## Review Article

# Ferroptosis: From Basic Research to Clinical Therapeutics in Hepatocellular Carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is one of the most common and highly heterogeneous malignancies worldwide. Despite the rapid development of multidisciplinary treatment and personalized precision medicine strategies, the overall survival of HCC patients remains poor. The limited survival benefit may be attributed to difficulty in early diagnosis, the high recurrence rate and high tumor heterogeneity. Ferroptosis, a novel mode of cell death driven by iron-dependent lipid peroxidation, has been implicated in the development and therapeutic response of various tumors, including HCC. In this review, we discuss the regulatory network of ferroptosis, describe the crosstalk between ferroptosis and HCC-related signaling pathways, and elucidate the potential role of ferroptosis in various treatment modalities for HCC, such as systemic therapy, radiotherapy, immunotherapy, interventional therapy and nanotherapy, and applications in the diagnosis and prognosis of HCC, to provide a theoretical basis for the diagnosis and treatment of HCC to effectively improve the survival of HCC patients.

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## Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and causes a severe burden because of its mortality, as it is the third cause of cancer-related death worldwide.[1,2] Despite the gradual enhancement in treatment strategies, including surgical treatment, immunotherapy, targeted therapy, or combination therapy; the proportion of the effective population, and the availability of effective drugs and duration of efficacy, the overall survival of HCC patients is still limited.[3] Studies have shown that a complex liver disease background, high tumor heterogeneity, and a high recurrence rate are major factors that limit the treatment and prognosis of HCC patients.[4,5] Because of a lack of obvious clinical symptoms and early diagnostic markers at the early stage of the disease, most HCC patients cannot undergo radical surgical resection because they are in an advanced stage of the disease at the time of the visit.[2,3] Sorafenib is a multikinase inhibitor that is used to treat patients with unresectable HCC.[3–7] Sorafenib is the first drug used for systemic therapy of advanced HCC patients, and it effectively prolongs survival HCC, but drug resistance and adverse drug reactions limit the survival benefit. In two randomized phase III clinical trials of patients with advanced HCC, the overall response rate of sorafenib was 2–3%, the time to progression was only 5.5 months, and the median survival time was only 10.7 months[6,7] Consequently, it is crucial to explore the pathogenesis and drug resistance mechanism of HCC, to further identify new therapeutic targets and develop safe and effective treatment regimens.

Ferroptosis is a newly discovered special form of regulated cell death (RCD), that differs from apoptosis, necroptosis, autophagy, and pyroptosis, and is characterized by the accumulation of iron-dependent lipid peroxides.[8] Accumulating evidence indicates that ferroptosis is closely related to the pathogenesis of various diseases, such as neurodegenerative diseases,[9] ischemia-reperfusion injury,[10] autoimmune diseases,[11] liver fibrosis,[12] and various cancers, including HCC.[13–15] During tumorigenesis, ferroptosis has a dual role in tumor promotion and suppression, which depends on the release of damage-associated molecular patterns and the activation of immune responses triggered by ferroptotic damage within the tumor microenvironment.[16] Furthermore, ferroptosis affects the efficacy of chemotherapy, radiotherapy, and immunotherapy in cancer patients.[15,17,18] Therefore, although the regulatory mechanism of ferroptosis is not yet fully understood, based on its connection with various tumors, ferroptosis may become a key
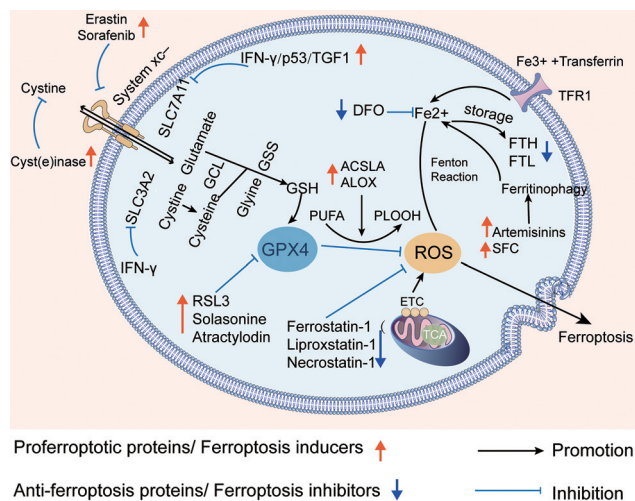
**Fig. 1. Key regulators and related mechanisms of ferroptosis.** Ferroptosis, a form of iron-dependent RCD driven by excessive accumulation of lipid peroxidation. The cystine/glutamate transporter (also known as system Xc-) imports cystine into cells with a 1:1 counter-transport of glutamate. GPX4 reduces lipid hydroperoxides to lipid alcohols by using GSH as a reducing cofactor. Several proteins control ferroptosis through the regulation of iron metabolism. Reagents that induce or inhibit ferroptosis are shown (also see Table 1). ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX, arachidonate lipoxygenase; DFO, deferoxamine; ETC, electron transport chain; FTH1, ferritin heavy chain 1; FTL, ferritin light polypeptide; GCL, glutamate-cysteine ligase; GPX4, glutathione peroxidase 4; GSH, glutathione; GSS, glutathione synthetase; IFN-γ, interferon-gamma-γ; RCD, regulated cell death; ROS, reactive oxygen species; RSL3, ras-selective lethal small molecule 3; SFC, saponin formosanin C; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; TCA, tricarboxylic acid cycle; TFR1, transferrin receptor protein 1; TGF-β1, transforming growth factor β1; TRF1, transferrin receptor 1.

part of HCC treatment in the future, and some researchers also believe that ferroptosis may become a critical factor in the diagnosis and prognosis of HCC.[19] Hence, this review discusses the regulatory mechanism and application of ferroptosis in HCC in detail, to provide reference for the diagnosis, treatment, and prognosis of HCC.

## Overview of ferroptosis

Ferroptosis, a form of iron-dependent RCD driven by excessive accumulation of lipid peroxidation, was first proposed by Dixon *et al*.[8] in 2012. In contrast to apoptosis, autophagy, necrosis, pyroptosis, and other forms of programmed cell death, morphologically, the mitochondrial outer membrane of ferroptotic cells is ruptured and shrunken, and mitochondrial cristae are reduced (disappear). For cellular components, ferroptosis is often accompanied by the accumulation of iron ions, the elevation of reactive oxygen species (ROS), decreased nicotinamide adenine dinucleotide phosphate, and changes in some characteristic genes.[8,20] Ferroptosis is triggered by inhibiting cell membrane translocators such as cystine/glutamate translocators (also known as system Xc-) or by activating transferrin, as well as by blocking intracellular antioxidant enzymes such as glutathione peroxidase 4 (GPX4). Additionally, iron accumulation and lipid peroxidation are two key signals that initiate membrane oxidative damage during ferroptosis (Fig. 1).[8,16] Therefore, the regulation of ferroptosis mainly focuses on system Xc regulation, glutathione (GSH) metabolism and GPX4 activity regulation and iron and ROS regulation. System Xc- exchanges glutamate for cystine in a 1:1 ratio with solute carrier family 7 member 11 (SLC7A11) and transports it into the cell for

GSH synthesis, and inhibition of system Xc- activity drives ferroptosis.[8,21] GSH, a substrate of GPX4, protects cells from lipid peroxidative damage, and both the inhibition of GSH synthesis and the inactivation of GPX4 induce ferroptosis.[22,23] Most tumors show highly invasive growth by increasing iron storage within a certain range, but excess iron concentrations lead to membrane lipid peroxidation and cell death.[24,25] Moreover, the rapid proliferation of tumor cells requires the support of high mitochondrial metabolism, and mitochondria are the main source of ROS.[26] Excessive ROS-induced oxidative stress damages tissues and cells.

The high iron requirement, active metabolism, and increased ROS load make cancer cells more sensitive to ferroptosis. Studies have shown that ferroptosis inhibits tumor growth and promotes tumor cell chemosensitivity, so the induction of ferroptosis has promise as tumor treatment strategy.[16,20] Compounds (either inducers or inhibitors) that precisely regulate ferroptosis have an important role in elucidating the mechanisms of ferroptosis-related diseases, so the identification of ferroptosis inducers or inhibitors is indispensable. Ferroptosis inducers can be divided into four categories according to their potential induction mechanisms, inhibition of System Xc- activity, direct inhibition of GPX4, depletion of GPX4 protein and CoQ10, and induction of lipid peroxidation. Ferroptosis inhibitors can be divided into two categories, those that reduce intracellular iron accumulation and those that inhibit lipid peroxidation (Table 1).[8,27-40]

## Ferroptosis and sorafenib in HCC

Sorafenib is an oral multitarget, multikinase inhibitor that blocks platelet derived growth factor, vascular endothelial growth factor, Fms-like tyrosine kinase 3, c-Kit (CD117) upstream of the signal transduction pathway of tumor and tumor angiogenic cells, and the downstream RAF/MEK/ERK signaling pathway and exerts anticancer effects by inhibiting proliferation, promoting apoptosis and reducing tumor angiogenesis.[6,7] Studies have shown that the iron chelator deferoxamine significantly reduces the cytotoxic effect of sorafenib on an HCC cell line (Huh7), demonstrating that sorafenib exerts anticancer activity by inducing ferroptosis as a single agent in HCC cells, rather than through multikinase inhibitory effects.[27,28] Moreover, in some HCC patients treated with sorafenib, concentration of serum oxidative stress response markers was associated with progression-free survival, suggesting that sorafenib-induced ferroptosis plays an important role in patient survival.[41] Sorafenib has been recognized as an inducer of ferroptosis, which blocks cystine uptake by inhibiting system Xc- activity, reduces GSH biosynthesis, and thus induces ferroptosis and promotes oxidative stress to induce ferroptosis by increasing mitochondrial ROS production. The mechanism of action depends on the retinoblastoma status of HCC cells.[27,28,42] A recent study suggested that sorafenib does not qualify as a *bona fide* ferroptosis inducer and does not induce ferroptosis in a range of tumor cell lines, in contrast to the cognate system Xc- inhibitors sulfasalazine and erastin.[43] Interestingly, sorafenib both induces ferroptosis and protects HCC cells from erastin-induced ferroptosis by increasing the availability of amino acids for GSH synthesis through inhibition of protein biosynthesis.[27,28,44] The existence of modes of antagonism may explain the apparent paradox, although further research is needed to explain it. Although sorafenib-induced ferroptosis also occurs in melanoma, pancreatic cancer, and colon cancer, both pharmacological inhibition (ferroptosis inhibitors) and genetic interference (RNA interference techniques) readily inhibit the antitumor effectiveness of sorafenib.[27] Therefore, the precise mechanism of

**Table 1. Representative ferroptosis inducers and inhibitors**

|  | Reagent | Potential mechanism | Reference |
|---|---|---|---|
| **Representative ferroptosis inducers** | | | |
| Class I | Erastin | Inhibits the activity of system Xc- and depletes GSH | 8 |
|  | Sorafenib | Inhibits cystine uptake through system Xc- | 27,28 |
|  | Sulfasalazine | Inhibits the activity of System Xc- | 8,29 |
|  | Glutamate | Inhibits the activity of System Xc-; High concentrations of extracellular glutamate inhibit cystine uptake | 30 |
| Class II | RSL3 | Covalently binds to the selenocysteine residue of GPX4 and thereby inhibits GPX4 | 31 |
|  | Solasonine | Inhibitor of GPX4 that causes accumulation of lipid peroxidation | 32 |
|  | Atractylodin | Inhibitor of GPX4 that causes accumulation of lipid peroxidation | 33 |
| Class III | FIN56 | Depletion of GPX4 and CoQ10 | 34 |
| Class IV | Artesunate | Oxidizes $Fe^{2+}$ ions and promote intracellular accumulation of ROS | 35 |
|  | CH004 | promotes accumulation of lipid peroxidation | 36 |
| **Representative Ferroptosis Inhibitors** | | | |
| Class I | Deferoxamine | Depletes iron and prevents iron-dependent lipid peroxidation | 37 |
| Class II | Ferrostatin-1 | Scavenges ROS and inhibits lipid peroxidation | 37,38 |
|  | Liproxstatin-1 | Scavenges ROS and inhibits lipid peroxidation | 38 |
|  | Vitamin E | Blocks propagation of lipid peroxidation, may inhibit lipoxygenases | 39 |
|  | Necrostatin-1 | Scavenges ROS and inhibits lipid peroxidation | 40 |

GPX4, glutathione peroxidase 4; GSH, glutathione; RSL3, ras-selective lethal small molecule 3; ROS, reactive oxygen species.

the ferroptosis-inducing effect of sorafenib needs further study to improve its cytotoxicity and weaken the drug resistance of patients.

Nuclear factor E2-related factor 2 (NRF2) is a key regulator of antioxidative and electrophilic stress,[45] and the activation and inactivation of NRF2 influences sorafenib-induced ferroptosis in HCC. For example, quiescin sulfhydryl oxidase 1 interacts with epidermal growth factor receptor to enhance its ligand-induced endosomal transfer and lysosomal degradation, resulting in moderation of NRF2 activation, disrupting redox homeostasis, and sensitizing HCC cells to oxidative stress, thereby enhancing sorafenib-induced ferroptosis.[46] Glutathione S-transferase zeta 1 expression was found to be significantly decreased in sorafenib-resistant HCC cells, and downregulation of glutathione s-transferase zeta 1 inhibited sorafenib-induced HCC cell ferroptosis by increasing the levels of NRF2 and ferroptosis-related genes (GPX4 and SLC7A11).[47] With sorafenib and erastin, p62/sequestosome-1 mediates the inactivation of Kelch-like ECH-associated protein 1 to prevent NRF2 degradation and enhance subsequent nuclear accumulation. NRF2 interacts with MAF bZIP transcription factor G and activates the transcription of genes involved in ROS and iron metabolism to confer ferroptosis resistance to HCC cells. Genetic or pharmacological inhibition of NRF2 expression/activity in HCC cells increases the anticancer activity of erastin and sorafenib in vitro and in vivo, indicating that the p62-Keap1-NRF2 antioxidant signaling pathway is a key negative regulator of ferroptosis in HCC cells.[15] Another study showed that disulfiram (DSF)/Cu significantly impaired mitochondrial homeostasis, increased the free iron pool, and enhanced lipid peroxidation, leading to ferroptotic cell death. Inhibition of NRF2 expression via RNA interference or pharmacological inhibitors significantly facilitated the accumulation of lipid peroxidation, and rendered HCC cells more

sensitive to DSF/Cu induced ferroptosis, which facilitated the synergistic cytotoxicity of DSF/Cu and sorafenib.[48] Activation of NRF2 is essential for upregulation of metallothionein-1G (MT-1G) expression following sorafenib treatment, and MT-1G facilitates sorafenib resistance through inhibition of ferroptosis. Consequently, inhibition of MT-1G during therapy may be an option for HCC treatment.[49] Sorafenib also induces ATP-binding cassette subfamily C member 5 expression through the phosphatidylinositol-3-kinase/AKT/NRF2 signaling pathway. Accumulation of ATP-binding cassette subfamily C member 5 increases intracellular GSH by interacting with and stabilizing SLC7A11, thereby attenuating lipid peroxidation and inhibiting ferroptosis.[50] Shan *et al*.[51] found that ubiquitin-like modifier activating enzyme 1 regulated the HCC cell phenotype and ferroptosis through the NRF2 signaling pathway to participate in the development of HCC.[51] Thus, NRF2 is an important target of the ferroptosis network in HCC cells.

Sigma 1 receptor (S1R) is a protein regulator associated with oxidative stress metabolism.[52] Knockdown of S1R increases GSH depletion and inhibits the expression of ferritin heavy chain 1 and transferrin receptor protein 1 to promote iron enrichment and ROS accumulation to exert the anticancer activity of sorafenib.[53] Haloperidol, an S1R antagonist, may benefit sorafenib-treated HCC patients by reducing the dose of sorafenib or enhancing the drug's effectiveness.[54] In conclusion, S1R protects HCC cells against sorafenib-induced ferroptosis. A better understanding of the role of S1R in ferroptosis may provide new insights into HCC treatment.

The existence of sorafenib resistance is an important factor limiting the survival benefit of patients with advanced HCC. Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) induces the expression of SLC7A11 in a transcriptional enhanced associate domain (TEAD)-dependent manner. Moreover, YAP/TAZ maintains

activating transcription factor 4 protein stability and transcriptional activity by limiting its polyubiquitination, which in turn synergistically induces SLC7A11 expression, thereby making HCC cells resistant to sorafenib-induced ferroptosis. The results indicate that the transcription factor YAP/TAZ is a key driver of sorafenib resistance in HCC.[55] Other studies have demonstrated that YAP sensitizes HCC cells to ferroptosis by transcriptionally upregulating arachidonate lipoxygenase 3 leading to an increase of lipid peroxidation,[56] and O-GlcNAcylation increases the ferroptosis sensitivity of HCC cells through the YAP/transferrin receptor pathway,[57] suggesting that YAP may be an effective biomarker for predicting the response of HCC cells to ferroptotic induction. Deletion of azoospermia-associated protein 1 interferes with the ferroptotic effect of sorafenib on HCC cells by affecting the SLC7A11/GPX4 pathway.[58] MiR-23a-3p is upregulated in sorafenib-resistant cells and recognizes and binds to acyl-CoA synthetase long-chain family member 4 (ACSL4) to limit accumulation of chelatable iron and negatively regulate sorafenib-induced HCC cell ferroptosis.[59] Genetic and pharmacological inhibition of ACSL4 rescued sorafenib-induced ferroptosis in HCC cells *in vitro* and xenograft growth inhibition *in vivo*, suggesting that ACSL4 expression is a good candidate biomarker for predicting the ferroptotic sensitivity of HCC cells.[60]

*In vivo* and *in vitro* experiments have shown that sorafenib activates family with sequence similarity 134 member B-mediated autophagy of the endoplasmic reticulum in HCC, and targeting family with sequence similarity 134 member B-mediated reticulophagy activates sorafenib-induced ferroptosis in HCC cells.[61] Deletion of LIFR promotes HCC tumorigenesis and confers resistance to sorafenib-induced ferroptosis. Mechanistically, loss of LIFR activates nuclear factor-κB signaling through Src homology region 2 domain-containing phosphatase-1, leading to upregulation of lipocalin 2 iron-chelating cytokine, thereby depleting intracellular iron to confer ferroptosis resistance in HCC cells.[62] Upregulation of the secreted protein acidic and rich in cysteine promotes lactate dehydrogenase release and ROS production in HCC cells, sensitizing HCC cells to sorafenib.[63] CDGSH iron sulfur domain 2 knockout promotes uncontrolled autophagy in sorafenib-resistant HCC cells to restore sorafenib-induced HCC cell ferroptosis and reverse drug resistance.[64] CIARS (hsa_circ_0008367) was shown to be a promoter of ferroptosis in HCC cells after sorafenib treatment, in part due to the activation of human AlkB homolog H5-mediated autophagy and ferritin phagocytosis.[65] Overall, the mechanism of sorafenib resistance is regulated by numerous complex gene networks, and the regulation of expression of the identified resistance-related genes during sorafenib treatment may be effective in improving it clinical benefit.

## NcRNAs regulate ferroptosis in HCC

Research on noncoding RNAs (ncRNAs) is increasing, and many studies have shown that ncRNAs such as microRNAs, long noncoding RNAs (lncRNAs), and circular RNAs are key regulators in the tumorigenesis and development of HCC.[66–68] However, whether ncRNAs mediate HCC cell ferroptosis remains unclear. Bai *et al*.[69] demonstrated that miR-214 enhanced erastin-induced HCC cell ferroptosis by targeting activating transcription factor 4 expression in HCC cells. Exposure to erastin, the upregulated lncRNA GABPB1-AS1 in HCC inhibits peroxiredoxin-5 by blocking GABPB1 translation, leading to suppression of the cellular antioxidant capacity and cell viability.[70] Peroxidases are key cellular antioxidant enzymes that block the destructive process of peroxidative damage to membranes caused by accumulated

hydroxyl radicals. Xu *et al*.[71] showed that circIL4R acts as an oncogene and relieves the inhibitory effect of miR-541-3p on GPX4 expression by sponging miR-541-3p, thereby upregulating GPX4 expression to inhibit ferroptosis in HCC cells. Similarly, Lyu *et al*.[72] found that the circ0097009/miR-1261/SLC7A11 axis mediates HCC progression by regulating ferroptosis. Collectively, the studies demonstrated a mechanistic link between ncRNAs and the ferroptotic response in HCC that helps to elucidate the underlying mechanisms of ferroptosis in HCC cells, establishing ncRNAs as attractive therapeutic targets for HCC.

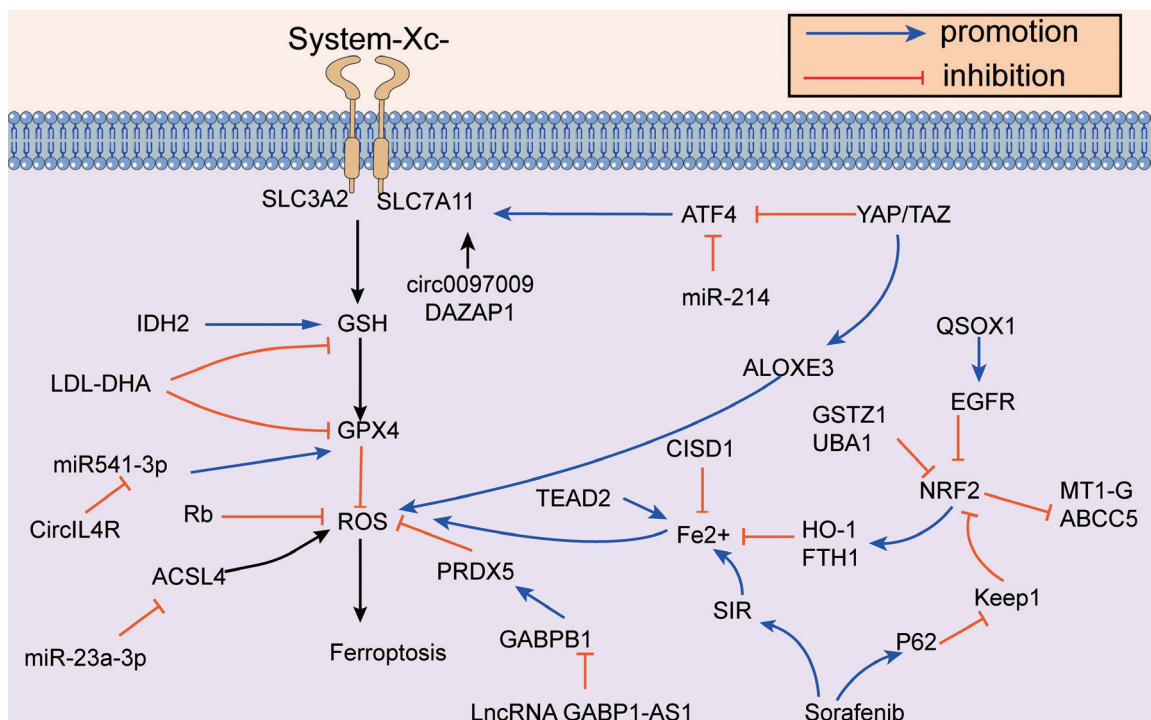## Other targets regulate ferroptosis in HCC

Ferroptosis is closely related to the development and treatment response of various cancers, and the inhibition of tumor progression by ferroptosis-inducing therapy may serve as a new therapeutic strategy for HCC.[16] Sorafenib-induced ferroptosis promotes the antitumor mechanism of sorafenib, and ncRNAs have been shown to mediate HCC cell ferroptosis. In addition, other molecular targets that regulate ferroptosis in HCC have been described. Table 2 summarizes some molecular targets of ferroptosis in HCC.[15,17,27,28,42,47–51,53–56,59,61–65,69–85] Figure 2 shows the regulatory pathways and some of the targets of ferroptosis in HCC.

A previous report showed that YAP/TAZ promotes HCC cells to overcome sorafenib-induced ferroptosis in a TEAD-dependent manner.[55] Integrative bioinformatics and experimental analysis revealed that TEAD can serve as a novel prognostic target for HCC, and that knockdown of TEAD2 induces ferroptosis through iron accumulation and subsequent oxidative damage.[73] P53, a tumor suppressor implicated in the cell cycle, apoptosis, and cell senescence, has been reported to promote ferroptosis by inhibiting SLC7A11 expression and cystine uptake,[74] whereas mutant p53 has been shown to inhibit the ferroptotic capacity of cells.[86] Furthermore, zinc finger protein 498 inhibits the transcriptional activity of p53 by interfering with p53 Ser46 phosphorylation, thereby inhibiting apoptosis and ferroptosis in HCC cells.[87] p53 has also been reported to negatively regulate ferroptosis, p53 limits erastin-induced ferroptosis in colorectal cancer cells by promoting the nuclear localization of dipeptidyl peptidase 4 and increasing the expression of SLC7A11.[88] The above studies revealed that the dual effect of p53 on ferroptosis may depend on the cell type, a pivotal finding that provides the basis for the development of ferroptosis-inducing therapies based on p53-dependent tumor suppression. Tumor cells alter their susceptibility to ferroptosis through various gene expression and regulatory mechanisms, such as the increased glucose-6-phosphate dehydrogenase expression in HCC cells leading to an anti-ferroptotic state by inhibiting cytochrome P450 oxidoreductase expression.[75] HCC cells with low H-ferritin expression are more sensitive to ras-selective lethal small molecule 3-induced ferroptosis.[31] Xue *et al*.[76] found that Rb1-inducible coiled-coil 1-induced upregulation of coiled-coil helix coiled-coil helix domain-containing protein 3 expression to stimulate mitochondrial function and increase ROS production, resulting in increased sensitivity of HCC cells to ferroptosis, and suggesting that Rb1-inducible coiled-coil 1 is a promising target for ferroptosis-based antitumor therapy. The occurrence of ferroptosis is accompanied by obvious morphological changes in mitochondria, and mitochondria are the main source of ROS,[8,26] study of the regulators of mitochondrial function will help to elucidate the regulatory mechanism of ferroptosis. It has been reported that the RNA-binding protein alpha-enolase inhibited mitochondrial respiration through the alpha-enolase/iron regulatory protein 1/mitoferrin-1 axis, resulting in mitochondrial iron en-

**Table 2. Molecular targets of ferroptosis in hepatocellular carcinoma**

| Targets | Molecular regulatory pathway | Functions | Reference |
|---|---|---|---|
| Rb | / | Inhibits sorafenib-induced ferroptosis | 27,28,42 |
| NRF2 | QSOX1/EGFR/NRF2, GSTZ1/ NRF2, p62/Keap 1/NRF2 | Regulates redox homeostasis and the accumulation of lipid peroxidation | 15,47–48 |
| MT-1G | NRF2/MT-1G | Inhibits GSH depletion and lipid peroxidation | 49 |
| ABCC5 | NRF2/ABCC5/SLC7A11 | Increases intracellular GSH and inhibits ferroptosis | 50 |
| UBA1 | UBA1/NRF2 | Regulates redox homeostasis and the accumulation of lipid peroxidation | 51 |
| S1R | S1R/FTH1/TFR1 | Inhibits the cellular levels of Fe2+ and GSH depletion | 53–54 |
| YAP/TAZ | YAP/TAZ/ATF4/SLC7A11, YAP/ ALOXE3 | Mediates sensitivity to sorafenib-induced ferroptosis | 55–56 |
| miR-23a-3p | MiR-23a-3p/ACSL4 | Limits chelatable iron accumulation | 59 |
| FAM134B | / | Mediates reticulophagy | 61 |
| LIFR | LIFR/SHP1/LCN2 | Maintains stable intracellular iron concentration | 62 |
| SPARC | / | Promotes LDH release and ROS production | 63 |
| CISD2 | / | Inhibits ferroptosis | 64 |
| CIARS | CIARS/ALKBH5 | Mediates autophagy and ferritin phagocytosis | 65 |
| miR-214 | miR-214/ATF4 | Enhances erastin-induced ferroptosis | 69 |
| GABPB1-AS1 | GABPB1-AS1/PRDX5 | Suppresses the cellular antioxidant capacity and cell viability | 70 |
| circIL4R | circIL4R/miR-541-3p/GPX4 | Inhibits ferroptosis | 71 |
| circ0097009 | circ0097009/miR-1261/SLC7A11 | Inhibits ferroptosis | 72 |
| TEAD2 | / | Inhibits ferroptosis | 73 |
| P53 | P53/SLC7A11 | Inhibits SLC7A11 expression and cystine uptake | 74 |
| G6PD | G6PD/POR | Inhibits ferroptosis | 75 |
| RB1CC1 | RB1CC1/CHCHD3 | Stimulates mitochondrial function and increases ROS production | 76 |
| ENO1 | ENO1/IRP1/Mfrn1 | Promotes mitochondrial iron enrichment and excessive accumulation | 77 |
| CISD1 | / | Regulates mitochondrial iron uptake and respiration | 78 |
| IDH2 | IDH2/NADPH/GSH | Maintains the mitochondrial homeostasis | 79 |
| HCAR1 | HCAR1/MCT1/AMPK/SREBP1/SCD1 | Increases the production of anti-ferroptotic MUFAs | 80 |
| BCAT2 | AMPK/SREBP1/BCAT2 | Activates system Xc- activity | 81 |
| CLTRN | NRF1/DLD/CLTRN | Enhances the radiosensitivity by inducing ferroptosis | 17 |
| COMMD10 | COMMD10/HIF1α/SLC7A11 | Induces intracellular Cu accumulation | 82 |
| IFN-γ | IFN-γ/JAK/STAT/SLC7A11 | Inhibits system Xc- activity and promotes mitochondrial damage-related lipid peroxidation | 83 |
| TGF-β1 | TGF-β1/Smad/SLC7A11 | Inhibits xCT (the catalytic subunit of the system Xc-) expression | 84 |
| METTL14 | HIF-1α/METTL14/YTHDF2/SLC7A11 | Mediates ferroptosis | 85 |

ABCC5, ATP-binding cassette subfamily C member 5; ACSL4, acyl-CoA synthetase long-chain family member 4; ALKBH5, AlkB homolog H5; ALOXE3, arachidonate lipoxygenase 3; AMPK, AMP-activated protein kinase; BCAT2, branched-chain amino acid transaminase 2; CHCHD3, coiled-coil helix coiled-coil helix domain-containing protein 3; CISD1, CDGSH iron sulfur domain 1; CISD2, CDGSH iron sulfur domain 2; CLTRN, collectrin; COMMD10, copper metabolic gene MURR1 domain 10; DLD, dihydrolipoamide dehydrogenase; EGFR, epidermal growth factor receptor; ENO1, enolase; FAM134B, family with sequence similarity 134 member B; FTH1, ferritin heavy chain 1; GABPB1-AS1, GA-binding protein transcription factor subunit beta-1 antisense RNA 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSTZ1, glutathione S-transferase zeta 1; G6PD, glucose-6-phosphate dehydrogenase; HCAR1, hydroxycarboxylic acid receptor 1; HIF1α, hypoxia-inducible factor-1α; IDH2, isocitrate dehydrogenase 2; IFN-γ, interferon-gamma-γ; IRP1, iron regulatory protein1; JAK, Janus kinase; Keap 1, kelch-like ECH-associated protein 1; LCN2, lipocalin 2; LDH, lactate dehydrogenase; MCT1, monocarboxylate transporter 1; METTL14, methyltransferase-like 14; Mfrn1, mitoferrin-1; MT-1G, metallothionein-1G; MUFAs, monounsaturated fatty acids; NADPH, nicotinamide adenine dinucleotide phosphate; NRF1, nuclear respiratory factor 1; NRF2, nuclear factor E2-related factor 2; POR, P450 oxidoreductase; PRDX5, peroxiredoxin-5; QSOX1, quiescin sulfhydryl oxidase 1; Rb, retinoblastoma; RB1CC1, Rb1-inducible coiled-coil 1; ROS, reactive oxygen species; SCD1, stearoyl-coenzyme A desaturase-1; SHP1, Src homology region 2 domain-containing phosphatase-1; SLC7A11, solute carrier family 7 member 11; Smad, small mother against decapentaplegic; SPARC, secreted protein acidic and rich in cysteine; SREBP1, sterol regulatory element-binding protein 1; STAT, signal transducer and activator of transcription; S1R, Sigma 1 receptor; TAZ, transcriptional coactivator with PDZ-binding motif; TEAD, transcriptional enhanced associate domain; TFR1, transferrin receptor protein 1; TGF-β1, transforming growth factor β1; UBA1, ubiquitin-like modifier activating enzyme 1; YAP, Yes-associated protein; YTHDF2, YTH domain family 2.

**Fig. 2. Regulatory pathway and possible targets of ferroptosis in HCC.** ABCC5, ATP-binding cassette subfamily C member 5; ACSL4, acyl-CoA synthetase long-chain family member 4; ALOXE3, arachidonate lipoxygenase 3; ATF4, Activating transcription factor 4; CISD1, CDGSH iron sulfur domain 1; DAZAP1, deleted in azoospermia associated protein 1; FTH1, ferritin heavy chain 1; GABPB1-AS1, GA-binding protein transcription factor subunit beta-1 antisense RNA 1; GPX4, glutathione peroxidase 4; GSH, glutathione; GSTZ1, glutathione S-transferase zeta 1; HCC, hepatocellular carcinoma, IDH2, isocitrate dehydrogenase 2; Keap 1, kelch-like ECH-associated protein 1; MT-1G, metallothionein-1G; NRF2, nuclear factor E2-related factor 2; PRDX5, peroxiredoxin-5; QSOX1, quiescin sulfhydryl oxidase 1; Rb, retinoblastoma; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; S1R, Sigma 1 receptor; TAZ, transcriptional coactivator with PDZ-binding motif; TEAD, transcriptional enhanced associate domain; UBA1, ubiquitin-like modifier activating enzyme 1; YAP, Yes-associated protein.

richment and excess accumulation of ROS in HCC cells.[77] CDGSH iron sulfur domain 1 (CISD1), is a mitochondrial outer membrane protein that regulates mitochondrial iron uptake and respiration.[89] Genetic inhibition of CISD1 potentiates erastin-induced ferroptosis by enhancing mitochondrial function, suggesting that CISD1 may be a negative regulator of ferroptosis in HCC cells.[78] Ferritin heavy chain may serve as an intervention target for ferroptosis-inducing therapy, as it promotes ferroptosis resistance in HCC cells by regulating iron metabolism and maintaining mitochondrial homeostasis.[90] Knockdown of isocitrate dehydrogenase 2 reduces the level of nicotinamide adenine dinucleotide phosphate, which is a key factor in maintaining the GSH-dependent mitochondrial antioxidant defense system, thereby promoting erastin-induced ferroptosis in HCC cells.[79] Although the above reports have revealed the important role of mitochondrial homeostasis in ferroptosis, one study showed that mitochondria-deficient cells can still undergo ferroptosis.[91] Therefore, the specific role of mitochondria in HCC cell ferroptosis needs further exploration. Normally differentiated cells mainly rely on mitochondrial oxidative phosphorylation for energy, whereas most tumor cells metabolize glucose into lactate by glycolysis under aerobic conditions to allow proliferation and invasion of cancer cells.[92] High concentrations of lactate produced by aerobic glycolysis in HCC cells activates hydroxycarboxylic acid receptor 1 receptors on the plasma membrane and enhances monocarboxylate transporter 1-mediated lactate uptake, promotes ATP production, and deactivates the energy sensor, AMP-activated protein kinase (AMPK), resulting in upregulation of the expression of sterol regu-

latory element-binding protein 1 (SREBP1) and its target stearoyl-coenzyme A desaturase-1 (SCD1) to increase the production of anti-ferroptotic monounsaturated fatty acids. Additionally, high intracellular lactate concentrations inhibit ACSL4-mediated promotion of ferroptosis, which may synergize with the hydroxycarboxylic acid receptor 1/monocarboxylate transporter 1/AMPK/SREBP1/SCD1 axis-regulated anti-ferroptotic effect to amplify resistance to ferroptotic damage induced by common ferroptosis inducers such as ras-selective lethal small molecule 3 and erastin. The discovery of a lactate-mediated ferroptosis regulatory mechanism highlights its translational potential as a therapeutic target for ferroptosis-based tumor treatment.[80] Notably, the AMPK/SREBP1 signaling pathway also influences the transcription of branched-chain amino acid transaminase 2. As a key regulator of glutamate metabolism, branched-chain amino acid transaminase 2 activates system Xc-activity through ectopic expression, protecting HCC cells from ferroptosis in vitro and in vivo.[81]

## Ferroptosis in HCC therapy

### Systemic therapy

Systemic therapy involves anticancer drugs such as conventional cytotoxic and targeted agents to prevent tumor progression by inducing the death of cancer cells. However, the existence of intrinsic and acquired resistance limits the efficacy of drugs to a certain extent. The emergence of

ferroptosis-inducing therapeutic strategies would effectively improve the resistance of cancer cells to anticancer drugs, and ferroptosis inducers can synergize with traditional antitumor drugs to better inhibit tumor progression. Several drugs that are already in clinical use or have a strong potential for clinical translation are known to promote ferroptosis (Table 1). Sorafenib is the first multikinase inhibitor approved for the treatment of patients with unresectable HCC, and is first-line targeted drug for advanced HCC[6,7,27,28,41] The mechanism of sorafenib in HCC is described in detail in the previous discussion of ferroptosis and sorafenib in HCC.

Natural products are an important source of anticancer drugs, and some natural products contain components that can decrease the viability of HCC cells by inducing ferroptosis.[93] For example, in the presence of ferrostatin-1, saponin formosanin C-induced ROS formation was reduced, and inhibition of HCC cell viability was attenuated, suggesting that saponin formosanin C may act as a novel ferroptosis inducer.[93] In addition to its antimalarial activity, artemisinin and its derivatives have been further validated for their anticancer properties *in vivo* and *in vitro*. Artesunate not only induces apoptosis and also triggers ferroptosis in HCC cells by promoting ferritinophagy and increasing intracellular free iron. Notably, artesunate was found to significantly enhanced the inhibitory effect of low-dose sorafenib in HCC cell lines and nude mouse xenografts by promoting lysosomal activation, ferritin degradation, lipid peroxidation, and subsequent sequential responses, including ferroptosis.[35] Dihydroartemisinin induced ferroptosis by promoting the formation of phosphatidylethanolamine-binding protein 1/15-lipoxygenases and promoting cell membrane lipid peroxidation, thereby exerting anti-HCC activity.[94] Of course, the cytotoxicity of artemisinin and dihydroartemisinin in normal cells is not negligible, and it remains to be determined whether the minimal toxicity profile observed in clinical trials can enable their cell death-promoting activity to be utilized. Heteronemin also induces both apoptosis and ferroptosis of HCC cells, but its cytotoxicity limits its use. Hepatic arterial infusion chemotherapy is a feasible strategy to deliver drugs directly to the tumor and minimize systemic toxicity.[95] Another study showed that solanine promoted ferroptosis in HCC cells via GPX4-induced disruption of the GSH redox system.[32] In addition, the Chinese medicine atractylodin induced ferroptosis in HCC cells by inhibiting GPX4 expression and upregulating ACSL4 expression.[33] In conclusion, the above natural products may be used as ferroptosis inducers to exert anticancer effects, but further clinical trials are needed to verify their efficacy and explore their side effects.

Increased GSH depletion via cysteine deprivation or cysteinase inhibition enhances oxidative stress and mitochondrial ROS accumulation, leading to lipid peroxide overload and ferroptosis. Therefore, modulating extracellular cysteine levels may open up new therapeutic options for ferroptosis-inducing cancer therapy, especially in combination with ROS-inducing drugs, such as synergistic cysteine depletion with sorafenib, increasing the susceptibility of HCC cells to ferroptosis.[96] There are also some drugs that lead to HCC cell ferroptosis by inducing strong mitochondrial dysfunction to induce ROS overproduction combined with the breakdown of the antioxidant defense system, such as the nuclear protein 1 inhibitor ZZW-115.[97]

### Radiotherapy

Radiotherapy benefits patients with unresectable or advanced HCC, but its effectiveness is hampered by radioresistance and side effects.[98] Radiotherapy has been reported to induce ferroptosis in cancer cells, including HCC, fibro-sarcoma, and breast cancer cells, by inhibiting SLC7A11 or activating ACSL4 expression, thereby increasing lipid peroxidation and subsequent oxidative damage.[17,99] In addition, ferroptosis inducers enhances the antitumor activity of radiation in selected xenograft tumor models,[100] suggesting that induction of ferroptosis may be an option to overcome radioresistance. Studies have shown that collectrin, regulated by the nuclear respiratory factor 1/Ran (Ras-related nuclear protein)/dihydrolipoamide dehydrogenase protein complex, acts as a radiation target and enhances the radiosensitivity of HCC cells by inducing ferroptosis.[17] Low expression of the copper metabolic gene MURR1 domain 10 induced by ionizing radiation promotes hypoxia-inducible factor-1α (HIF1α) nuclear translocation and transcription of ceruloplasmin (CP) and SLC7A11 by inducing intracellular Cu accumulation, which jointly inhibits HCC ferroptosis leading to radioresistance. In addition, elevated CP enhances the expression of HIF-1α, forming a positive feedback loop of HIF1α/CP, thereby promoting HCC radioresistance.[82] CP inhibits ferroptosis by maintaining Cu-Fe homeostasis in HCC cells (Fig. 3).[101] Gene sensitization therapy effectively improves the efficacy of radiotherapy while reducing the dose of radiotherapy and the side effects of radiotherapy. Radiotherapy synergistically overexpressing collectrin and copper metabolic gene MURR1 domain 10 may effectively improve the survival benefit of HCC patients.
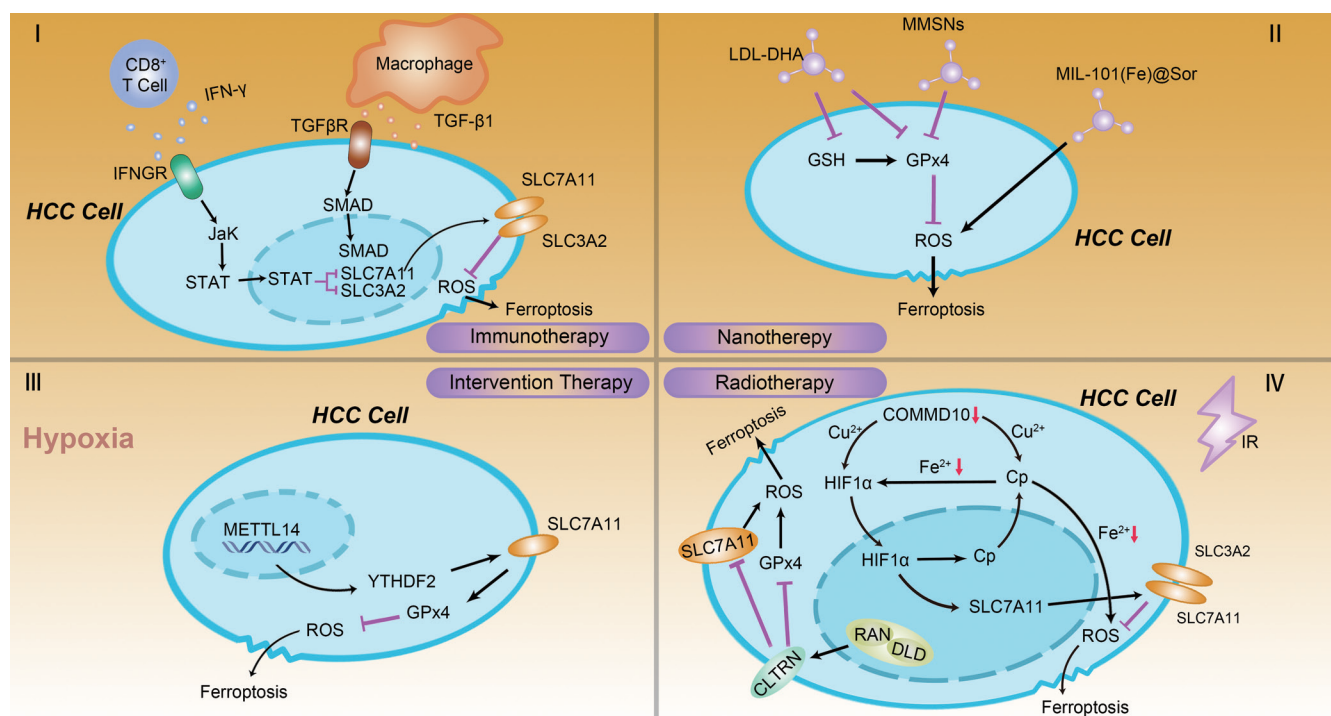
### Immunotherapy

The advent of immunotherapy based on immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 and its ligands programmed death-ligand 1 and cytotoxic T lymphocyte-associated protein 4 has improved the prognosis of HCC patients.[102] Immunotherapy mainly exerts anticancer effects by activating potent cytotoxic T cell-driven antigen-antibody responses. Studies have revealed that activated cytotoxic T cells under immunotherapy downregulate the expression of solute carrier family 3 member 2 and SLC7A11 by releasing interferon-gamma-γ to activate the Janus kinase/signal transducer and activator of transcription signaling pathway to inhibit system Xc- activity and promote mitochondrial damage-related lipid peroxidation, thereby inducing HCC cell ferroptosis.[83] Moreover, ferroptotic HCC cells release tumor-associated antigens that improve the immunogenicity of the tumor microenvironment and enhance the effect of immunotherapy.[18,83] Furthermore, anti-programmed death-ligand 1 monoclonal antibodies and ferroptosis inducers synergistically inhibit tumor growth *in vitro* and *in vivo*.[18] Transforming growth factor β1 released by macrophages induces HCC cell ferroptosis by activating the small mother against decapentaplegic to inhibit xCT (the catalytic subunit of the system Xc-) expression in a time- and dose-dependent manner.[84] Some immune cells in the tumor microenvironment, such as monocytes, macrophages, and natural killer cells, may be involved in the maintenance of iron homeostasis.[103] Therefore, ferroptosis is expected to provide new ideas and targets for improving the efficacy of immunotherapy in HCC patients (Fig. 3). In addition, signatures constructed and validated based on ferroptosis- and immune-related genes can effectively predict the expression levels of ICI-related targets, and provide insights into the selection and efficacy prediction of ICIs in HCC patients.[104,105]

### Interventional therapy

Interventional therapy, which causes ischemic necrosis of tumor tissue by blocking the blood supply to the tumor, has

**Fig. 3. Role of ferroptosis in immunotherapy, radiotherapy, interventional therapy, and nanotherapy.** CLTRN, collectrin; COMMD10, copper metabolic gene MURR1 domain 10; CP, ceruloplasmin; DLD, dihydrolipoamide dehydrogenase; GPX4, glutathione peroxidase 4; GSH, glutathione; HIF1α, hypoxia-inducible factor-1α; IFN-γ, interferon-gamma-γ; JAK, Janus kinase; METTL14, methyltransferase-like 14; ROS, reactive oxygen species; SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; Smad, small mother against decapentaplegic; STAT, signal transducer and activator of transcription; TGF-β1, transforming growth factor β1; YTHDF2, YTH domain family 2.

been used as a safe and effective treatment option for unresectable HCC.[106] However, the activation of HIF-1α and vascular endothelial growth factor in the hypoxic microenvironment by transcatheter arterial chemoembolization increases the potential of tumors for angiogenesis, recurrence, and metastasis.[107,108] Hypoxia induced by interventional embolization treatment inhibits methyltransferase-like 14 (MET-TL14) expression in a HIF-1α-dependent manner, thereby blocking METTL14/YTH domain family 2/SLC7A11 axis-mediated ferroptosis and promoting HCC progression. These investigations highlight hypoxia-regulated ferroptosis in HCC cells and identify the HIF-1α/METTL14/ YTH domain family 2/SLC7A11 axis as a potential therapeutic target for HCC interventional embolization treatment (Fig. 3).[108]

### Nanotherapy

Using nanoparticles to deliver and control drug release has unique advantages, such as high drug loading, targeting of specific tissues and organs, and improved pharmacokinetic properties.[109] Constructing efficient ferroptosis- related nanoplatforms and developing novel ferroptosis inducers will increase the efficacy of existing ferroptosis inducers and make full use of existing clinical anti-HCC drugs to expand their therapeutic value (Fig. 3). For example, a novel cascaded copper-based metal-organic framework therapeutic nanocatalyst developed by Tian *et al*.[110] activates ferroptosis by GSH depletion and promotes substantial accumulation of lipid peroxidation, resulting in cascade-amplified ferroptosis mediated HCC therapy. Low-density lipoprotein docosahexaenoic acid nanoparticles have been shown to induce ferroptotic cell death in HCC by pronounced lipid peroxidation, depletion of GSH and inactivation of the lipid

antioxidant GPX4.[111] Nanoparticles loaded with ferroptosis inducers have also been studied. Tang *et al*.[112] reported that spontaneous degradation of manganese-oxygen bonds in sorafenib-loaded manganese-doped mesoporous silica nanoparticles together with the on-demand release of sorafenib achieved dual depletion of GSH and blocked its synthesis, thereby exerting an efficient tumor suppressor effect. Similarly, the antitumor activity of sorafenib was enhanced upon delivery of sorafenib-loaded MIL-101(Fe) nanoparticles.[113] Combination therapy can overcome the shortcomings of monotherapy and reduce resistance induced by a single agent.[114] Nanoplatforms incorporating ferroptosis inducers, chemotherapy drugs, or other therapies such as sonodynamic therapy can effectively inhibit HCC progression. Zhou *et al*.[115] designed a multifunctional nanoplatform with the potential to integrate cancer diagnosis, treatment, and monitoring. It provided a novel clinical antitumor therapeutic strategy to induce ferroptosis via the consumption of GSH, disrupt redox balance by the Fenton reaction and doxorubicin-supplied hydrogen peroxide, synergistic cytotoxicity of doxorubicin inhibition of recurrence and metastasis of HCC, and reversing drug resistance in translational therapy. Chen *et al*.[116] assessed the prospect of nanobubbles combined with SDT and ferroptosis for treating HCC. Because of their low immunogenicity, low cytotoxicity, and high biocompatibility, nanosized vesicle exosomes can be used as drug delivery systems.[117] Du *et al*.[118] designed engineered exosomes composed of CD47, erastin, and rose bengal that delivered erastin and rose bengal to tumor tissues with high specificity. They avoided phagocytosis by the mononuclear phagocyte system and achieved high distribution in tumor tissues, thereby inducing intensive ferroptosis in HCC with minimal liver and kidney toxicity.

## Ferroptosis participates in the diagnosis and prognosis of HCC

Clinical management emphasizes early and effective disease screening, diagnosis, treatment, and prognostic prediction, so the development of biomarkers for tumor detection and diagnosis is extremely important. Accumulating evidence suggests that ferroptosis is involved in cancer development and treatment response, and the identification of ferroptosis-related genes and pathways will provide references for the clinical management of HCC patients. Investigators used comprehensive bioinformatics analysis to screen out genes associated with HCC and ferroptosis, such as ubiquitin-like modifier activating enzyme 1,[51] heat shock protein beta-1,[119] six-transmembrane epithelial antigen of the prostate family member 3,[120] ATP-binding cassette transporter 6 of subfamily B,[19] cysteine-preferring transporter 2,[121] SLC7A11,[122] and some lncRNAs.[123,124] The differential expression of those genes may be associated with poor prognosis of HCC patients and they may also serve as effective biomarkers for the diagnosis of HCC patients. The tumor node metastasis classification system has been widely used to predict prognosis and guide treatment in clinical practice, but patients at the same stage may have different prognoses. Therefore, generation of an accurate, safe, and effective novel prognostic model is needed to assist and supplement the tumor node metastasis classification system. Prognostic models constructed and validated by some teams based on ferroptosis-related genes can predict the OS of HCC patients.[125–127] However, the heterogeneity of HCC and the complexity of the tumor microenvironment limit the specificity and sensitivity of ferroptosis-related gene-based prognostic models. In another study, prognostic models constructed by combining ferroptosis-related genes with immune-related genes,[104,105] pyroptosis-related genes,[128] and hypoxia-related genes[129–130] accurately predicted patient prognosis and provided a reference for the selection and prediction of the efficacy of immune checkpoint inhibitor therapy for HCC patients. Of course, the prognostic models are constructed based on retrospective data analysis, lack validation by multicenter prospective cohort studies, and have certain biases. More *in vitro* and *in vivo* studies are required for further verification.

## Ferroptosis in other liver diseases

Iron overload and oxidative stress are important triggers of most liver diseases,[16] ferroptosis can affect various liver diseases including ischemia/reperfusion-related injury,[16] alcoholic liver disease,[131] and nonalcoholic fatty liver disease[132] by regulating the levels of iron and ROS. Interestingly, inhibition of ferroptosis can counteract the pathophysiological progression of liver diseases such as alcoholic liver disease and nonalcoholic fatty liver disease.[131,132] However, induction of ferroptosis enhances the sensitivity of HCC patients to sorafenib.[55,58] The inflammatory reaction caused by long-term chronic liver injury and repair is conducive to liver fibrosis and even HCC. Therefore, it is crucial to explore the optimal time to intervene in ferroptosis to prevent the progression of chronic liver disease to HCC. Differences in the pathogenesis of liver diseases will determine differences in preferred treatment. The mechanism of ferroptosis in different liver diseases should be fully considered to determine its mode of action.

## Conclusions and perspectives

In recent years, major progress in research on ferroptosis in cancer prevention, diagnostics, prognostics, and treatment has been reported. This review briefly introduces ferroptosis-related regulatory pathways and typical ferroptosis inducers and inhibitors, and describes the regulatory mechanism by which sorafenib inhibits HCC progression by inducing ferroptosis. It describes new targets of ferroptosis in HCC cells and the use of ferroptosis in the treatment, diagnosis, and prognosis of HCC. The complex regulatory network of ferroptosis in HCC pathophysiology and therapy indicates that its clinical translational anticancer strategy may be laborious, and that further research is needed to optimize individualized and precise treatment strategies for HCC patients and improve survival benefits. In addition, the differential susceptibility of HCC patients with a complex genetic background to ferroptosis-inducing therapy will limit the individualized and precise treatment of HCC patients, so it is critical to identify biomarkers associated with responsiveness through liquid biopsy of blood, bile, and urine, and tumor tissue sample analysis to identify HCC patients who are sensitive to ferroptosis-inducing therapy. The following issues still to be resolved. First, the ferroptotic response is regulated by a complex network of epigenetic, transcriptional, post-transcriptional and post-translational mechanisms. Although some targets have been identified, further investigation of underlying signal transduction pathways and key transcriptional regulators of ferroptosis in HCC is needed. In addition to drug resistance, the role of ferroptosis in other malignant phenotypes of HCC such as invasion, metastasis, metabolism, and autophagy cannot be ignored. Second, the development of drugs that directly target ferroptotic pathways might provide new strategies for tumor treatment. Ferroptosis-induced therapy combined with other anticancer therapies, such as immunotherapy or radiotherapy effectively suppress tumor growth by inducing a mixed-type RCD, but the identification of ferroptosis inducers remains to be done in cell and animal experiments. Clinical use is still in the future. In addition, the side effects of ferroptosis inducers are still unclear, the effectiveness of the lowest dose of ferroptosis inducers has not yet been determined, and the effectiveness of sorafenib in clinical use is limited by drug resistance. Therefore, reducing the side effects of ferroptosis inducers or reversing drug resistance remains a challenge in clinical oncology. Of course, exploring the complex crosstalk between ferroptosis and other RCDs will provide a reference for translational medicine based on ferroptosis. Tackling the key issues discussed in this review will deepen our understanding of the significant role that ferroptosis plays in HCC, thus providing a new scientific basis for targeting ferroptosis to prevent and treat HCC.

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## Conflict of interest

JWPY has been an editorial board member of *Journal of Clinical and Translational Hepatology* since 2021. The other authors have no conflict of interests related to this publication.

## Author contributions

All authors have made a significant contribution to this study and have approved the final manuscript (ZH, HX, YC, JWPY, YX), contributed equally to this work and share first authorship (ZH, HX), All authors contributed to the study conception and design (ZH, HX, YC, JWPY, YX), literature search; data analysis and drafting of the manuscript (ZH), critical revision of the manuscript for important intellectual content (ZH, HX, YC, JWPY, YX).

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