Cell Communication and Signaling

REVIEW

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From mechanisms to medicine: Ferroptosis as a Therapeutic target in liver disorders

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Abstract

In recent 10 years, ferroptosis has become a hot research direction in the scientific research community as a new way of cell death. Iron toxicity accumulation and lipotoxicity are unique features. Several studies have found that ferroptosis is involved in the regulation of the hepatic microenvironment and various hepatic metabolisms, thereby mediating the progression of related liver diseases. For example, NRF2 and FSP1, as important regulatory proteins of ferroptosis, are involved in the development of liver tumors and liver failure. In this manuscript, we present the mechanisms involved in ferroptosis, the concern of ferroptosis with the liver microenvironment and the progression of ferroptosis in various liver diseases. In addition, we summarize recent clinical advances in targeted ferroptosis therapy for related diseases. We expect that this manuscript can provide a new perspective for clinical treatment of related diseases.

Keywords Ferroptosis, Liver microenvironment, Gut-Liver Axis, NAFLD, DILI, Liver Diseases

Introduction

Over the past decade, the scientific community has witnessed a surge of interest in ferroptosis, a novel form of regulated cell death [1]. The term "ferroptosis" is derived from its characteristic features, primarily the accumulation of iron and the peroxidation of polyunsaturated fatty acids within the cell membrane, leading to cell death. The unique nature of ferroptosis, with its dependence on iron metabolism and vulnerability to lipid peroxidation, positions it as a pivotal player in the pathogenesis of liver diseases.

Liver diseases constitute a significant global public health challenge, with mechanisms of cellular death playing a pivotal role in the initiation and progression of a variety of hepatic disorders [2]. Ferroptosis, a distinct form of regulated cell death, has garnered attention for its involvement in a spectrum of liver diseases. Particularly in NAFLD, iron deposition and oxidative stress, which arise from metabolic disorders, may induce ferroptosis, thereby promoting the progression of liver disease. In ALD, chronic ethanol-induced ROS overproduction and oxidative stress may trigger ferroptosis in hepatocytes, promoting liver disease progression. In HCC, ferroptosis is implicated not only in tumorigenesis but also potentially influences the response to therapeutic agents such as sorafenib.

In recent years, the study of ferroptosis has advanced rapidly in hepatic medicine. Targeting ferroptosis in hepatology presents a promising therapeutic approach for liver diseases. Traditional drugs, including Deferoxamine, Deferiprone, Vitamin E and Selenium, have shown potential in reducing liver damage (Table 1). This article further reviews the latest progress in iron-targeting drug

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Table 1 Pharmacological inducers and inhibitors of ferroptosis

	Reagent	Target	Effect	Refs
Pharmacological inducers	Erastin	Ferritin/FPN	Increasing iron levels	[3]
	Sorafenib	The ERK pathway	Increasing the FSP1 ubiquitination and degradation	[4]
	Glutamate	System Xc^- and GSH	Increasing the accumulation of lipid peroxides	[5]
	Sulfasalazine	System Xc^-mediated cystine uptake	Increasing oxidative stress	[6]
	TMZ	The NRF2/HO-1 pathway	Increasing iron deposition	[7]
	MMRi62	Ferritin heavy chain, mutant p53	Increasing lysosomal degradation of FTH1	[8]
	NDP4928	The CoQ10/FSP1 pathway	Increasing the levels of ROS and autophagy	[9]
	Cu-SF(RSV) NPs	The CoQ10/FSP1 pathway	Increasing the release of ferrous ion	[10]
	Simvastatin	GPX4, ferrous ion	Increasing oxidative stress	[11]
	ML-162, RSL3, FIN56	GPX4, CoQ10	Increasing toxic lipid hydroperoxide accumulation	[12]
	DHA	GPX4, GSH	Increasing lipid peroxidation	[13]
	FAC	Ferrous ion	Increasing mitochondrial lipid Peroxidation	[14]
	Trigonelline	The NRF2-ARE pathway	Increasing GSH and ROS production	[15]
	BSO	Glutamate-cysteine ligase, GSH	Decreasing the synthesis of GSH and the activity of GPX4	[16]
	FINO(2)	GPX4	Increasing direct iron oxidation	[17]
	Brequinar	DHODH	Decreasing the reduction of ubiquinone to ubiquinol	[18]
Pharmacological inhibitors	Fer-1	Cytosolic and lipid ROS, GSH/GPX4 axis	Decreasing lipid peroxidation	[19]
	Lip-1	Lipid peroxidation	Decreasing the activation of lipid metabolism	[20]
	ATV	Iron content, MDA levels, ROS levels, GSH	Decreasing lipid peroxidation	[21]
	Trolox	Hydroxyl radicals	Decreasing lipid peroxidation	[22]
	CoQ10	FSP1, GPX4	Decreasing dysregulation of cholesterol metabolism	[23]
	VitE	Hydroxyl radicals, GPX4	Decreasing lipid peroxidation	[24]
	Deferoxamine, Deferiprone, Piroctone olamine	Iron chelator	Decreasing iron levels	[25]
	Tangeretin	GPX4, NRF2	Decreasing lipid peroxidation	[26]
	SAK	The NRF2 signaling pathway	Increasing the expression of antioxidant genes	[27]
	Naringenin	The SIRT1/FOXO3a signaling pathway	Increasing cellular susceptibility to ferroptosis	[28]
	Taurine	OGT/GPX4 signaling	Decreasing iron levels	[29]
	AA-861, Zileuton, PD-146176	LOX-induced lipid peroxidation	Decreasing the generation of lipid peroxides	[30]
	Selenium, Sodium, Selenite	GPX4, System Xc^-	Increasing the expression of antioxidant genes	[31]

Abbreviation: FPN1 ferroportin, *TMZ* Temozolomide, *Cu-SF(RSV) NPs* Copper-Silk Fibroin (Rosuvastatin) Nanoparticles, *DHA* Docosahexaenoic acid, *FAC* Ferric ammonium citrate, *BSO* L-buthionine (S, R)-sulfoximine, *FINO(2)* Ferroptosis inducer NO2, *Fer-1* Ferrostatin-1, *Lip-1* Liproxstatin-1, *ATV* Atorvastatin, *VitE* Vitamin E, *SAK* Sakuranetin, *FTH1* ferritin heavy chain, *ARE* antioxidant response element, *GSH* glutathione, *CoQ10* Coenzyme Q10, *ACSL4* Acyl-CoA synthetase long-chain family member 4, *SLC7A11* Solute carrier family 7 member 11, *FSP1* Ferroptosis suppressor protein 1, *System Xc^-(xCT)* cystine/glutamate antiporter

development, encompassing natural compounds (e.g., Diosgenin, Nuciferine, Xanthohumol), artificial extracts (e.g., sulfated polysaccharides), small molecule inhibitors (e.g., GLX351322), modifications of traditional drugs (e.g., Donafenib), and novel nanomaterials (e.g., GOA/miR-targeted nanocomposites, mitochondrial-targeted antioxidants like MitoTEMPO and MnO2Nfs), while also examining the potential limitations of these strategies.

This review aims to provide a comprehensive overview of the current understanding of ferroptosis, highlighting its significance in the context of liver health and disease. We will discuss the key regulatory proteins involved in

ferroptosis, such as NRF2, FSP1, and GPX4, and their implications in the development of liver tumors and failure. Furthermore, we will explore the multifaceted interactions between ferroptosis and the hepatic microenvironment, including iron homeostasis, glucose and lipid metabolism, amino acid metabolism, gut-liver axis and the mitochondria. Delving into the intricate mechanisms of ferroptosis, its association with the liver microenvironment, and its role in the progression of various liver diseases. These discussions will be grounded in the latest research findings, providing a platform for understanding the complex interplay between ferroptosis and liver diseases.

Three pivotal features of ferroptosis in research foci

So far, it has been demonstrated that subcellular cells undergoing ferroptosis may evolve at least three different pivotal features. These primarily involve the iron toxicity accumulation from disrupted iron-homeostasis, phospholipid peroxidation caused by excessive intracellular lipid reactive oxygen species [32], and the occurrence of iron-induced apoptosis in cells characterized by abnormal mitochondrial morphology (Fig. 1). By investigating the profound alterations in iron metabolism, we can acquire a meticulous comprehension of the onset and progression of ferroptosis-related disorders.

Iron toxicity accumulation

Over ten years ago, the term " ferroptosis " was first introduced as an innovative form of cell death and remains an attractive field of investigation [1]. Ferroptosis, as the name indicates, is inexorably tied to poisonous iron accumulation. Iron homeostasis normally firmly regulates the systemic circulatory system. One aspect, dietary iron absorption ensures that the body has enough iron, while also preventing harmful iron sediment. Iron accumulation can directly cause varying

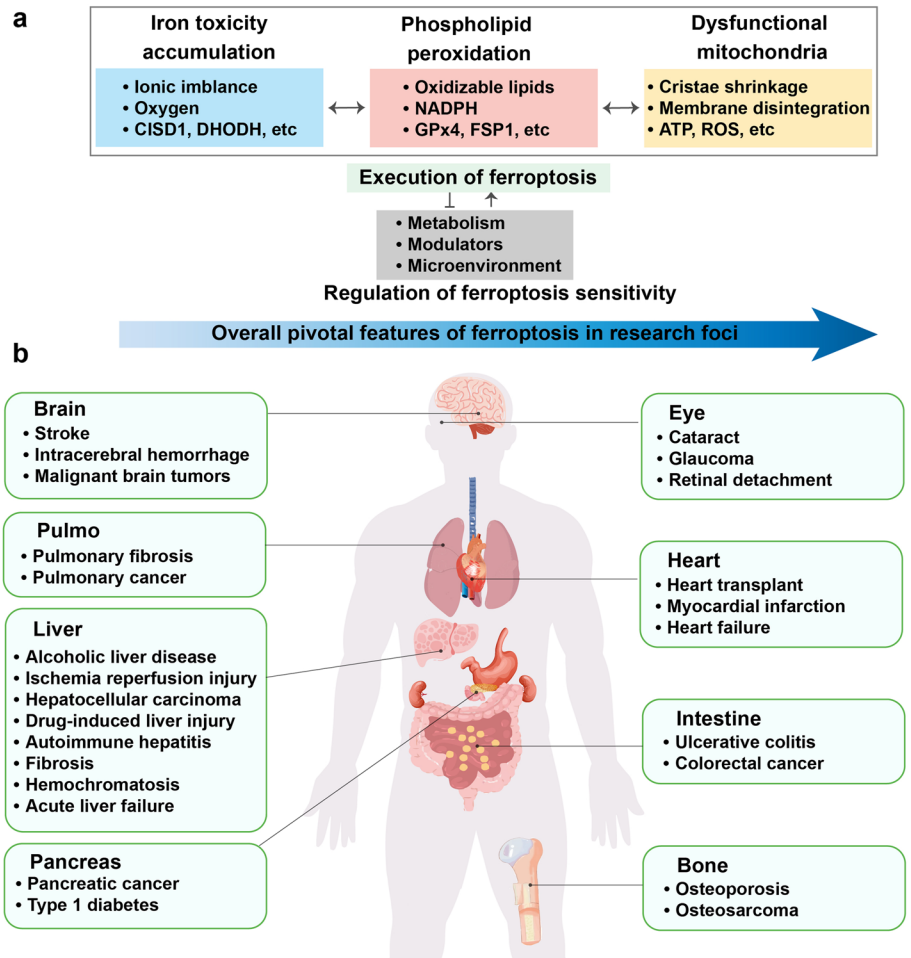

Fig. 1 **a** The overall pivotal features of ferroptosis in research foci; (**b**) Ferroptosis plays a role in the pathogenesis and progression of a spectrum of diseases across various organs and tissues

degrees of toxicity in different organs, such as the kidney and pancreas [33, 34].

Phospholipid peroxidation

In healthy human tissues, the generation of ROS is a natural physiological occurrence. In pathological conditions, heightened metabolic activity and increased oxidative stress often leads to the catalysis of the Fenton reaction, resulting in the production of hydroxyl radicals (•OH). This can surpass the antioxidant capacity of cells, causing damage to biomolecules [35].In the absence of universal standards for diagnosing iron toxicity, oxidized phospholipids are often used as indicators [36].Research suggests that polyunsaturated fatty acids (PUFAs) are particularly prone to peroxidation and may contribute to ferroptosis [37].

Dysfunctional mitochondria

In ferroptotic cells, morphological assessments reveal notable changes such as cell rounding, mitochondrial cristae shrinkage, and cytoplasmic membrane disintegration, with the nucleus often remaining unaffected [38, 39]. Additionally, mitochondria exhibit structural anomalies like reduced size and increased membrane density, which are indicative of cellular injury in ferroptosis [40].However, the precise mechanisms by which aberrant mitochondria mediate ferroptosis remain an area of inquiry that warrants further exploration. In their physiological role, mitochondria primarily serve as the powerhouses of the cell, orchestrating adenosine triphosphate (ATP) production [40]. Mitochondrial dysfunction, potentially through impaired oxidative phosphorylation, may precipitate ferroptosis by escalating ROS production beyond the cell's antioxidant threshold [41]. Additionally, mitochondrial-associated molecules, structural proteins, and metabolic disruptions may also mediate the onset of ferroptosis. Aberrant mitochondrial GPx4, DHODH, and ACSL family expressions correlate with cellular vulnerability to iron-overload, representing a research focus [42]. CISD1, a CDGSH iron-sulfur domain protein, suppresses iron-catalyzed cell death by regulating mitochondrial iron deposition [43]. Ferroptotic cell death is closely linked to mitochondrial metabolic dysregulation, which includes impaired mitochondrial protein degradation, metabolic reconfiguration, and mitochondrial stress signaling [44].

Regulatory molecules involved in ferroptosis

GPX4

GPX4 is a peroxidase that relies on the presence of glutathione (GSH) and contains selenium [45]. It primarily occurs in the cytoplasm and mitochondria of mammals. It has the capacity to eliminate toxins such as GSH and lipid hydroperoxide by converting them into harmless lipid ethanol [45, 46]. Additionally, it acts as a key inhibitor of ferroptosis, displaying distinct properties. Multiple investigations have demonstrated that it serves as the primary regulator of ferroptosis. GPX4 depletion causes the disruption of the lipid peroxidation cascade, leading to the death of non-apoptotic cells [45–48]. Once GPX4 is increased, it can prevent iron-induced cell death and safeguard different cells and tissues from harm [47]. More precisely, the transcription factor or the protein itself regulates GPX4 expression. Compounds like sulfasalazine and sorafenib, known as ferroptosis inducers, have the ability to impede its function, conversely, the activity of this substance can be enhanced by intracellular selenium or glutathione supplementation [47].

GPX4 has been demonstrated to play an essential part in the development and prognosis of numerous disorders. It is worth mentioning that GPX4 deficiency in neurological diseases causes cognitive impairment and neurodegeneration, which can be alleviated by iron-death inhibitions [48]. GPX4 is essential for the liver, and its low level primarily ensures the integrity of PL-PUFA in a healthy liver, but this stable condition may be altered in several metabolic problem liver disorders [49]. Furthermore, GPX4 is widely recognized as a tumor suppressor, and the GSH/GPX4 axis plays a crucial role in restraining the metabolism of cancer cells when catalytically active iron is present (Fig. 2) [50].

System Xc$^-$

System Xc^- is an antiporter composed of two subunits: SLC7A11 and SLC3A2 [51].Cells utilize SLC7A11 and SLC3A2 to transport amino acids. SLC7A11 transports cystine, while SLC3A2 is a heavy chain component of amino acid transporters (HATs) that ferry important amino acids alongside SLC7 family members [51]. Cysteine availability is crucial for GSH synthesis, and System Xc^- mostly absorbs extracellular cystine via exchanging glutamate in cells to preserve redox equilibrium [52, 53]. Blocking the system will decrease cysteine levels, disrupt glutathione (GSH) synthesis, impair the activity of the GPx4 enzyme, and ultimately result in ferroptosis due to iron accumulation [53]. To summarize, blocking antiporters can increase cell susceptibility to ferroptosis by decreasing the production of GSH [52].

SLC7A11 gene translation is finely transcriptionally directed, with oxygen exhaustion and amino acid depletion conditions stimulating factor, hence dependently inducing its production. In the SLC7A11 systemic knockout mouse model, depletion of GSH levels was observed, but did not cause spontaneous hepatic iron deficiency, but rather increased sensitivity to ferroptosis [52]. Further, SLC7A11 knock-out cell showed

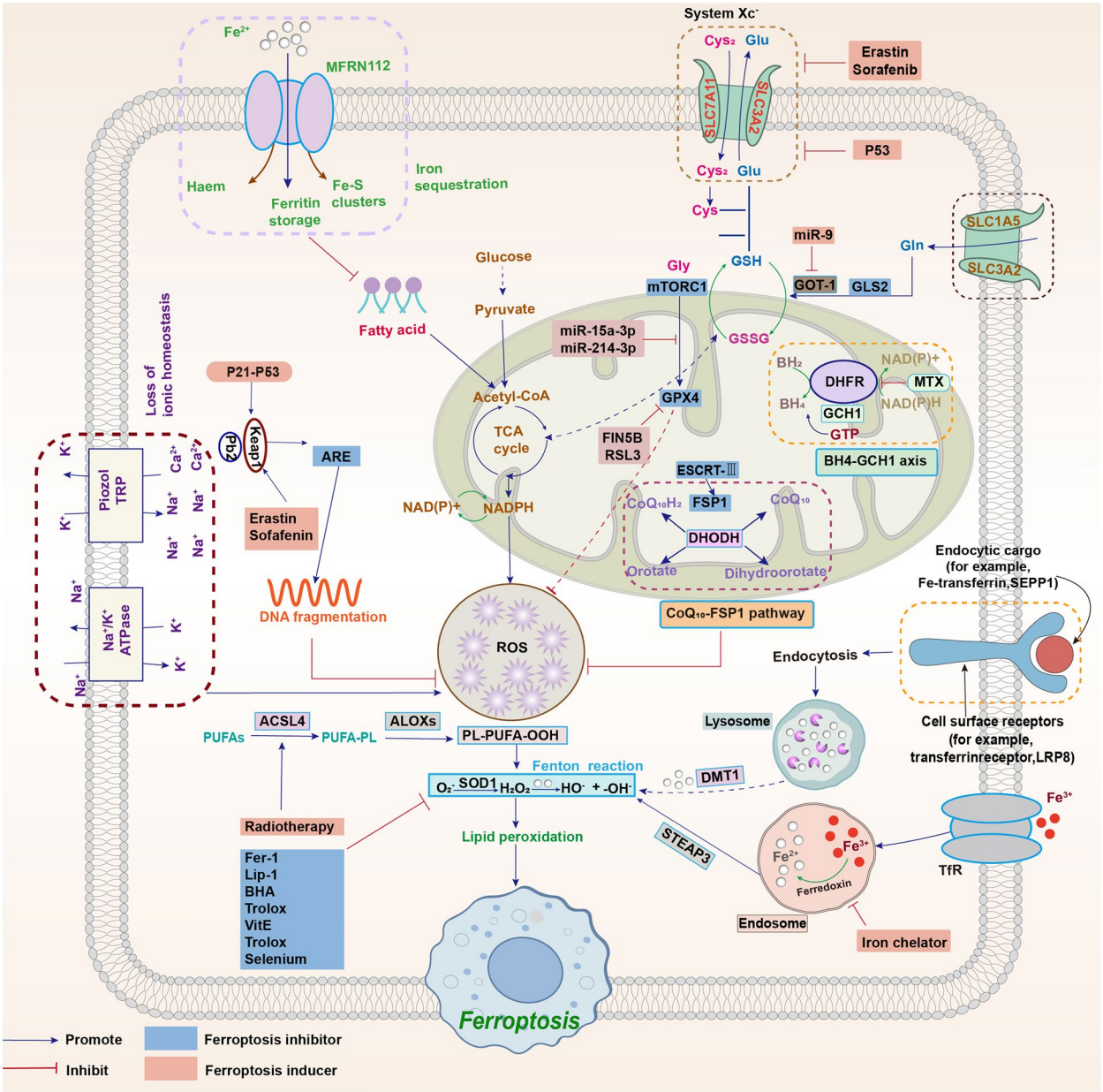

Fig. 2 Regulatory modulators and mechanism involved in ferroptosis. In particular, the GSH metabolism, iron sequestration and metabolism, GPX4 inactivation, PUFA synthesis, and the loss of membrane ionic homeostasis are all orchestrally engaged in the modulation of ferroptosis, with pathways such as the CoQ_{10}-FSP1 axis, DHODH, and NRF2 contributing to this sophisticated regulatory mechanism. Abbreviations: Cys, cysteine; Glu, glutamate; Gln, glutamine; GLS2, glutaminase 2; HO-1, heme oxygenase-1; KGM, konjac glucomannan; GOT-1, glutamic oxaloacetic transaminase 1; MTORC 1, mechanistic target of rapamycin complex 1; Gly, glycine; miR-9, microRNA-9; DHFR, dihydrofolate reductase; GCH1, GTP cyclohydrolase 1; MTX, methotrexate; BH4, tetrahydrobiopterin; GPX4, glutathione peroxidase 4; FIN5B, FYVE and coiled-coil domain containing 2; FSP1, farnesyl pyrophosphate synthase 1; CoQ_{10}, coenzyme Q_{10}; ESCRT-III, endosomal sorting complexes required for transport III; DHODH, dihydroorotate dehydrogenase; ARE, antioxidant response element; Keap1, kelch-like ech-associated protein 1; ACSL4, acyl-coA synthetase long-chain family member 4; ALOXs, arachidonate lipoxygenases; BHA, butylated hydroxyanisole; DMT1, divalent metal transporter 1; PUFA-PL, phospholipid containing polyunsaturated fatty acid chain; STEAP3, six transmembrane epithelial antigen of the prostate 3; TCA, tricarboxylic acid cycle; SLC1A5, solute carrier family 1 (neutral amino acid transporter), member 5; SLC3A2, solute carrier family 3 (activatory amino acid transporter), member 2

significant inhibition of tumor proliferation [52]. Remarkably, deletion of SLC7A11 in normal cells does not directly trigger iron-death, but may enhance cellular sensitivity to ferroptosis [54]. The iron-death inhibitory molecule p53 downregulates System Xc^- expression, resulting in cystine deficiency and sensitivity to ferroptosis, favoring anticancer [55]. These findings emphasize SLC7A11 in controlling cellular reactions to iron-toxicity and could offer innovative approaches for treatment (Fig. 2).

NRF2

Nuclear factor erythroid 2-related factor 2 [56] is a fundamental local transcription element that promotes resistance to ferroptosis and is crucial for preserving the balance of antioxidants and metabolic stability in cells [56]. NRF2 possesses a conserved basic leucine zipper (bZIP) domain and encounters the capability to create heterodimers with other proteins, which then attach to anti-oxidative stress elements (ARE) [56]. Typically, NRF2 expression remains consistently low because it binds to a cytoplasmic protein called Keap1 and is then broken down through ubiquitination [57]. During stress-induced oxidation signaling, NRF2 dissociates from Keap1, avoids degradation, moves into the nucleus to begin the transcription of downstream genes. NRF2 is an essential upstream regulator that controls the expression of antioxidant genes, it controls the activities of GPX4 and the System Xc^-, which are vital for glucose metabolism [58]. Also, the p62-Keap1-NRF2 signaling cascade is linked to the upregulation of genes entailed in ferroptosis and ROS metabolic processes, demonstrating the diverse impact of NRF2 [59].

NRF2 has a dual function, whereby reducing its expression can enhance the susceptibility to cancer cells to iron-death, while raising NRF2 levels can impede the ferroptosis process [15, 60]. In hepatocellular carcinoma (HCC), the activation of NRF2 leads to increased resistance to sorafenib by up-regulating Metallothionein-1G(MT-1G), which hinders lipid metabolism [61]. In vitro models, lowering NRF2 expression by molecular biological methods enhances the effectiveness of anticancer treatments [61]. Activated the p62-Keap1-NRF2 axis shields cancerous cells from iron-induced cell death by inhibiting the degradation of NRF2 [59]. NRF2 may mitigate iron-death in Acute Lung Injury(ALI) by upregulating the production of antioxidant enzymes and associated genes, protecting alveolar epithelial cells, and minimizing lung damage [62]. These findings show that NRF2 and its downstream signaling pathways could be an innovative therapy for triggering ferroptosis (Fig. 2).

FSP1

The recently discovered endogenous robust Ferroptosis-suppressor protein 1 (FSP1) may function in tandem with coenzyme Q_{10} to preserve mitochondrial function and shield them from oxidative damage [63, 64]. Its precursor is apoptosis-inducing factor mitochondria-2 (AIFM2), more precisely re-termed FSP1 due to its vital function in the distinct FSP1–Q_{10}–NADPH mechanism, independent of the classical GSH-GPx4 anti-ferroptosis pathway [63]. Specifically, FSP1 can also function in a new electron transport mechanism that reduces coenzyme Q10 to prevent iron-induced cytotoxic damage when GSH is depleted.

Furthermore, FSP1 is postulated to operate in a parallel mechanism to GPX4, and its expression positively correlates with cellular resistance to GPX4, hence maintaining tumor cell proliferation [63]. FSP1 also impacts iron death-associated metabolic enzymes, sustaining the biological function of S-adenosylhomocysteine hydrolase (SAHH), whose continued presence is necessary to avert ferroptosis [65]. Research has revealed that FSP1 can effectively limit the iron-death by engaging in intricate interactions with regulatory pathways [65, 66]. Besides, ESCRT-III (endosomal sorting complex required for transport III)-dependent membrane repair mechanisms can hinder ferroptosis. The activation of these mechanisms processes generates a suitable environment for survived tumor cells and indirectly supports the role of FSP1 (Fig. 2) [66].

DHODH

The ferroptosis defense mechanism is typically classified into three types depending on intracellular localization: cytosolic and mitochondrial GPx4, plasma membrane-localized FSP1, and mitochondrial dihydroorotate dehydrogenase (DHODH) [67]. These three systems are independent and interact to provide antioxidant effects, the first two system parts were previously described in detail, and we will now focus on the mitochondrial inner membrane enzyme DHODH [68]. It catalyzes de novo pyrimidine ribonucleotide synthesis, and cancer cells proliferate and require more nucleotides, hence it has been investigated researched as cancer treatment [69].Metabolomic profiling studies have demonstrated the involvement of DHODH and mito-GPX4 in scavenging reactive oxygen species (ROS) and their unique roles in inducing apoptosis, irrespective of their usual function in nucleotide synthesis [18, 70].

Lowering the expression of DHODH promotes intracellular GSH levels, hence enhancing the antioxidant effectiveness of GPX4 and preventing iron-induced toxicity [71]. Utilizing its catalytic CoQ10H2 (ubiquinol) in

the mitochondrial electron transport chain, performs antioxidant activities and reduces peroxidation of mitochondrial membrane phospholipids, protecting against iron-death [71]. Although there were initial efforts to manage tumor growth by employing DHODH inhibitors, the effectiveness of drugs in early clinical trials did not reach expectations [72, 73]. This underscores the necessity for thorough investigation into the impacts of DHODH inhibitors on the ferroptosis process in tumors, which in turn affects the effectiveness evaluation of drugs (Fig. 2).

GOT-1

Incorporating the miRNA-associated epigenetic modifications discussed earlier, we focus on an enzyme referred to as glutamic-oxaloacetic transaminase-1 (GOT-1). MiR-9 specifically targets GOT-1 by interacting in the 3'-untranslated region (3'-UTR), modifying GOT1 expression, whereas inhibiting miR-9 increases its expression [74]. More precisely, an excessive amount of miR-9 causes a decrease in both the mRNA and protein levels of GOT-1, consequently diminishing the intracellular Fe2 + accumulation induced by glutamate and sulfasalazine [74]. Specifically, GOT-1 is involved in the metabolic process of glutamine, where glutamine is transformed into glutamate by the enzyme glutaminase (GLS), and then GOT-1 changes glutamate into alpha-ketoglutarate (α-KG) [54, 75]. Variations in GOT-1 can affect the catabolism of glutamine, thereby influencing the balance of glutamate and cysteine, playing a pivotal role in ferroptosis (Fig. 2).

ACSL4

The enzyme acyl-CoA synthetase long-chain family member 4 (ACSL4), pivotal in chemical process of lipids, facilitates iron overload and mitigates hepatic damage as well as fatty acid peroxidation [76]. It is the main function that it attaches coenzyme A to long-chain polyunsaturated fatty acids (PUFAs) and converts free fatty acids into fatty coenzyme A esters, a process that is mainly carried out on mitochondria and the outer membrane of the endoplasmic reticulum [77]. When embedded inside membranes, PUFAs initiate oxidation, subsequently triggering extensive lipid peroxidation and the onset of iron-death [78].

Molecular screenings have been conducted on several cell lines to assess the ACSL family members, which include ACSL1, ACSL3-6. Among them, ACSL4 has been identified as a significant activator in the ferroptosis-induced death [77, 79]. Reduced production of peroxided lipids and induction of iron overload were observed in an ACSL4 conditional deletion mouse, conversely, the phenotype was reversed upon overexpression of ACSL4. [77]. Likewise, the reduction of ACSL4 made cells resistant to iron overload, whereas its increased expression intensified susceptibility to RSL3-induced iron-death [80]. Particularly, ACSL4 levels are higher in cells susceptible to ferroptosis than in those exhibiting resistance. Additionally, individuals showing positive responses to sorafenib exhibit increased ACSL4 levels compared to those with inadequate responses to the drug [77, 81]. The findings indicate that targeting ACSL4 could be a new approach to trigger iron-death and could potentially be used as a predictive factor for overall long-term and illness-free survival in patients with advanced liver cancer following sorafenib treatment (Fig. 2) [81, 82].

BH4-GCH1

Tetrahydrobiopterin (BH4) is a lipophilic reductant that plays a vital part as a coenzyme for numerous enzymes that regulate key metabolic pathways [83]. BH4 is vital for the biological function of iron-death and serves as both a reactive antioxidant, protecting cells from lipid-induced peroxidation, but also for the biosynthesis of coenzyme Q_{10} (a powerful antioxidant) [83, 84]. Guanosine triphosphate cyclohydrolase-1 (GCH1), has been demonstrated to hinder ferric ptosis in laboratory conditions by its overexpression. This is achieved by avoiding the crucial hydrolysis of phosphatidylcholine and PUFA chains [85]. CRISPR-based genome assays detected GCH1, an important enzyme in BH4 production, being a strong inhibitor of ferroptosis, and this inhibition occurs regardless of the presence of GPX4 [83, 84]. Furthermore, the GCH1-BH4 axis could serve as a promising focus in cancer treatment, as its expression is strongly linked to cancer cell resistance against ferroptosis (Fig. 2).

Pharmacological and genetic modulators of ferroptosis

In the realms of pharmacology and genetics, drugs and compounds are typically classified as inducers and inhibitors based on their impact on biological processes. In the field of ferroptosis-related pharmacology, inducers are primarily categorized into three classes. Class I ferroptosis promoters are compounds that target the system Xc^- and activate ferroptosis by inhibiting this system, leading to the depletion of intracellular GSH and the inactivation of GPX4, such compounds include Erastin [86], Sorafenib [87], and Glutamate [5]. Class II ferroptosis promoters are direct inhibitors of GPX4 that covalently bind to GPX4 to suppress its function, resulting in the accumulation of toxic lipid peroxides and the induction of ferroptosis. Examples include RAS-selective lethal protein 3(RSL3) [36]and ML-162 [12]. Other types may affect the abundance of GPX4 or other fundamental regulators of ferroptosis through alternative pathways. Classical pharmacological inhibitors include Fer-1 [19, 86], vitamin E

[22], and Trolox [22],which possess lipophilic antioxidant properties,see Table 1.

At the genetic level, ferroptosis activators and inhibitors can be categorized based on their mechanisms of action, which involve a variety of iron-regulatory molecules. For a detailed summary, see Table 2 and Fig. 2.

Ferroptosis and other classic forms of regulated cell death

Cellular death is not merely a cessation of cell life, but rather an intricately orchestrated biological process designed to remove cells that are damaged, senescent, or no longer required. Cell death mechanisms are divided into two main types: non-lytic and immunologically silent, such as apoptosis, where cells emit the phagocytosis signals for phagocytic clearance without rupturing; and the lytic and pro-inflammatory type, including ferroptosis, necroptosis, and pyroptosis, which release cellular contents upon rupture, inducing inflammation [111].

Ferroptosis and apoptosis

Apoptosis is vital for development, immune tolerance, and tissue homeostasis, and is a key area of research in cell death [112]. Apoptosis is primarily initiated through the activation of caspase family cysteine proteases [113]. Extrinsic apoptosis is initiated through the activation of caspase-8, while intrinsic apoptosis is mediated by the mitochondrial release of cytochrome c and SMAC/DIABLO, leading to the activation of caspase-9, which in turn activates downstream effector caspases such as caspase-3 and caspase-7 [112, 114]. These effector caspases cleave a multitude of protein substrates, resulting in the orchestrated dismantling of the cell. Ferroptosis is an iron-dependent form of non-apoptotic cell death that occurs without caspase activation and is not reversible by caspase inhibitors [115]. As previously mentioned, NRF2, a key antioxidant transcription factor in ferroptosis, has been shown to play an opposite role in apoptosis [116]. BCL-2 family proteins are primarily associated with apoptosis, but the inactivation of certain members like BCL-2, BCL-xL, and MCL-1, which induce mitochondrial damage, can indirectly affect ferroptosis by altering mitochondrial function [114]. In technological applications, ferroptosis provides an alternative therapy for apoptosis-resistant tumor cells. Two-dimensional Ca2Mn8O16 nanosheets mimic enzyme activities, generate ROS, and induce Ca2 + overload, amplifying the synergistic effects of ferroptosis and apoptosis [117].

Ferroptosis and necroptosis

Scholars have proposed that apoptosis, necroptosis, and pyroptosis be collectively referred to as 'programmed cell death' [112]. Necroptosis was initially characterized by the suppression of non-caspase-mediated necrosis following treatment with necrostatin-1 [118]. In apoptosis-impaired conditions, the activation of specific receptors by their ligands can induce necroptosis, with RIPK1 being a pivotal mediator [119]. Necroptosis and ferroptosis are both forms of lytic cell death with membrane rupture. Morphologically, necroptosis typically presents as cellular swelling, whereas ferroptosis is characterized by reduced mitochondrial volume and decreased cristae [120]. Additionally, they differ in their mechanisms of executing cell death: necroptosis typically serves as an alternative pathway when apoptosis is inhibited, mediated by the activation of the pseudokinase MLKL, hereas ferroptosis is triggered by the accumulation of iron-dependent lipid peroxides [121].

Ferroptosis and autophagy

In the process of autophagy, lysosomal fusion merge with autophagosomes to form autolysosomes, which are crucial for sustaining cellular renewal and metabolic processes [122]. Autophagy is a normal physiological process, and the formation of autophagosomes occurs as a result of disruptions in intracellular metabolic activity, and its suppression can result in necroptosis [123]. Extensive research highlights the involvement of autophagy in ferroptosis [124]. Certain necroptosis inhibitors can mitigate ferroptosis by modulating the autophagy pathway. For instance, KW-2449 inhibits the activity of ULK1 kinase, thereby blocking the autophagy process and preventing ferroptosis. Similarly, Necrostatin-1 has been found to inhibit ferroptosis by modulating the autophagy pathway [125]. Moreover, ferroptosis is viewed as an autophagy-dependent cell death mechanism, with autophagy modulating iron metabolism through increased ferritin degradation [126]. Autophagy elevates free iron concentrations in subarachnoid hemorrhage animal models, resulting in iron toxicity accumulation [127].

Ferroptosis and pyroptosis

Cellular pyroptosis, mediated by caspases, is an inflammatory type of programmed cell death marked by membrane disruption and the release of pro-inflammatory cytokines, which amplifies local inflammation [128]. Dysregulation of pyroptosis can lead to diseases such as sepsis, autoimmune diseases, and neuroinflammation. It exhibits parallels with ferroptosis, characterized by membrane disruption, phospholipid peroxidation, and iron toxicity accumulation [129]. Plasma membrane rupture involves the permeation of pore-forming proteins including gasdermin D, and natriuretic peptide 1 [130]. Iron within cells catalyzes ROS production via oxidase

Table 2 Genetic inducers and inhibitors of ferroptosis

	Gene	Target	Mechanism	Refs
Genetic inducers	*ACSL4*	Free fatty acids	Increasing conversion of free fatty acids to fatty coenzyme A esters	[88]
	p53	SLC7A11	Inhibiting System Xc^-	[55]
	miR-672-3p	FSP1	Inhibiting the FSP1-CoQ10-NAD(P)H pathway	[89]
	miR-129-5p	ACSL4	Inhibiting lipid peroxidation	[90]
	IFN-γ	SPOCD1	Inhibiting the GSH/GPX4 axis	[91]
	BAP1	SLC7A11	Inhibiting System Xc^-	[92]
	SLC39A14	Iron transport	Increasing iron levels	[93]
	TFR1, IRP2	Transferrin	Increasing iron levels	[94]
	LOXs	Polyunsaturated fatty acid	Increasing phospholipid peroxidation	[36]
	NOXs	NADPH	Increasing lipid ROS	[35]
	CYB5R1	Polyunsaturated phospholipid	Increasing membrane polyunsaturated phospholipid peroxidation	[95]
	HO-1	NRF2	Decreasing heme; releasing free iron	[96]
	SQS, SQLE	Squalene	Increasing squalene-2,3 epoxide levels and cholesterol synthesis	[97]
	LPCAT3	Lysophospholipids	Increasing biosynthesis of phospholipids	[35]
	NCOA4	Ferritin	Increasing NCOA4-mediated ferritinophagy	[98]
Genetic inhibitors	*NFE2L1*	ACSL4	Upregulating the proteasomal activity	[99]
	DKK1	SLC7A11	Upregulating the GSH/GPX4 axis	[100]
	OTUB1	SLC7A11	Upregulating SLC7A11 stability	[101]
	STEAP3	Iron homeostasis-related genes	Increasing metalloreductase converts Fe^{3+} to Fe^{2+}	[102]
	FANCD2	Iron homeostasis-related genes	Decreasing cellular iron levels	[102]
	FPN1	Iron transport	Decreasing cellular iron levels	[103]
	CISD1	Iron transport	Decreasing mitochondrial iron uptake and respiratory capacity	[43]
	mTORC1	PI3K-AKT-mTOR signaling pathway	Upregulating SREBP1/SCD1-mediated lipogenesis	[104]
	LIFR	SHP1	Decreasing LIFR-NF-κB-LCN_2 axis	[105]
	NRF2	SLC7A11	Upregulating antioxidant genes, up-regulation of SLC7A11	[12]
	KEAP1	NRF2	Upregulating and stabilizing NRF2	[106]
	GPX4, TXNRD1	Lipid peroxides	Decreasing phospholipid hydroperoxides	[107]
	SLC7A11	Cystine	Upregulating antioxidant element stability	[54]
	CD44v	System Xc-	Decreasing phospholipid hydroperoxides	[108]
	HSPB1	Actin dynamics	Upregulating iron uptake and GPX4 abundance	[109]
	FTH1	Iron storage	Upregulating intercellular iron storage protein subunit	[110]
	GCH1	BH4 synthesis	Upregulating cellular susceptibility to ferroptosis	[84]
	FSP1	CoQ10	Decreasing membrane phospholipid peroxidation	[64]
	DHODH	CoQ10	Upregulating CoQ10 to CoQ10H2 in mitochondria	[71]

Abbreviation: ACSL4 Acyl-CoA synthetase long-chain family member 4, *SLC7A11* Solute carrier family 7 member 11, *FSP1* Ferroptosis suppressor protein 1, *IFN-γ* Interferon-γ, *p53* tumor protein 53, *miR-672-3p* microRNA-672-3p, *miR-129-5p* microRNA-129-5p, *SPOCD1* SPOC domain containing 1, *BAP1* BRCA1-associated protein 1, *SLC39A14* Solute carrier family 39 member 14, *LOX* Lipoxygenases, *NOXs* NADPH oxidases, *HO-1* Heme oxygenase 1, *TFR1* Transferrin receptor protein 1, *IRP2* Iron responsive element binding protein 2, *SQS* Squalene synthase, *LPCAT3* Lysophosphatidylcholine acyltransferase 3, *HSPB1* Heat shock protein beta-1, *NCOA4* Nuclear receptor coactivator 4, *NFE2L1* The transcription factor nuclear factor erythroid-2, like-1, *DKK1* Dickkopf WNT signaling pathway inhibitor 1, *OTUB1* Ovarian tumor (OTU) family 1, *STEAP3* Six-transmembrane epithelial antigen of prostate 3, *FANCD2* Fanconi anemia complementation group d2, *CISD1* CDGSH iron-sulfur domain–containing protein 1, *mTORC1* Mechanistic target of rapamycin complex 1, *CD44v* CD44 variant, *NRF2* Nuclear factor erythroid 2-related factor 2, *KEAP1* Kelch like ECH associated protein 1, *TXNRD1* Thioredoxin reductase 1, *GCH1* Guanosine triphosphate cyclohydrolase 1, *FTH1* Ferritin heavy chain 1, *DHODH* Dihydroorotate dehydrogenase

enzymes and lipoxygenase, and excess ROS triggers oxidative stress, activating caspases that cleave ferritin, resulting in its degradation [131].

Ferroptosis and cellular senescence

Typically, moderate and sustained levels of ROS induce cellular senescence by causing DNA damage, oxidation

of proteins and lipids, and subsequently activate cell cycle arrest-related signaling pathways, such as p53-p21 [132]. Excessive ROS target polyunsaturated fatty acids in the cell membrane, culminating in membrane rupture and ferroptosis [63]. The relationship between ferroptosis and cellular senescence is intricate, not simply additive. In vitro analyses of senescent cells have shown compromised ferritinophagy and enhanced resilience against ferroptosis [133]. Certain ferroptosis inducers can selectively eliminate senescent cells, offering potential for anti-aging therapies. Under Erastin treatment, the proportion of SA-β-gal positive cells, a classic marker of senescence, significantly decreased with the addition of the ferroptosis inhibitor Fer-1 [134]. Treatment with FIN56 significantly reduced the survival of primary and paracrine senescent cells, while TRX-CBI showed cytotoxicity against senescent cells at low concentrations, with minimal effects on non-senescent cells [135]. Senescent cells accumulate in tissues, disrupting iron metabolism and leading to iron accumulation, which increases the risk of ferroptosis, creating a vicious cycle that is regulated by ROS and autophagy. Autophagy delays senescence, but its dysfunction increases ROS accumulation, accelerating senescence [125]. DHA clears senescent cells via autophagy-dependent ferroptosis, modulating the AMPK/mTOR pathway to enhance antioxidant capacity and reduce ROS [136]. Chronic inflammation promotes the production of ROS, exacerbating oxidative damage, which further extends cellular senescence and ferroptosis, leading to age-related pathologies. In Alzheimer's disease, the iron toxicity accumulation and phospholipid peroxidation are linked to neuronal death [137], while in cardiovascular diseases, ferroptosis can result in endothelial dysfunction and atherosclerosis [138].

Ferroptosis in the liver microenvironment

Glucose metabolism: a dynamic regulator of iron homeostasis

Iron homeostasis is maintained by balancing iron supply with iron loss, erythropoiesis being a major part of iron demand, while iron supply arises primarily from intestinal absorption and iron cycling in macrophages [139, 140]. Hepcidin, a 25-residue peptide signaling molecule produced and released mainly by hepatocytes, disseminates through the bloodstream and is eliminated by renal excretion [141, 142]. Mutations in the gene regulating this molecule can lead to disorders characterized by iron-overload [143]. Research has demonstrated that the liver has an iron-sensing function; specifically, the liver can integrate signals to control the production of hepatic protein hormones when the iron level of plasma, tissue, or cells changes abruptly [144]. Hepatocytes obtain transferrin-bound iron (TBI) through TFR1, and the liver mainly maintains balance through these mechanisms [145]. The hepatic iron-sensing apparatus is a multifaceted regulatory hub that synergizes diverse mechanisms, including the IRP/IRE system, HIF-mediated responses, and the BMP-SMAD signaling pathway, to dynamically adjust hepcidin expression in accordance with cellular iron demands and systemic iron balance [146–148].

Although there are no set standards for identifying ferroptosis, lipid peroxidation and a decrease in nicotinamide adenine dinucleotide phosphate (NADPH) in its reduced form are the most frequently reported indicators [36, 46, 149]. Research indicates that NADPH functions in concert with FSP1 to convert CoQ10 into CoQ10-H_2, a strong antioxidant that stops peroxidation of fatty acids from spreading across cell membranes(Fig. 3) [63]. The processes by which the liver maintains glucose homeostasis are bidirectionally regulated by iron homeostasis. In type 2 diabetes and NAFLD, increased hepatic gluconeogenesis contributes to hyperglycemia, while mitochondrial electron transport chain (ETC) dysfunction leads to ROS accumulation and disrupted iron homeostasis [150]. Mitochondrial complex defects (e.g., Cox10 deficiency) inhibit pyruvate-to-acetyl-CoA conversion, upregulate PDK4, and thereby block glucose metabolism and exacerbate lipid accumulation, forming a vicious cycle [151]. Current research predominantly focuses on the unidirectional impact of hyperglycemia on iron homeostasis, while the mechanisms by which iron overload feedback-regulates glucose metabolism (e.g., insulin resistance) remain unclear. Additionally, whether the mechanism by which metformin reduces hepatic gluconeogenesis through mitochondrial ETC inhibition is related to iron metabolism requires further validation.

Aberrant lipid metabolism: a catalyst for ferroptosis

The interplay between hepatic lipid metabolism and ferroptosis is particularly pronounced [64]. Fatty acid β-oxidation primarily depends on the mitochondrial electron transport chain (ETC) to generate NADH and $FADH_2$. Dysfunction of the ETC, such as deficiencies in Complex III or V, leads to fatty acid accumulation and reduced histone acetylation levels, ultimately impeding hepatocyte proliferation [151]. ACSL4, a crucial component in lipid metabolism implicated in the fundamental regulatory molecules of ferroptosis, exhibits a protective role against hepatocellular toxicity and lipid accumulation upon its conditional deletion [152]. The investigation by Singh et al. [153] has elucidated that the downregulation of hepatic ACSL4 in hepatocytes within a murine model fed a hyperlipidemic diet results in a diminished accumulation of lipids and an exacerbation of insulin resistance. Another lipid metabolic modulator, lysophosphatidylcholine acyltransferase 3

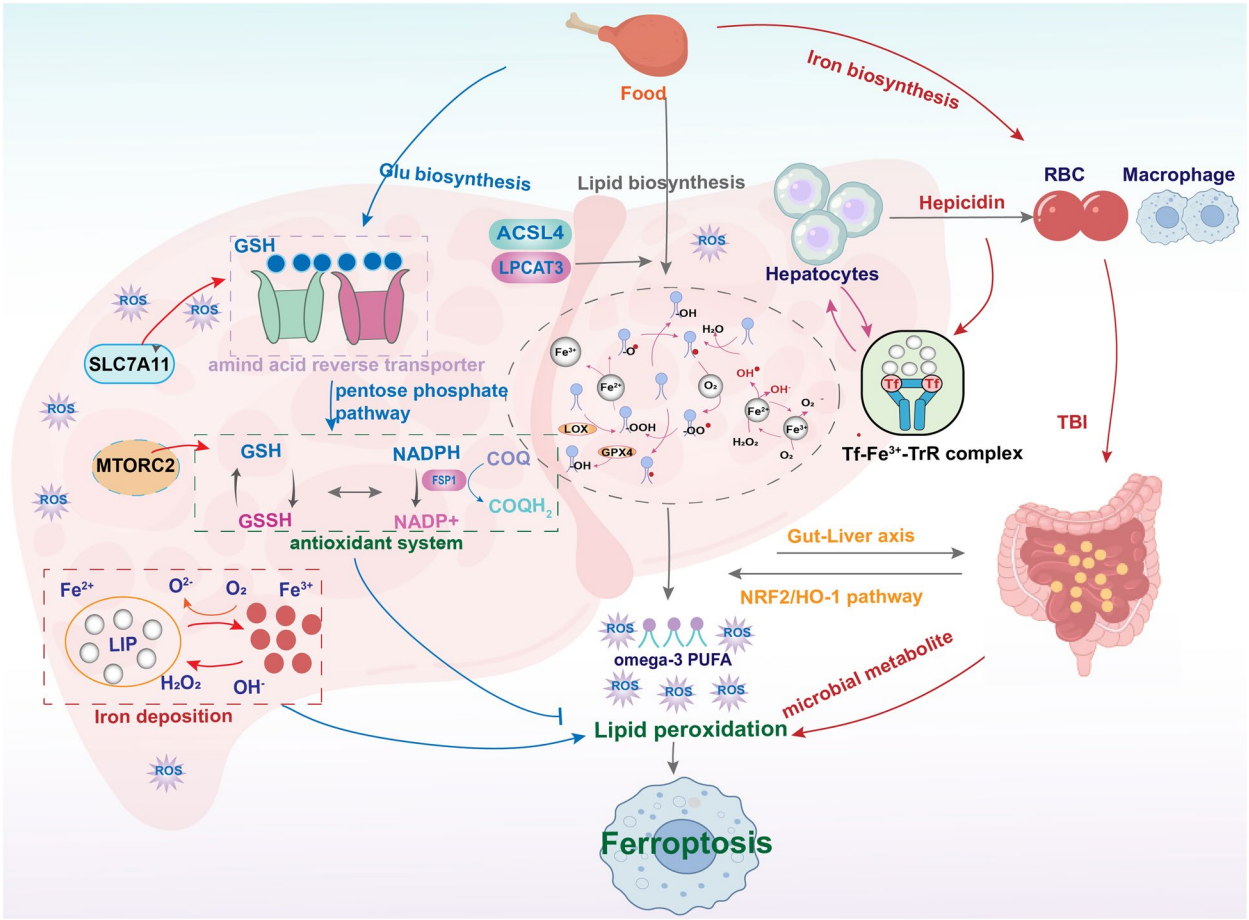

Fig. 3 The liver microenvironment orchestrates ferroptosis through its pivotal signaling pathways. The liver serves as a pivotal organ in regulating the metabolism of various nutrients, encompassing lipids, carbohydrates, and the synthesis of iron. After glycolysis, dietary components are converted into fatty acids under the regulation of lipid metabolic factors ACSL4 and LPCAT3. LOX catalyzes lipid peroxidation of ROS and PUFAs within cells, producing lipid ROS. When these overwhelm the liver's antioxidant defenses, ferroptosis in hepatocytes is triggered. Postprandially, glucose rapidly enters the liver, generating energy through glycolysis and producing NADPH via the pentose phosphate pathway. The liver is also the site of GSH synthesis, where SLC7A11-mediated cysteine uptake is crucial for GSH production, which can inhibit ferroptosis. mTORC2, acting as an amino acid sensor, suppresses ferroptosis by enhancing intracellular NADPH levels. Specifically, Hepatocytes synthesize and secrete hepcidin, which facilitates iron uptake through the endocytosis of Tf-Fe3^{+}-TrR complex. Erythropoiesis is the major consumer of iron, supplied primarily by intestinal absorption and macrophage recycling. Gut microbiota activates the Nrf2/HO-1 pathway, promoting phospholipid peroxidation in the liver. Heterogeneous iron deposition is linked to ferroptosis and associated with various liver diseases. Abbreviations: GSH, glutathione; GSSH, glutathione persulfide; ACSL4, acyl-coenzyme synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; SLC7A11, solute carrier family 7, member 11; MTORC2, mammalian target of rapamycin complex 2; Tf-Fe3^{+}-TrR complex, Transferrin-Ferric Iron-Transferrin Receptor complex; TBI, Transferrin-bound iron

(LPCAT3), has been identified through genetic analysis, which can induce iron-death by accumulating fatty acids [79]. Doll's team found that ACSL4 deficiency enhances cellular resistance to GPX4-deficient ferroptosis, whereas LPCAT3 knockout fails to afford robust protection, implying a potential alternative system between these enzymes [88]. Naturally occurring omega-3 PUFAs serve as principal peroxidation precursors in ferroptosis, exhibiting certain tumor suppressive mechanisms (Fig. 3) [154].

Lipid peroxidation, catalyzed by mitochondria-associated membranes through calcium transport and lipid remodeling, accelerates ferroptotic cell death by promoting the peroxidation of PUFAs [155]. In MDS patients, hepatocyte mitochondrial DNA depletion leads to ROS accumulation, which drives lysosomal ferritin degradation and iron release, triggering a lipid peroxidation-ferroptosis cascade [156]. Although peripheral lipolysis has been confirmed as a major source of lipids in the regenerating liver [151], the role of hepatic de novo lipogenesis

in ferroptosis remains to be elucidated. Furthermore, it remains questionable whether lipid metabolites such as ketones have protective effects.

Amino acid metabolism: the double-edged sword of iron homeostasis

Amino acids indirectly affect hepatic metabolism by modulating glucagon secretion [157]. Dysregulation of these macronutrients can lead to oxidative damage, induce liver disease, and potentially result in organ failure [158]. Research indicates that certain amino acids are directly associated with the modulation of ferroptosis. GSH acts as a universal endogenous antioxidant and inhibition of its transport via the amino acid reverse transporter SLC7A11 is adequate to provoke iron toxicity via depleting GSH levels [159]. Gu et al.'s research has uncovered that mTORC2 is intricately involved in the regulation of cystine uptake and GSH metabolism, linking changes in growth factor receptor signaling, amino acid metabolism, and ROS regulation in cancer [160]. This finding also underscores the pivotal role of cystine/cysteine in mediating ferroptosis within cells, establishing a link to disease pathology (Fig. 3).

Recent studies have indicated that the absence of other amino acids, such as arginine, prevents cysteine depletion from triggering ferroptosis, highlighting the complementary roles of multiple amino acids in modulating iron-death [104]. In NAFLD, elevated plasma amino acids activate mTORC1 signaling, promoting hepatocyte proliferation while exacerbating iron toxicity [161]. In hereditary hemochromatosis, downregulation of the cystine-glutamate transporter directly exacerbates ferroptosis-driven liver injury, while N-acetylcysteine supplementation restores glutathione levels and inhibits ferroptotic cell death [54]. We hypothesize that the variable regulatory roles of amino acid metabolism in ferroptosis may be due to differences in the differing amino acid ratios. Future research should address:(I)the specific mechanisms by which BCAA/AAA ratios modulate iron metabolism; (II) the potential role of amino acid metabolites (e.g., α-ketoglutarate) in regulating iron-related gene expression through epigenetic modifications.

Gut-liver axis: the hidden regulator of ferroptosis

Ferroptosis within the tumor microenvironment is well-studied; however, the hepatic microenvironment remains understudied and represents a burgeoning area of inquiry. The gut-liver axis is indispensable in the study of the hepatic microenvironment. Specifically, intestinal barrier disruption leads to microbiota translocation and endotoxinemia, triggering hepatic immune cell activation and the secretion of inflammatory cytokines, which can further exacerbate hepatic injury [162]. A plethora of preclinical study models has substantiated that the dysregulation of the gut-liver axis and the impetus of inflammatory mediators exert a biphasic effect on the process of ferroptosis, with a mechanism that is intricate. For instance, certain metabolic byproducts of intestinal bacteria have the capacity to suppress the process of ferroptosis in the context of intestinal ischemia–reperfusion injury [163, 164]. Whereas certain metabolites of bile acids are found to promote ferroptosis [165].

In a hepatic sepsis model, elevated levels of iron-overload markers including ROS, MDA, and TNF-α indicate a possible link between ferroptosis and inflammatory responses [166]. The imbalance of the gut-liver axis, together with the impetus of ferroptosis, can sometimes have a complex and additive effect on the evolution of liver disease. In NAFLD, gut-liver axis imbalances reduce beneficial microbes and increase intestinal permeability, leading to heightened microbial metabolite levels that drive inflammation, which are key factors in NAFLD progression [167, 168]. Ferroptosis intensifies NAFLD progression by inducing insulin resistance, excessive ROS production, and hepatic fibrosis through the accumulation of toxic iron levels [169]. Research also indicates that hepatocyte iron burden promotes fibrosis progression by upregulating HO-1 expression and increasing FGF21 levels, thereby amplifying ferrous cell apoptosis [170]. Yu et al. [171] have identified the NRF2/HO-1 pathway as a crucial regulator of the hepatic microenvironment in ferroptosis, with its activation playing a protective role against oxidative stress in intestinal and hepatic cells. There is an anticipation for further investigation into the role of ferroptosis within the microenvironment of the gut-liver axis, potentially offering new treatment strategies for various liver diseases in the future (Fig. 3).

Mitochondria: the nexus of iron-dependent mechanisms

As previously discussed, mitochondrial morphological aberrations are the among pivotal features of ferroptosis. In probing the mechanisms of ferroptosis within the hepatic microenvironment, we question whether such mitochondrial anomalies are a driving force or simply a corollary of ferroptosis?

Mitochondria, pivotal in the TCA cycle, mediate the metabolism of carbohydrates, lipids, and GSH-related amino acids. Research indicates that the TCA cycle heightens cellular susceptibility to iron toxicity, particularly when cysteine is scarce [172]. Furthermore, a multitude of key anti-ferroptotic components are also localized in the mitochondria, such as the CoQ-FSP1 pathway, the BH4-GCH1 axis, and GPX4. Mitochondria function as the nexus for iron processing and metabolism, and they amplify the cell's vulnerability to ferroptosis by facilitating increased iron import via Mitoferrin 1

(MFRN1) [173]. Mitochondria contribute to ferroptosis via several mechanisms: (I)Energy Metabolism Imbalance: ETC dysfunction reduces ATP synthesis, activates AMPK signaling, and promotes lipid peroxidation [156]; (II)Organelle Interactions: MAM-mediated ER-mitochondrial calcium signaling and lipid exchange directly modulate ferroptosis sensitivity [155]; (III)Mitophagy: Impaired mitophagy of damaged mitochondria leads to ROS accumulation and ferroptosis induction. In DGUOK mutation-associated mitochondrial DNA depletion syndrome, abnormal mitochondrial-lysosomal interactions drive ferritin degradation and iron release, contributing to liver failure [156]. In summary, we propose that mitochondria serve dual roles as both "triggers" and "defenders" in the process of ferroptosis.

Pathogenic narratives of liver-related diseases in ferroptosis

NAFLD

Globally, the prevalence of nonalcoholic fatty liver disease (NAFLD), now increasingly referred to as metabolic dysfunction-associated steatotic liver disease (MASLD), is eacalating, impacting approximately one-quarter of the world's population and solidifying its position as a leading cause of chronic liver conditions and hepatic damage [174]. NAFLD includes two pathological conditions: nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), and its main pathological manifestations are lipid accumulation in the liver, apoptosis of hepatocytes and fibrosis processes from mild to significant [175].

Twenty years ago, researchers noticed that over ninety percent of patients with NAFLD had substantially greater concentrations of plasma oxidation indicators, such as malondialdehyde [69] and 4-hydroxynonenal (4-HNE) [176]. Metabolic dysfunction-induced iron surplus may escalate the severity of NAFLD, as indicated by the presence of hepatic iron deposition in affected individuals, with the amelioration of hepatic injury following iron removal [177, 178]. Recent highlight research indicates that in a murine model of nonalcoholic steatohepatitis (NASH) induced by a choline-deficient and ethionine-supplemented [25] diet, the administration of Trolox, a vitamin E analogue, has significantly decreased the levels of serum hepatic injury markers, attenuated the count of necrotic cells staining positively for specific biomarkers, and mitigated inflammatory responses [179]. Nagita et al. [180]demonstrated that in MASLD, compromised GSH-GPX4 axis and decreased lipophilic antioxidants enhance ferroptosis, resulting in hepatic mitochondrial dysfunction. Metabolomic investigations show that hepatocellular GSH concentrations are lower in a specific group of patients with MASLD, which is accompanied by poor production of VLDL [181]. The gut microbiota modulates bile acid metabolism, with metabolites like lithocholic acid triggering ferroptotic cell death among MASLD patients [165]. Additionally, hepatocytes undergoing ferroptosis release molecules that can activate adjacent immune cells, such as Kupffer cells, thereby influencing hepatic inflammation and fibrotic processes [182]. Targeting this vulnerability with sorafenib or similar agents could represent a novel therapeutic approach, selectively inducing ferroptosis resistance in cancer cells [183, 184]. Understanding the mechanisms of ferroptosis in NAFLD is essential for devising innovative treatment approaches (Fig. 4).

ALD

Within the spectrum of chronic liver diseases, in addition to NAFLD and MASLD, alcoholic liver disease (ALD) is also a prevalent condition. Alcohol abuse stands as a significant contributor to global morbidity and mortality, with ALD being a prevalent consequence of such misuse [185]. The condition arises from the toxic effects of excessive alcohol, whose metabolites disrupt cellular functions like protein homeostasis, lipid synthesis, redox equilibrium, culminating in hepatocyte death [186]. Iron-overload is a critical factor leading to chronic hepatic injury, and its inhibition can effectively reverse the detrimental effects on the liver [67]. In a murine model of ALD subjected to ethanol feeding for approximately two weeks, it has been demonstrated that the ferroptosis inhibitor, Ferrostatin-1, can ameliorate hepatic injury and toxicity [187]. Likewise, dimethyl fumarate protects against alcohol-induced oxidative stress by suppressing iron-death through the activation of the Nrf2 element, which enhances cellular resistance to this form of cell death [188].

Specifically, there is debate surrounding the mechanisms leading to ferroptosis in hepatocytes due to chronic ethanol accumulation. Luo et al. [189]indicated that merely inhibiting GPx4 does not suffice to trigger ferroptosis, implying that prolonged ethanol exposure might disrupt the methionine cycle, eventually leading to significant GSH depletion and the indirect inactivation of GPx4. Other researchers suggest that GPx4 remains intact at both transcriptional and translational levels, possibly due to a cysteine-consuming mechanism that hinders the System Xc^- cystine-glutamate antiporter [190]. Briefly, ferroptosis is a downstream process caused by excessive ethanol buildup, which results in hepatocyte damage. Additionally, ferroptosis also participates in the genesis and progression of ALD through interactions with other organs within the hepatic microenvironment, primarily involving the liver-gut and the liver-adipose tissue axis [191]. Sirtuin1

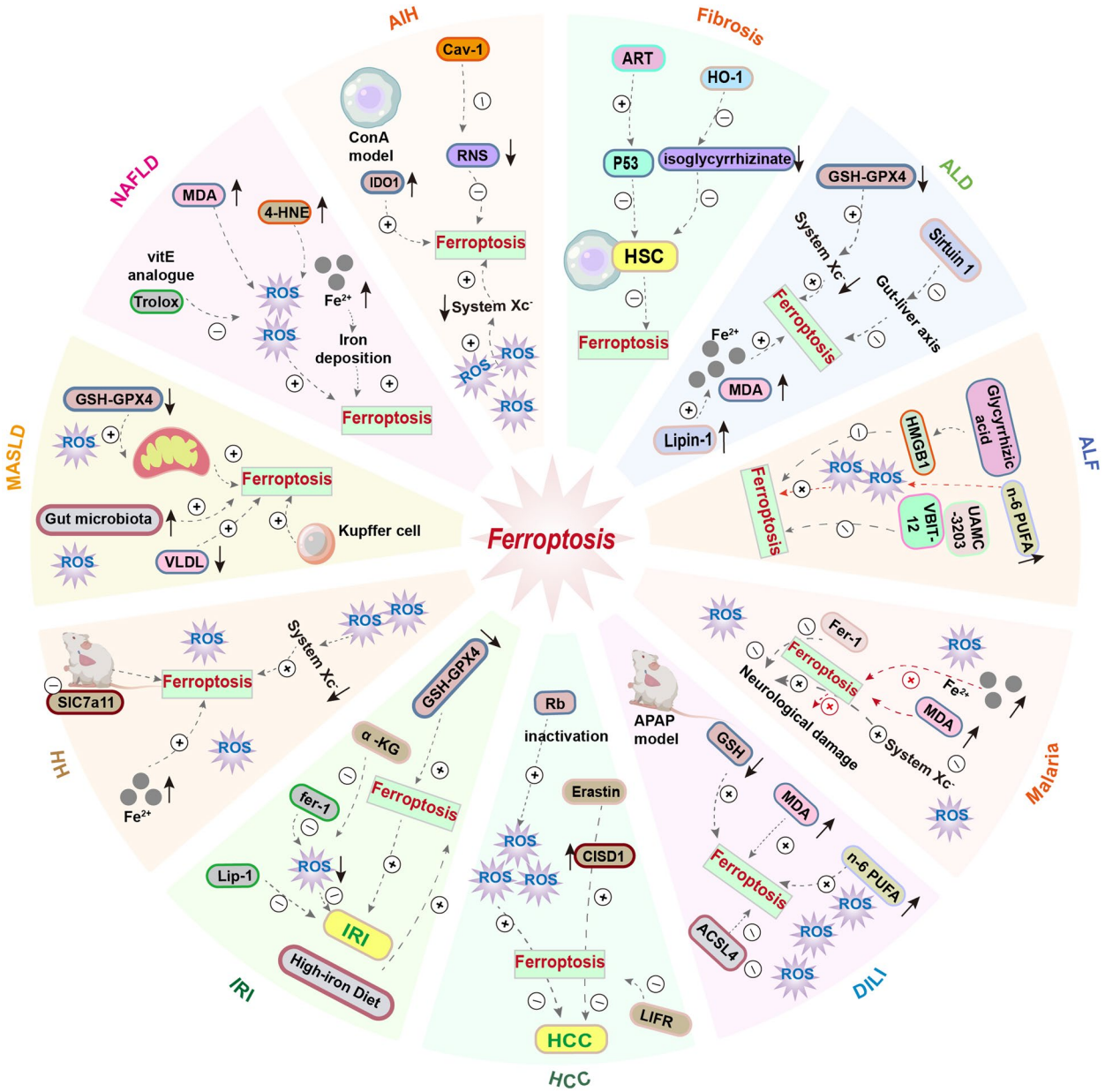

Fig. 4 Pathogenic narratives of liver-related diseases in ferroptosis. Ferroptosis is implicated in range of liver diseases, including non-alcoholic fatty liver disease, metabolic dysfunction-associated steatotic liver disease, alcoholic liver disease, Ischemia reperfusion injury and so on. Abbreviations: 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; VLDL, very Low Density Lipoprotein; Lip-1, liproxstatin-1; Fer-1, ferrostatin-1; α-KG, α-Ketoglutaric acid; CISD1, CDGSH iron-sulfur domain-containing protein 1; IDO1, indoleamine 2,3-dioxygenase 1; RNS, reactive nitrogen species; ART, artemether; HSC, hematopoietic stem cell; HO-1, heme oxygenase-1; HMGB1, high mobility group box 1; ACSL4, acyl-coenzyme synthetase long-chain family member 4; HH, hemochromatosis; HCC, hepatocellular carcinoma; DILI, drug-induced liver injury; ALF, acute liver failure

(SIRT1), a well-established histone deacetylase enzyme with significant protective effects against alcoholic hepatitis [192]. Elevating the levels of SIRT1 in the gut counteracts the negative effects of alcohol on iron balance and stops the onset of ferroptosis, therefore promoting the healing process of liver damage [193]. In the context of liver-adipose tissue axis, elevated lipin-1 levels aggravate abnormal iron deposition and increases hepatic MDA levels in GPx4-independent manner, thereby aggravating alcoholic steatohepatitis and hepatobiliary injury [193]. In chronic liver disease, SIRT1 activation, intestinal enzyme modulation, and liver-adipose tissue axis are key in mitigating ALD-induced ferroptosis and liver injury (Fig. 4).

IRI

Ischemia reperfusion injury (IRI) is also a common type of chronic liver disease. Strictly speaking, IRI is a pathological state, with impacts that are not confined to the liver but also occur in other vital organs, including the heart and kidneys, leading to a series of adverse physiological reactions [194]. In the field of liver transplantation, IRI is a pivotal issue, triggering local inflammation and immune responses that could escalate into rejection, negatively impacting graft function and patient outcomes [195]. During surgery, the liver inevitably experiences an ischemic period followed by reperfusion, leading to IRI. This process induces cellular stress and triggers ferroptosis-associated death pathways.

Significantly, research has confirmed the pathophysiological link between ferroptosis and IRI in liver models [196]. The dysregulation of the GSH/GPX4 axis, precipitating ferroptosis, significantly promotes IRI and the inhibitor lip-1 effectively counteracts hepatic damage [196]. Yamada et al. [197]revealed that elevated serum ferritin, a biomarker of ferroptosis in donors, is an independent risk factor for liver damage post-pediatric living donor liver transplantation. Notably, ferroptosis inhibitors like fer-1 and alpha-tocopherol significantly reduce hepatic injury, lipid peroxidation, and inflammation, whereas the high-iron diet intensifies liver-IRI [197]. Hence, elucidating the mechanisms of ferroptosis in liver transplantation is crucial for devising new treatments to ameliorate IRI and enhance graft survival (Fig. 4).

HCC

Hepatocellular carcinoma (HCC) is a grave malignant neoplasm, ranking as the globe's sixth frequently occurring cancer and stands as the third primary source of cancer-related mortality [198]. The etiology of HCC is multifactorial, with early symptoms often being insidious [199]. Chronic liver diseases previously discussed, including NAFLD, MASLD, and ALD, may progress to cirrhosis and potentially escalate to hepatocellular carcinoma [198]. Following its approval by the FDA in 2007, Sorafenib, an oral multi-targeted tyrosine kinase inhibitor, has emerged as a foundational component of the primary therapeutic regimen for HCC [200]. Nevertheless, the emergence of drug resistance limits the therapeutic efficacy of sorafenib, posing an ongoing challenge in the management of HCC. An array of studies has demonstrated a significant correlation between sorafenib resistance and the onset of ferroptosis in hepatocytes, with multiple key molecules of the ferroptosis pathway implicated in the initiation, progression, and prognosis of HCC.

Iron, an essential trace element, has been demonstrated to accelerate the onset of HCC through high-iron diets, a phenomenon that may be intimately linked to the activation of the ferroptosis pathway [201]. HCC cells can be protected from ferroptosis by activating the p62-Keap1-Nrf2 path, which blocks the degradation of iron-death resistant components [87]. The retinoblastoma protein (Rb), a pivotal tumor suppressor, is commonly deactivated in the pathogenesis of various malignancies [202]. Interestingly, loss of Rb activity does not worsen HCC progression; rather, by exacerbating ferroptosis, it improves sorafenib's effectiveness to treat liver cancer [202].

According to this study, the mechanism would entail a disturbance of iron homeostasis, which would lead to a build-up of lipid ROS and subsequently improve sorafenib's therapeutic efficacy. CDGSH iron-sulfur domain 1 (CISD1) functions as a negative regulator of ferroptosis in HCC, with upregulation observed following erastin treatment [43]. Reducing iron toxicity accumulation and mitochondrial dysfunction through CISD1 gene inhibition enhances the process of erastin-induced iron ptosis, which does not involve GPx4 [43]. The aforementioned fundamental regulator of ferroptosis, ACSL4, also serves as a key predictor of cellular susceptibility to ferroptosis [88]. In liver tissues of patients who exhibit a positive response to sorafenib, ACSL4 is highly expressed, whereas the opposite is observed in patients with poor treatment outcomes [88]. In advanced HCC patients treated with sorafenib, ACSL4 potentially acts as a prognostic indicator for both overall and disease-free survival [203].

Exploring the mechanism of sorafenib-induced ferroptosis in hepatocellular carcinoma cells is a valuable research domain. Yao's research reveals that the leukemia inhibitory factor receptor (LIFR) is crucial in the context of sorafenib-induced ferroptosis [204]. The absence of LIFR expression in cells hinders the ability of sorafenib to initiate this form of cell death [204]. In addition, ferroptosis holds significant research value in HCC prognosis. The high-risk group had a much lower overall survival rate than the low-risk group in the latest study that used a machine-learning model to classify patients into risk groups and find a new genetic marker for HCC prognosis associated to iron deposition (Fig. 4) [205].

DILI

Drug-induced liver injury (DILI) refers to hepatic harm that occurs during the therapeutic use of medications, attributable to the drugs themselves or their metabolites. DILI is a rare adverse event that occurs in about 14 to 19 occurrences per 100,000 people and can manifest as either acute or chronic, with a spectrum of clinical presentations ranging from asymptomatic elevations in liver enzymes to severe hepatic dysfunction [206].

In the academic discourse, the prevailing research delineates DILI into two principal subclasses: intrinsic hepatotoxicity and idiosyncratic hepatotoxicity. The medications implicated in intrinsic DILI are typically lipophilic, enabling them to permeate freely through the lipid membrane that surrounds hepatocellular [207]. Acetaminophen (APAP)-induced intrinsic DILI is relatively common in clinical practice, constituting majority of the cases that progress from intrinsic DILI to acute liver failure [208, 209]. Idiosyncratic hepatotoxicity is an uncommon condition, affecting a select population and lacking a clear dose-dependent relationship [210]. It represents an unpredictable form of liver injury associated with a genetically susceptible individual's unique response to medication. Accordingly, the APAP-induced DILI model is the most prevalent experimental model in animal studies, effectively mimicking the intrinsic DILI toxicity mechanisms observed in humans [211].

Research indicates that in APAP-induced models, a reduction in GSH levels is a common occurrence [212]. Given the exhaustion of GSH is a pivotal mechanism in ferroptosis, these findings support the notion that ferroptosis may be a key pathological process in intrinsic DILI. Similarly, some scholars have found a decrease in GSH and an increase in MDA levels in APAP cellular models [213]. In animal models, APAP also induces a cascade of reactions associated with ferroptosis [76]. Through mass spectrometry analysis, investigators observed an elevation in the levels of lipid peroxides derived from n-6 PUFAs subsequent to APAP treatment, predominantly reflecting the oxidation of arachidonic acid (AA), with this oxidation primarily occurring via an autoxidation mechanism [76]. Upon treatment with ferroptosis inhibitors, a significant reduction in the pathophysiological manifestations was observed in the murine models, concomitant with a substantial increase in overall survival rates [76]. Furthermore, the elimination of ACSL4 significantly attenuates the iron accumulation toxicity induced by APAP, highlighting the potential therapeutic relevance of targeting ACSL4 in counteracting APAP-induced hepatotoxicity [76].

In a recent study incorporating methodologies from the field of biomaterials science, the EaV probe was utilized to monitor alterations within acetaminophen-induced liver injury models. The study unraveled the diminished esterase activity and heightened viscosity during DILI, which may be associated with the generation of ROS during ferroptosis [214]. Research into ferroptosis has uncovered novel therapeutic targets and shed light on the pathophysiology of DILI (Fig. 4).

AIH

Autoimmune Hepatitis (AIH) is a chronic liver condition characterized by aberrant immune system attacks on the liver, predominantly mediated by autoantibodies, and is typically associated with elevated levels of immunoglobulin G (IgG) [215]. AIH exhibits a spectrum of severity, with clinical manifestations ranging from mild dysfunction to severe hepatic impairment. Without effective treatment, AIH can progress to cirrhosis, hepatic failure, or HCC. Consequently, patients often require long-term immunosuppressive therapy to manage disease progression. The histological characteristics of AIH predominantly encompass extensive lymphocytic infiltration and the formation of rosette-like structures by hepatocytes, however, the precise mechanisms underlying these phenomena remain to be elucidated [216]. Concanavalin A (ConA) induces acute liver injury, mimicking AIH, and serves as a key model for studying its mechanisms and treatments [208]. The preliminary treatment with apoptosis inhibitors does not improve ConA-induced liver damage, indicating that this model is suitable for investigating the specific function of necroptotic cell death in the setting of autoimmune hepatitis [217].

Indoleamine 2,3-dioxygenase 1(IDO1), an intracellular heme enzyme, predominantly engages in the modulation of immune responses [218]. The activation of IDO1 enhances lipid peroxidation, which constitutes a pivotal event in the process of ferroptosis [219]. In the ConA-induced murine model of AIH, the upregulation of IDO1 is closely associated with liver injury, an increase in reactive nitrogen species (RNS), and the promotion of ferroptosis [220]. Conversely, the inhibition of IDO1 can mitigate hepatocyte ferroptosis by activating the expression of SLC7A1, also known as xCT [220]. Caveolin-1 (Cav-1), serving as a crucial plasma membrane signaling protein, plays a pivotal protective role in the process of ferroptosis during AIH [221]. Cav-1 exerts a protective effect in AIH by diminishing reactive nitrogen species (RNS), thereby alleviating hepatocyte ferroptosis and shielding the liver from immunologically driven damage [221]. The modulation of Cav-1 expression is intricately linked to the regulation of ferroptosis and RNS, highlighting its critical role in AIH pathogenesis (Fig. 4).

Fibrosis

Hepatic fibrosis represents an early pathological state of the liver, wherein the activation of hepatic stellate cells (HSCs) constitutes the cornerstone of the fibrogenic process [222, 223]. Sustained inflammation and oxidative stress can promote the activation and proliferation of HSCs, exacerbating the deposition of extracellular matrix and leading to the formation of fibrosis [224]. Research

suggests that one possible therapeutic approach for healing fibrosis could be to regulate iron-death. Scholarly research has shown that improving hepatic fibrosis in mouse models can be achieved by increasing the iron-chelating action generated by sorafenib [225].Artemether (ART) prevents stimulated HSCs from causing fibrogenicity by restoring normal iron homeostasis and lipophilic peroxidation through increasing p53 transcription and nuclear binding [226]. HO-1, an intracellular enzyme implicated in anti-ferroptotic mechanisms, ameliorates fibrosis by inhibiting the expansion and stimulation of HSCs upon induction with magnesium isoglycyrrhizinate [227] (Fig. 4).

ALF

Acute liver failure [208] represents a rapidly progressive and severe hepatic condition, which typically afflicts individuals without a pre-existing history of chronic liver disease, culminating in profound hepatic impairment over a short period [228]. ALF is most clinically associated with APAP, but it can also result from hepatotoxicity due to a variety of other medications [229]. The initiation of ferroptosis in the acetaminophen-induced ALF experimental model is accompanied by a marked elevation in peroxides that manufactured from n-6 PUFAs [76]. Furthermore, by preserving mitochondrial functional homeostasis, it has been observed that the iron-overload inhibitors UAMC-3203 and VBIT-12 both mitigate ferroptosis in the model [230]. The other standard method for investigating ALF in mice entails administering lipopolysaccharide (LPS) and D-galactosamine (GalN) to induce hepatic injury [231]. Reducing iron-overload by by using glycyrrhizic acid, an inhibitor of HMGB1, has been demonstrated to reduce liver damage by lowering cellular oxidative damage [231]. Collectively, these investigations imply that ferroptosis could represent a promising therapeutic target for ALI, but additional data are essential to elucidate the intricate mechanisms involved(Fig. 4).

HH

Hemochromatosis [232] is a genetic disorder arising from mutations in genes associated with iron homeostasis [233]. The disorder enhances intestinal iron absorption, leading to iron deposition in parenchymal cells, which in turn induces liver injury and organ dysfunction, with other factors like alcohol abuse and hemorrhage also aggravating iron accumulation [233]. Although the precise role of ferroptosis in the pathogenesis of HH remains unclear, recent research suggests that it may be involved in the pathological processes of HH [234]. Investigators have observed the occurrence of ferroptosis in murine models of HH and have discerned a potentially significant role for ferroptosis in the pathogenic processes of HH [54]. Further gene expression analysis revealed that iron treatment upregulates the expression of solute carrier family 7 member 11 (Slc7a11), a gene previously implicated in ferroptosis [54]. Slc7a11 knockout mice exhibit increased susceptibility to ferroptosis under high-iron conditions, indicating a protective role for Slc7a11 in iron-overload-induced cell death [54]. Subsequent studies should further explore the link between ferroptosis and HH to better understand its pathology and inform new treatment approaches(Fig. 4).

Malaria

Ferroptosis plays a complex role in pathogen infection, with some pathogens potentially leveraging ferroptosis to facilitate their survival and dissemination, while host cells may induce ferroptosis to restrict pathogen infection. Malaria represents a grave public health challenge on a global scale, caused by infections with Plasmodium parasites, predominantly transmitted to humans through the bite of infected female Anopheles mosquitoes [235]. Cerebral malaria [198] is one of the most severe complications associated with malaria, and even with treatment and recovery, it can lead to significant neurological sequelae [236]. Liang et al. [237] have observed a significant elevation of markers indicative of iron-death, MDA and intracellular Fe2+, in a murine model. In the CM model, neuronal damage is positively correlated with the downregulation of GPX4 expression, and Fer-1 can partially reverse this damage [237]. The iron toxicity and oxidative damage regulated by the System Xc^-/GPX4 axis in hepatocytes may control malaria parasite infection, according to an experimental research [238]. Despite advancements, there is a paucity of research on ferroptosis in malaria, warranting further investigation into its mechanisms(Fig. 4).

Ferroptosis manifests several common features across various liver diseases, such as iron metabolism dysregulation, phospholipid peroxidation, and dysfunctional mitochondria. Nevertheless, distinct liver diseases exhibit unique characteristics in the triggers, sensitivity, and clinical treatment strategies of ferroptosis. Etiological factors of various liver diseases are detailed in the preceding text. Notably, these diseases show varying sensitivities to ferroptosis, requiring distinct pharmacological modulation strategies. Most inflammatory liver diseases require ferroptosis inhibitors to reduce the number of necrotic hepatocytes in order to reverse disease progression. Pharmacological modulation of ferroptosis in distinct hepatic microenvironments exhibits subtle differences in the treatment of drug-resistant hepatocellular carcinoma and other liver disorders. Several ferroptosis inducers have been proven to be effective in treating various types of cancer cells that exhibit insensitivity to

apoptosis [239]. Notably, in 2019, researchers initiated exploration into the potential of combining immunotherapy with ferroptosis induction for cancer treatment. Anti-PD-L1 antibodies activate T cells to secrete IFN-γ, leading to downregulation of system xc^-, enhancing cancer cells' susceptibility to ferroptosis and facilitating the cancer cell death process [240].

Clinical treatment strategies by targeting ferroptosis

In the realm of ferroptosis research, significant advancements have been made from elucidating mechanisms to medicine. This review encapsulates recent advancements in research, highlighting novel targets and agents, such as natural compounds, synthetic inhibitors, and clinical trial-stage candidates, all centered on ferroptosis strategies, to offer guidance for future therapeutic developments (Table 3).

In NAFLD, there is currently no standard clinical intervention. Many researchers are exploring new approaches based on mechanisms related to ferroptosis. Researchers have employed a high-fat diet to induce a NAFLD model in $APOE^{-/-}$ mice, revealing that testosterone deficiency can exacerbate hepatic iron deposition in hepatocytes by modulating BMAL1 [267]. Qiu et al. [241] have identified that Nuciferine can ameliorate the accumulation of ferrous iron by modulating the PPARα signaling pathway, suggesting their potential as therapeutic agents. In natural compounds, diosgenin and AP-derived polysaccharides show promise in mitigating ferroptosis and hepatic lipid accumulation, while the small molecule inhibitor GLX351322 combats oxidative damage by upregulating GPX4 [242, 243, 245]. Recent findings also indicate a notable negative correlation between lipophilic vitamins and MAFLD [246].

In the field of ALD research, scholars have constructed models of long-term ethanol exposure in cells, mice, and zebrafish to explore the efficacy of various drugs and targets. Research indicates that inhibiting the secretion of extracellular nicotinamide phosphoribosyltransferase (eNAMPT) from brown adipose tissue (BAT) induced by ethanol can reduce cellular ferroptosis, showing promise as a potential therapeutic target for ALD [268]. Additionally, artificially extracted sulfated polysaccharides have been shown to reduce iron toxicity accumulation and reverse liver damage [247]. Quercetin mitigates ethanol-induced liver damage by modulating PERK-dependent MAMs formation and inhibiting ferroptosis [248]. Poria cocos polysaccharides ameliorate ALD-induced liver damage by suppressing the NF-κB-mediated inflammatory pathway [249]. Selenium and ferrostatin-1 mitigate alcohol-induced oxidative damage by upregulating GPX4 and SLC7A11, with selenium exhibiting greater effectiveness [250].

IRI, a state of functional impairment post-organ transplantation, has seen recent advancements in targeted therapies for hepatocyte ferroptosis. Traditional Chinese medicine has demonstrated value in the study of liver IRI. Wogonin exerts hepatoprotective effects in IRI by inhibiting inducible nitric oxide synthase (iNOS) and mitigating phospholipid peroxidation [251]. Rehmannia glutinosa mitigates iron toxicity accumulation in liver IRI by inhibiting ZIP14 and promoting iron ion efflux mediated by transferrin, thereby alleviating ferroptotic damage [253]. Ticlopidine, primarily known for its antiplatelet aggregation effects, also demonstrates hepatoprotective properties in IRI by reducing the expression of the ferroptosis marker PTGS2 [254].

The role of ferroptosis in HCC differs from its role in other liver diseases, thus necessitating a distinct therapeutic approach based on ferroptosis. Sorafenib serves as the primary treatment for HCC, but its high resistance limits efficacy. Donafenib, a newer alternative, features enhanced tritium atom stability in its chemical structure [269]. Research findings indicate that Donafenib can downregulate the expression of ferroptosis resistance factors SLC7A11 and GPX4, enhancing ferroptosis and apoptosis in hepatic cells, thereby demonstrating its therapeutic potential [256]. In a parallel-controlled Phase II-III clinical trial, donafenib demonstrated significantly better overall survival than sorafenib, with a median OS of 12.1 months versus 10.3 months, and exhibited superior safety and tolerability profiles [270]. To address sorafenib resistance, researchers have investigated novel therapies using sorafenib-resistant hepatocellular carcinoma cell lines as experimental models. Inhibiting GSTA1 enzyme enhances sorafenib sensitivity and ferroptosis in hepatic cells, improving sorafenib efficacy [260]. And the use of the SOCE inhibitor SKF96365 in conjunction with sorafenib significantly enhances the responsiveness of SR cells to sorafenib [261]. In 2024, researchers developed GOA/miR-targeted nanocomposites that efficiently encapsulate miRNA inhibitors, inducing non-iron-dependent ferroptosis to significantly inhibit hepatic cell growth [259]. These nanocomposites exhibit excellent biocompatibility and immune activation potential, offering a promising biotherapeutic strategy for HCC treatment [259].

Similar to various other injurious liver diseases, DILI can also be mitigated by targeting and inhibiting the ferroptotic pathway to alleviate hepatic damage. Recent studies have unveiled innovative strategies, demonstrating that both the novel drug mifepristone (RU486) and the natural compound xanthohumol [151] can protect against DILI by activating ferroptosis-resistant molecules

Table 3 Ferroptosis targets in liver disease

Liver diseases	Therapeutic drug	Ferroptosis-related targets	Model	Mechanism	Refs
NAFLD	Nuc	Ferrous ion	C57BL/6J mice, AML-12 cells	Upregulating the PPARα signaling pathway	[241]
	Diosgenin	NRF2	SD rats, AML-12 cells	Upregulating the expression of Nrf2 and its downstream ferroptosis-related genes	[242]
	NOX4 inhibitor (GLX351322)	Caveolin-1, GPX4	Male C57BL/6J mice	Upregulating the NOX4/ROS/GPX4 pathway	[243]
	PA	ACSL4, GPX4, SLC7A11	C57BL/6J mice	Inhibiting lipid metabolism	[244]
	AP	Lipid accumulation	Male C57BL/6J mice	Inhibiting the p53/mTOR Pathway	[245]
	Vitamin D	Ferrous ion, Lipid accumulation	Male C57BL/6J mice, HepG2 cells	Inhibiting serum lipid metabolism	[246]
ALD	EIP	GPX4, SLC7A11	Male C57BL/6J mice	Inhibiting lipid accumulation and iron deposition	[247]
	Quercetin	MAMs, PERK	C57BL/6J mice, AML12 cells	Upregulating PERK-dependent MAMs formation	[248]
	Poria cocos polysaccharides	NRF2, Ferrous ion	SD rats, BRL3A rat liver cells	Upregulating the NRF2 signaling pathway	[249]
	Selenium , Fer-1	GPX4, SLC7A11, ACSL4	C57BL/6J mice, Mouse normal hepatocytes (NCTC clone 1469)	Inhibiting oxidative stress	[250]
Liver IRI	Monomer wogonin	ALOX15, iNOS	SD rats, BRL-3A cells	Inhibiting lipid peroxidation	[251]
	Oleanolic acid	NRF2	SD rats, IAR20 and THLE-2 cells	Upregulating the KEAP1/NRF2 pathway	[252]
	RRP	ZIP14	C57BL/6J mice, BRL cells	Decreasing intrahepatocellular iron accumulation	[253]
	Ticlopidine	Ferrous ion	C57BL/6J mice	Decreasing iron accumulation in hepatic tissues	[254]
HCC	Iberverin	GPX4, SLC7A11	HLE and HCCLM3 cells	Upregulating iron accumulation	[255]
	Donafenib	GPX4, SLC7A11, ROS	Hepa1-6 and Huh7 cells	Upregulating apoptosis	[256]
	Schisandrin A	GPX4, SLC7A11, GSH	Huh7 cells	Upregulating the AMPK/mTOR pathway	[257]
	Bavachin	GPX4, SLC7A11, ACSL4, ROS	Huh-7 and HepG2 cells	Inhibiting the NRF2/HO-1 pathway	[258]
	GOA/miR-363-5pi nanocomplex and GOA/miR-765i nanocomplex	Histidine phosphatase	HepG2, SMCC-7721, and Bel-7402 cells	Upregulating LHPP expression and inactivating the PI3K/Akt pathway	[259]
	GSTA1 and CTNNB1 inhibitors	GSTA1/CTNNB1 axis	Huh7 and HepG2 cells, Chinese patients	The knockout of GSTA1 reinstates sorafenib sensitivity	[260]
	SOCE inhibitor SKF96365	SLC7A11, Glutathione	Hep3B, MHCC97H, and HEK293T cells	Inhibiting the SOCE-CaN-NFAT pathway	[261]
	Curcumin	GPX4, SLC7A11, ACSL4, PTGS2	HepG2 and SMMC7721 cells	Increasing MDA levels and iron ion levels, decreasing intracellular GSH levels	[262]

Table 3 (continued)

Liver diseases	Therapeutic drug	Ferroptosis-related targets	Model	Mechanism	Refs
DILI	Xanthohumol	NRF2, GPX4, KEAP1	C57BL/6J mice, HepaRG cells	Upregulating the the Nrf2/xCT/GPX4 signaling pathway	[263]
	Mifepristone (RU486)	NRF2, GSH, GPX4, FSP1, DHODH	C57BL/6J mice	Upregulating the GSH/GSTs/RLIP76&MRP1 anti-ferroptosis pathway	[264]
	MnO2nanoflowers	NRF2, GSH, GPX4, ROS	Male KM mice, primary hepatocytes	Upregulating the P62-NRF2-GPX4 antioxidation signaling pathway	[265]
	Microbial metabolites	Mitophagy and NRF2	C57BL/6J mice, NeHepLxHT cells	Upregulating the AMPK-ULK1-p62 signaling pathway	[266]

Abbreviation: BMAL1 Brain and muscle ARNT-like gene 1, *Nuc* Nuciferine, *AML-12 cells* Alpha mouse liver 12 cells, *NRF2* Nuclear factor erythroid 2-related factor 2, *SD rats* Sprague–Dawley rats, *GPX4* Glutathione peroxidase 4, *PA* Palmitoleic acid, *ACSL4* Acyl-CoA Synthetase Long-Chain Family Member 4, *SLC7A11* Solute Carrier Family 7 Member 11, *eNAMPT* Extracellular nicotinamide phosphoribosyltransferase, *MAMs* mitochondria-associated endoplasmic reticulum membranes, *PERK* Protein kinase RNA-like endoplasmic reticulum kinase, *PA* Palmitoleic acid, *AP* a polysaccharide from Atractylodes lancea rhizome, *EIP* sulfated polysaccharides extracted from Enteromorpha intestinalis, *Fer-1* Ferrostatin-1, *RRP* Rehmanniae Radix Praeparata, *ZIP14* Solute Carrier Family 39 Member 14, *PTGS2* Prostaglandin-endoperoxide synthase 2, *KEAP1* kelch-like ech-associated protein 1

like Nrf2 [263, 264]. Oral fecal microbiota capsules have been shown to induce mitophagy and activate antioxidant molecules, mitigating DILI-induced ferroptotic hepatocyte apoptosis, offering potential for improved treatment efficacy [266]. MnO2Nfs, a novel nanomaterial, shows promise in biomedicine by significantly boosting intracellular glutathione and reducing oxidative damage, acting as a powerful ferroptosis inhibitor in the future [265].

Overall, within the field of hepatology, targeting ferroptosis offers a promising avenue for the treatment of liver diseases. Traditional ferroptosis-targeting drugs mainly include iron chelators like deferoxamine and deferiprone, antioxidants such as glutathione and vitamin E, and Nrf2 activators including sulforaphane and curcumin, all of which have shown promise in mitigating liver damage (see Table 1). Expanding on this, the review highlights recent progress in iron-targeting drug development (Table 3): (I) natural compounds like Diosgenin, Nuciferine, and xanthohumol; artificially derived sulfated polysaccharides [241, 263]; and small molecule inhibitors such as GLX351322 have demonstrated favorable outcomes in experimental assessments [243]; (II) improvements in traditional drugs: Donafenib offers enhanced overall survival compared to sorafenib [256], and Ticlopidine provides additional benefits [254]; (III) Development of novel nanomaterials: GOA/miR-targeted nanocomposites, mitochondrial-targeted antioxidant MitoTEMPO, and MnO2Nfs as potent inhibitors of ferroptosis [96, 259, 265].

While drugs targeting ferroptosis hold promise, they also present challenges: (I) lack of specificity: where iron chelators may disrupt normal cellular iron metabolism and cause iron-deficiency anemia; (II) delivery efficiency: as oral administration can lead to insufficient drug concentrations in the liver due to gastrointestinal factors, thus reducing efficacy; (III) individual variability: where genetic background, disease state, and comorbidities can affect drug response; (IV) potential hepatotoxicity, with some drugs causing liver function abnormalities; (V) the experimental nature of new targeted therapies, where unreported negative results may exist.

Conclusion

Ferroptosis, a form of regulated cell death distinct from apoptosis, autophagy, and necrosis, has emerged as a critical player in the pathogenesis of various liver diseases [271]. Characterized by iron toxicity accumulation, phospholipid peroxidation and dysfunctional mitochondria, ferroptosis is intricately linked to the hepatic microenvironment, influencing and being influenced by factors such as iron homeostasis, glucose metabolism, lipid metabolism, amino acid metabolism, and the gut-liver axis.

In this review, we have explored the multifaceted role of ferroptosis in liver diseases, emphasizing its significance in both the progression and potential treatment of conditions such as NAFLD, ALD, IRI, HCC, DILI and AIH. Our analysis reveals that regulatory proteins like NRF2, FSP1, and GPx4 are not only central to the execution of ferroptosis but also to the development of liver tumors and liver failure.

Furthermore, we highlight the importance of understanding the liver microenvironment in ferroptosis. Iron

homeostasis, a key determinant of hepatic health, is disrupted in diseases such as hemochromatosis and fibrosis, leading to ferroptosis. Similarly, glucose and lipid metabolism disruptions, common in NAFLD, have been shown to induce ferroptosis, underscoring the metabolic nature of these conditions. The gut-liver axis also emerges as a significant factor in the modulation of ferroptosis. Disruptions in this axis can lead to increased susceptibility to ferroptosis, highlighting the importance of considering the holistic hepatic environment in disease pathogenesis.

Despite the burgeoning interest in ferroptosis and its implications in a spectrum of liver diseases, numerous gaps persist in the current understanding. The predominant research is confined to animal or cellular models, with a relative dearth of studies examining its role in human subjects [58, 272]. This disparity warrants further investigation. Moreover, while the upstream regulatory molecules of the ferroptotic process have been the focus of considerable attention, our knowledge of the downstream molecular players remains alarmingly scarce. The exploration of ferroptosis inhibitors is another area ripe for advancement; for instance, classic inhibitors such as fer-1 have been associated with issues of metabolic latency, indicating a need for more nuanced pharmacological strategies [273].

Building upon the preceding discourse, several queries and contemplations emerge: (I) At what juncture or stage should the ferroptosis process in specific pathological liver diseases be targeted for intervention? (II) Given the inherent heterogeneity in the efficacy of ferroptosis-related inhibitors and inducers across various liver diseases, can a unified assessment of intervention outcomes be achieved in the future? (III) In the context of liver cancer, is it possible to activate ferroptosis selectively in hepatocellular carcinoma cells without affecting healthy cells? (IV) Can combinatorial therapeutic strategies based on distinct ferroptosis regulatory molecules enhance treatment efficacy?

In conclusion, while ferroptosis presents a complex and nuanced mechanism in liver disease, it also offers a wealth of opportunities for therapeutic intervention. The development of targeted ferroptosis therapies, such as the use of small molecules to modulate key regulatory proteins, offers a promising frontier in the treatment of liver diseases. As our understanding of the molecular mechanisms of ferroptosis deepens, so does our potential to develop novel, effective treatments that can improve outcomes for patients with liver diseases.

Authors' contributions
JC and ZH were involved in the conception of the study. YH, YL, JS, MS, XN, HS, CX were involved in writing the article. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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