessive ATF4 activation may induce pro-death mediators such as CHOP and DRAM; together with GSH depletion and lipid peroxide accumulation, these changes promote ferroptotic cell death. STAT3 activation, for example through IL-6/JAK signaling, may suppress ferroptosis by upregulating SLC7A11 and GPX4 expression. The proposed ATF4-STAT3 cross-talk remains incompletely defined and requires further mechanistic validation in hepatocellular carcinoma models. ATF4, activating transcription factor 4; CHOP, C/EBP homologous protein; DRAM, damage-regulated autophagy-modulating protein; GPX4, GSH peroxidase 4; GSH, glutathione; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11.

in HCC. For example, the HCC-associated lncRNA *HEPFAL* is downregulated in HCC tissues; *HEPFAL* overexpression via transfection with a *HEPFAL* expression vector promotes SLC7A11 ubiquitination and degradation, reduces SLC7A11 stability, increases lipid ROS and iron levels, and enhances erastin-induced ferroptosis sensitivity (60). Conversely, the lncRNA *HULC* is highly expressed in HCC; *HULC* knockdown leads to increased lipid ROS, elevated malondialdehyde, GSH depletion and Fe^{2+} accumulation, and enhances sensitivity to erastin-induced ferroptosis, thus suggesting that *HULC* promotes HCC progression by inhibiting ferroptosis (61). Among the circRNAs, *circTTC13* is highly expressed in HCC tissues and is positively associated with tumor grade; in sorafenib-treated HCC cells, silencing *circTTC13* can increase lipid ROS, decrease *GPX4* and *SLC7A11* expression, and enhance sorafenib-induced ferroptosis, indicating that *circTTC13* suppresses ferroptosis and mediates sorafenib resistance via the microRNA-513a-5p/SLC7A11 axis (62). A circRNA associated with sorafenib resistance, *circRNA-SORE*, binds ubiquilin-1 (UBQLN1) to stabilize GPX4, thereby reducing intracellular lipid ROS (specifically inhibiting lipid peroxidation product accumulation), and enhances sorafenib resistance through the *circRNA-SORE*/UBQLN1/GPX4 axis (63,64). These findings expand the molecular network through which ncRNAs regulate ferroptosis and identify potential targets for HCC therapy.

4. Synergistic effects of ferroptosis inducers and conventional treatments

Synergistic effects of ferroptosis inducers and targeted therapies. Sorafenib is a first-line treatment for advanced HCC, and its antitumor activity partly involves SLC7A11 inhibition and ferroptosis induction (29). However, acquired resistance after long-term treatment remains a major obstacle. Preclinical studies have shown that sorafenib can induce ferroptosis by inhibiting SLC7A11, and ferroptosis resistance may contribute to sorafenib resistance in tumor cells (29,65). In sorafenib-resistant HCC samples, ferroptosis levels have been reported to be markedly lower than those in sorafenib-sensitive samples (41). Long-term sorafenib exposure may promote resistance through multiple mechanisms, including USP22-mediated CDK1 deubiquitination and DDX5 downregulation (32,54).

Several studies have therefore explored combining sorafenib with other ferroptosis inducers to enhance its efficacy (29,66-69). For example, the combination of chelerythrine and berbamine with sorafenib synergistically inhibits HCC cell proliferation, and has demonstrated antitumor effects in both *in vitro* and *in vivo* models (64). Furthermore, nanocarrier-mediated co-delivery of sorafenib and other ferroptosis inducers, such as salinomycin, may improve drug targeting and efficacy (70).

Combined use of ferroptosis modulators and chemotherapeutic agents. Combining ferroptosis inducers with chemotherapeutic agents may produce synergistic antitumor effects. This synergy may involve chemotherapy-induced oxidative stress and suppression of tumor cell antioxidant defenses by ferroptosis inducers (71). For example, erastin combined with cisplatin has been shown to markedly enhance cytotoxicity in HCC cells (72), whereas sulfasalazine promotes ferroptosis by activating the AMP-activated protein kinase/sterol regulatory element-binding protein 1 pathway and synergistically inhibits tumor growth when combined with 5-fluorouracil (71). Branched-chain amino acid transaminase 2 (BCAT2) has also been identified as a ferroptosis inhibitor, and BCAT2 targeting enhances chemotherapy-induced ferroptosis (71). These findings suggest potential therapeutic strategies for chemotherapy-resistant HCC, although clinical validation remains limited.

Role of ferroptosis sensitizers in overcoming drug resistance in HCC treatment. Ferroptosis sensitizers are compounds that enhance tumor-cell sensitivity to ferroptosis inducers and may help overcome treatment resistance in HCC. Emerging ferroptosis sensitizers include small-molecule inhibitors targeting ferroptosis-suppressive pathways, such as ferroptosis suppressor protein 1 (FSP1) inhibitors (73); compounds that modulate iron metabolism, including iron chelators or iron carriers (28); and nanomaterials, such as Fe_3O_4-PEI@HA-RSL3 nanocubes (74). Preclinical studies have shown that targeting the ferroptosis-induced inflammatory axis can enhance the *in vivo* efficacy of sorafenib (75-78). In addition, an oral delivery platform composed of butyrate-modified nanoparticles co-loaded with sorafenib and salinomycin can increase sorafenib uptake in HCC and induce ferroptosis, thereby improving therapeutic efficacy (70). Modulation of the USP22/H2BK120ub/TFRC axis also provides a potential target for sensitizer development (32). Together, these studies have identified several candidate strategies for overcoming drug resistance in HCC treatment.

Preclinical studies have observed that programmed death-ligand 1 (PD-L1) expression levels are associated with the efficacy of combining ferroptosis inducers with immune checkpoint inhibitors in HCC models (79,80). For example, in a study using sorafenib and PD-L1 small interfering RNA co-delivery systems, downregulation of PD-L1 was shown to enhance ferroptosis-induced tumor cell death and improve antitumor immunity (72). However, the direct mechanistic link between PD-L1 signaling and ferroptosis sensitivity remains incompletely defined. Possible hypotheses include PD-L1-mediated regulation of glucose or lipid metabolism, or indirect effects via tumor-immune crosstalk. Further studies are required to assess this relationship.

Despite these advances, the clinical translation of ferroptosis inducers remains at an early stage. Arsenic trioxide (ATO), an approved treatment for acute promyelocytic leukemia, has been investigated in mechanistic studies of ferroptosis in HCC. ATO can induce ferroptosis in HCC cells, and this effect can be reversed by the iron chelator desferrioxamine (81). ATO-induced ferroptosis may also promote the release of tumor-associated antigens and enhance immune responses. Notably, patients with low to moderate ferroptosis activation in tumors exhibited the highest risk of recurrence compared with those with no or high ferroptosis activation, and the ferroptosis-elicited inflammatory axis was associated with therapeutic resistance to sorafenib in HCC (78). However, the systemic toxicity of ATO, particularly cardiotoxicity and hepatotoxicity, limits its use as monotherapy for HCC (82). ATO-based nanodelivery systems, such as ATO@SP94-TMV and LP@MnAS, have demonstrated favorable targeting and biosafety in animal models, offering possible opportunities for the clinical translation of ATO (82,83). Among erastin derivatives, imidazole ketone erastin (IKE), a metabolically more stable SLC7A11 inhibitor, inhibits tumor growth in animal models of HCC after intraperitoneal administration, and dicoumarin can sensitize cells to IKE-induced ferroptosis (34).

Although novel ferroptosis-targeting agents remain largely preclinical in HCC, a small number of ferroptosis-related agents or strategies have entered early-phase clinical trials in other disease contexts. For example, eprenetapopt (APR-246), which targets *p53* mutations, has completed a phase II trial in myeloid tumors (NCT03588078) (84), and the iron-loaded nanocarbon formulation CNSI-Fe(II) has completed a phase I dose-escalation study in advanced solid tumors (NCT06048367) (85). In addition, sorafenib combined with stereotactic body radiation therapy has been evaluated in a phase II trial for colorectal cancer liver metastases, with proposed efficacy and safety benefits partly attributed to ferroptosis induction (86). PD-L1/BBζ chimeric switch receptor (CSR)-modified dual-target chimeric antigen receptor T cells, in which the CSR binds PD-L1 and converts the inhibitory signal into a 4-1BB costimulatory signal (87), have also entered a phase I clinical trial for pleural or peritoneal metastases (NCT04684459) (87), although this evidence remains indirect for HCC. However, these agents and strategies generally remain in the early stages of development. Clinical application of ferroptosis inducers in HCC will require improved drug-delivery efficiency, tumor-targeting specificity, toxicity control and clearer indication selection.

5. Current status of research on ferroptosis-related biomarkers

Biomarkers associated with ferroptosis sensitivity. Research on biomarkers associated with ferroptosis sensitivity provides an important basis for personalized treatment of HCC. Multiple studies have suggested that ferroptosis-related gene-expression profiles may have predictive value for treatment response in HCC (88). Potential biomarkers under investigation include ferroptosis regulatory molecules, such as GPX4, SLC7A11 and FSP1 (30,73,88); metabolism-related molecules, such as ACSL4 and lysophosphatidylcholine acyltransferase 3 (88); signaling molecules, such as *p53*, *ATF4* and *STAT3* (49,55); and ncRNAs (33). Table I summarizes

Table I. Summary of ferroptosis-related biomarkers.

Biomarker	Study type	Main results	(Refs.)
GPX4	Patient HCC tissue (n=106)	High expression is associated with shorter overall survival; GPX4 is a negative regulator of ferroptosis	(30)
SLC7A11	Patient HCC tissue and HCC cell lines	High expression promotes sorafenib resistance and inhibits ferroptosis	(29,90)
FSP1	HCC cell lines and mouse models (*KRAS*-mutant)	Protects *KRAS*-mutant cells from ferroptosis	(73)
ACSL4	Patient HCC tissue and HCC cell lines	Promotes ferroptosis (PUFA substrate), but may also promote HCC in the context of NASH	(46,47,88)
LPCAT3	HCC cell lines	Promotes lipid peroxidation and increases ferroptosis sensitivity	(88)
TP53	HCC cell lines	Wild-type *p53* inhibits *SLC7A11* transcription and promotes ferroptosis	(55)
ATF4	HCC cell lines and mouse models	Dual role: Suppresses ferroptosis in response to low/moderate stress, promotes ferroptosis in response to high stress	(45)
STAT3	HCC cell lines and mouse models	Suppresses ferroptosis via upregulation of SLC7A11/GPX4	(49)
ncRNAs (for example, *HEPFAL* and *HULC*)	HCC cell lines and mouse models	Regulate SLC7A11/GPX4 stability or expression	(33,60-64)

ACSL4, long-chain acyl-CoA synthetase 4; ATF4, activating transcription factor 4; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; HCC, hepatocellular carcinoma; LPCAT3, lysophosphatidylcholine acyltransferase 3; NASH, non-alcoholic steatohepatitis; ncRNA, non-coding RNA; PUFA, polyunsaturated fatty acid; SLC7A11, solute carrier family 7 member 11.

the evidence level and main results for each biomarker based on available studies.

In a HCC cohort (n=106), high GPX4 expression was reported to be associated with shorter overall survival (HR=2.34, P<0.01) and sorafenib resistance (30). In another cohort (n=89), high ACSL4 expression was revealed to be associated with microvascular invasion, but also with increased sensitivity to ferroptosis inducers (40); ACSL4 mRNA has been detected in serum exosomes (89)

ACSL4 promotes ferroptosis by converting polyunsaturated fatty acids into CoA esters; however, in NAFLD/NASH-associated HCC it may exacerbate hepatocyte injury and fibrosis, indirectly promoting HCC development (47). Thus, ACSL4 as a biomarker requires careful interpretation depending on disease stage and etiology.

Clinical evidence for key biomarkers. Among the aforementioned markers, GPX4, a key negative regulator of ferroptosis, has been associated with predictive or prognostic value in colorectal cancer and HCC (30); FSP1 is highly expressed in *KRAS*-mutated tumors (in models of pancreatic and lung cancer) and is associated with ferroptosis resistance (73), although its role in HCC requires further investigation; and abnormal expression of the FTO/YTHDF2/GPX4 signaling axis is associated with ferroptosis sensitivity in HCC (30). If validated, these biomarkers may help identify patient subgroups likely to benefit from ferroptosis-inducing therapies and support the development of molecular subtyping systems based on ferroptosis sensitivity. However, clinical-cohort validation of ferroptosis biomarkers remains limited. Although immunohistochemical studies have detected associations between GPX4 or SLC7A11 expression and prognosis in small HCC tissue cohorts, most studies have been retrospective, have included only several dozen to slightly more than 100 cases, and lacked multicenter prospective validation (90,91). Regarding detection feasibility, GPX4 and ACSL4 mRNA and protein levels can be measured in biopsy tissues or blood exosomes using reverse transcription-quantitative PCR, western blotting, enzyme-linked immunosorbent assay and immunohistochemistry (89,92,93).

Use of biomarkers in personalized treatment strategies. Personalized treatment strategies based on ferroptosis-related biomarkers are being explored in HCC. Analysis of ferroptosis-related gene expression profiles may help guide the future selection of precision therapies for patients with HCC (94). In immunotherapy, combined analysis of ferroptosis markers and tumor immune microenvironment characteristics may help optimize future combination regimens involving immune checkpoint inhibitors and ferroptosis inducers (95). The integration of nanotechnology with ferroptosis-based therapy may also support biomarker-guided personalized treatment. For example, in photothermal-ferroptosis combination therapy, real-time monitoring of iron metabolism-related molecules may enable dynamic adjustment of treatment regimens (96). Furthermore, interactions between lncRNAs and ferroptosis may provide a novel framework for biomarker screening during the development of nanomaterial-based combination therapies (97). As multi-omics technologies advance, ferroptosis-susceptibility prediction models integrating genomics,

transcriptomics and metabolomics data may improve the precision of personalized HCC treatment (96).

In parallel with ferroptosis-based biomarkers, non-invasive approaches to evaluate the tumor immune microenvironment have shown promise in predicting outcomes in HCC, which may complement ferroptosis-based prognostic strategies (98). Specifically, Wu *et al* (98) developed a radiomics-based non-invasive model [Radiomic Immunoscore (RIS)] to evaluate the tumor immune microenvironment and predict prognosis in patients with HCC. Using MRI-derived radiomics features, the RIS model accurately predicted immune status [area under the curve (AUC)=0.753] and showed potential in predicting anti-programmed cell death protein 1 immunotherapy response (AUC=0.731) in patients with advanced HCC. Such non-invasive strategies complement ferroptosis-based prognostic strategies in several manners: i) They provide information on the immune landscape, which influences ferroptosis sensitivity (for example, PD-L1 expression is associated with ferroptosis inducer efficacy); ii) they can be combined with ferroptosis-related gene signatures to build multi-dimensional prognostic models; and iii) they enable dynamic, real-time monitoring of tumor evolution without repeated biopsies, facilitating adaptive combination therapies that target both ferroptosis and immune checkpoints.

6. Limitations and controversies in current research

Unresolved issues in mechanistic research. Although research into ferroptosis has advanced substantially, several questions remain regarding its specific regulatory mechanisms in HCC. First, the functions of post-translational modifications of ferroptosis-associated proteins, such as ubiquitination and phosphorylation of SLC7A11 and GPX4, remain incompletely understood; these modifications may influence ferroptosis sensitivity in HCC cells by modulating protein stability and activity (99). Second, the mechanisms by which m6A modifications regulate ferroptosis in HCC remain unclear. Furthermore, ferroptosis sensitivity differs substantially across HCC cell lines, but the molecular determinants of this heterogeneity remain unclear.

Challenges in clinical translation. Ferroptosis inducers face multiple barriers to clinical translation in HCC treatment. A major issue is the incomplete understanding of ferroptosis mechanisms in human HCC, which limits rational drug development (40). Drug-delivery systems also remain limited, as conventional delivery methods may not achieve sufficient penetration or selective accumulation in HCC tissues (100). Furthermore, most ferroptosis inducers, such as ATO and erastin derivatives, remain experimental in HCC (101), and although nanomaterials such as Fe_3O_4-PEI@HA-RSL3 have shown promise, they remain distant from clinical application (74). Addressing these challenges will require integration of basic research, drug development, biomarker validation, toxicity assessment and clinical trial design.

Differences between animal models and human studies. Important differences exist between animal models and human HCC. Most mechanistic studies remain confined to cellular or animal models, limiting direct clinical extrapolation. For example, GPX4 has been identified as a major regulator of ferroptosis in mouse HCC models, but its applicability to human HCC requires verification (102). In animal studies, USP22 promotes HCC growth and inhibits sorafenib-induced ferroptosis; however, the complexity of the human HCC microenvironment may produce different outcomes (32). In addition, the chronic hypoxic microenvironment of HCC tissues is difficult to fully replicate in animal models, which may affect the evaluation of ferroptosis inducers (30). Therefore, animal models that more closely recapitulate human HCC biology are needed, along with stronger integration of mechanistic and clinical research.

Targeted toxicity of GPX4 inhibitors. As a key negative regulator of ferroptosis, GPX4 is a major target for ferroptosis-inducing strategies. However, targeting GPX4 presents two major challenges.

Toxicity to normal tissues. Classic GPX4 inhibitors, such as RSL3 and ML210, exert their inhibitory effects by covalently binding to the selenocysteine active site of GPX4; however, these compounds have poor selectivity and may damage normal tissues while inhibiting GPX4 in tumor cells (103). Non-selective ferroptosis induction may damage immune cells or disrupt microenvironmental homeostasis (104). Because the liver is central to iron metabolism and detoxification, it is particularly vulnerable to GPX4 inhibition: Reduced GPX4 activity can render normal hepatocytes susceptible to ferroptosis, leading to drug-induced liver injury (105,106). This toxicological profile substantially limits the clinical translation of GPX4 inhibitors.

Targeted delivery strategies. To address toxicity, researchers have developed strategies to enhance the selectivity of GPX4 inhibition. One approach involves nanodelivery systems that promote tumor-targeted accumulation; for example, Fe_3O_4-PEI@HA-RSL3 nanocubes can release RSL3 in the acidic tumor microenvironment, thereby reducing systemic exposure; in mouse HCC subcutaneous xenograft models, this strategy achieved selective GPX4 inhibition, ferroptosis induction and tumor growth inhibition without notable hepatotoxicity (74). Another approach involves GPX4 degraders, including proteolysis-targeting chimeras, which uses E3 ligases that are highly expressed in tumor cells to achieve cell-specific degradation; in mouse pancreatic cancer models as a proof-of-concept study, tumor-specific E3 ligase has been reported to achieve GPX4 degradation, reducing normal tissue toxicity (107). A third approach is screening for more selective GPX4 inhibitors, such as the small-molecule compound N6F11, which can selectively induce ferroptosis in tumor cells by triggering GPX4 ubiquitination and degradation while causing no marked damage to immune cells; this has been demonstrated in immunocompetent mouse models of pancreatic cancer (108). However, most of these strategies remain preclinical and their safety in humans requires systematic evaluation.

7. Outlook

Although ferroptosis research has advanced substantially, unresolved questions remain regarding its regulatory mechanisms in HCC, including the role of post-translational

modifications, the mechanisms of m6A modification and the molecular basis of cellular heterogeneity. For clinical translation, ferroptosis inducers still face challenges, including limited drug-delivery efficiency, insufficiently representative animal models and inadequate validation in human studies. Future research should focus on four priorities: i) Developing novel ferroptosis inducers and nanotechnology-based targeted delivery systems to improve drug selectivity and tumor accumulation; ii) elucidating heterogeneity in ferroptosis regulatory networks and using multi-omics technologies to construct ferroptosis-sensitivity prediction models for personalized combination therapy; iii) conducting biomarker-based prospective clinical trials to clarify the efficacy and safety of ferroptosis inducers in patients with advanced HCC; and iv) exploring synergistic mechanisms between ferroptosis and other forms of cell death or treatment modalities, such as cuproptosis and immunotherapy.

In summary, research on ferroptosis regulatory networks offers a useful framework for understanding HCC drug resistance and developing novel therapeutic strategies. However, the clinical value of ferroptosis-based strategies in HCC will depend on validated biomarkers, selective delivery systems, toxicity control and prospective human trials.

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Authors' contributions

MZ contributed to the conception and design of the review, and drafted and revised the manuscript. XH provided conceptual guidance and critical input during manuscript revision, and critically reviewed and edited the manuscript. Data authentication is not applicable. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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