



Involvement of ferroptosis in metabolic dysfunction-associated steatohepatitis-related liver diseases

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD), as a metabolic liver disease, is emerging as the most prevalent chronic liver disease worldwide. Metabolic dysfunction-associated steatohepatitis (MASH) is the severe form of MASLD, which progresses from simple steatosis to an inflammatory state, even fibrosis and hepatocellular carcinoma. Accumulating evidence has proved that cell death is a hallmark of MASH, while the specific pathogenesis remains unclear. Several cell deaths, including apoptosis, necroptosis, autophagy, and pyroptosis, have been studied in MASLD/MASH. In recent years, ferroptosis, a novel iron-dependent non-apoptotic form of cell death characterized by the excessive accumulation of intracellular iron and lipid peroxidation, has emerged as a promising target in MASLD/MASH. In this review, we mainly summarize the mechanism of ferroptosis and describe the role of ferroptosis in the progression of MASLD to MASH and related diseases, including liver fibrosis and hepatocellular carcinoma. Then, we discussed the crosstalk between ferroptosis and other cell deaths in MASLD/MASH. Finally, we focus on the potential therapeutic applications of targeting ferroptosis in MASH, which might shed light on the future directions of MASH treatment.

Keywords Cell death · Ferroptosis · MASLD · MASH · Therapy

Introduction

MASLD is the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality [1]. With a global prevalence estimated at 24%, MASLD continues to increase at an alarming rate, posing a heavy

burden on the world economy and healthcare system [2]. MASLD encompasses a spectrum of chronic metabolic liver disease, ranging from simple steatosis to steatohepatitis, cirrhosis, and even hepatocellular carcinoma (HCC). Among these, MASH is defined as a more severe process than simple steatosis, with inflammation and liver damage, often accompanied by fibrosis that may progress to cirrhosis [3, 4]. Notably, a substantial proportion of HCC cases occur in MASH patients before the development of cirrhosis, yet routine screening for HCC remains less common compared to other liver diseases [3, 4]. Epidemiological heterogeneity, such as sexual dimorphism, circadian rhythms, obesity, and type 2 diabetes, significantly influences the onset, progression, and therapeutic response of MASLD/MASH [5–7]. Consequently, elucidating the molecular pathogenesis, implementing risk prediction, and identifying precision medicine for MASLD/MASH are imperative.

Emerging evidence highlights the role of cell death mechanisms, particularly ferroptosis, in the progression of MASH [8–11]. As an iron-dependent non-apoptotic cell death, ferroptosis is featured by iron overload and lipid peroxidation. Clinical studies have reported that iron overload

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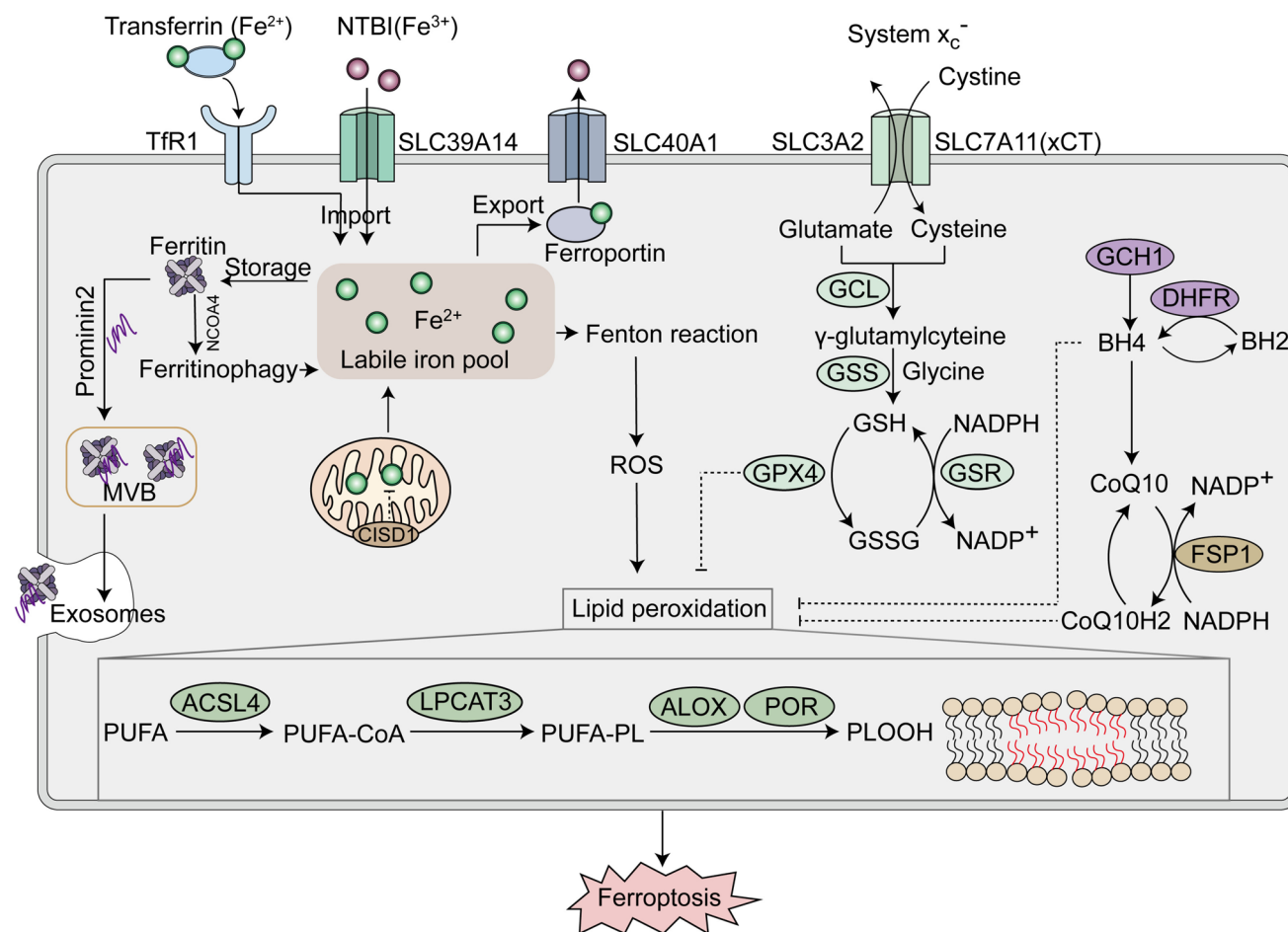


Fig. 1 Molecular mechanism and regulatory pathways of ferroptosis. The storage, release, import, and export of iron impact the ferroptosis sensitivity of cells. Disruption of iron homeostasis and intracellular iron overload can lead to the generation of ROS through the Fenton reaction, thereby promoting membrane lipid peroxidation and triggering ferroptosis. Ferroptosis is primarily regulated by three antioxidant axes: the system Xc⁻-GSH-GPX4 axis, the FSP1-CoQ-NADPH axis, and the GCH1-BH4-DHFR axis, all of which rely on NADPH as electron donors. ROS, reactive oxygen species; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; CoQ, coenzyme Q; NADPH, nicotinamide adenine phosphate dinucleotide; GCH1, guanosine triphosphate cyclohydrolase 1; BH4, tetrahydrobiopterin; DHFR, dihydrofolate reductase; ACSL4, acyl-CoA synthetase long-chain family member 4; Tfr1, transferrin receptor 1; NTBI, non-transferrin-bound iron; NCOA4, nuclear receptor coactivator 4; MVB, multivesicular bodies; GCL, glutamate-cysteine ligase; GSR, glutathione reductase; LPCAT3, lysophosphatidylcholine acyltransferase 3; ALOX, lipoxygenase; POR, cytochrome P450 oxidoreductase; CISD1, CDGSH iron-sulfur domain 1

is commonly witnessed in MASLD patients, and Tao et al. discovered that excessive iron accelerates MASH progression by inducing ferroptosis [12–14]. Besides, a higher systemic lipid peroxidation level was identified in MASH patients [15, 16]. Notably, a recent study found that hepatic ferroptosis plays an important role as the trigger for initiating inflammation in MASH [10]. Collectively, these findings strongly implicate ferroptosis as a critical pathogenic driver in MASH initiation and progression.

In this review, we provide a comprehensive summary of the mechanisms of ferroptosis, as well as the role of ferroptosis in MASH and its related liver diseases. Given that many research has indicated the intimate association between different cell deaths and MASH, we also

summarize the evidence of other cell deaths in MASH, including apoptosis, necroptosis, autophagy, and pyroptosis. Furthermore, we discuss the potential therapeutic strategies targeting ferroptosis in MASH and highlight key unresolved issues in this field.

Ferroptosis

Ferroptosis, an iron-dependent form of non-apoptotic cell death, is characterized by iron accumulation and lipid peroxidation [17]. We discussed the major mechanisms and main signaling pathways below (Fig. 1).

Iron metabolism

Iron is an essential trace element that is indispensable for the maintenance of physiological processes. However, when the homeostasis of the iron pool is disrupted and cellular labile iron levels are increased, iron can generate reactive oxygen species (ROS) through the Fenton reaction, promoting lipid peroxidation and ultimately inducing ferroptosis. Additionally, iron may enhance the activity of enzymes such as lipoxygenase (LOX) and cytochrome P450 oxidoreductase (POR), which are critical for lipid peroxidation and oxygen homeostasis [18, 19]. Given that the liver is the primary organ responsible for iron sensing and regulation, it is particularly vulnerable to iron overload and its associated pathological effects [20]. The hepatic iron content was found to increase as the stage progressed in MASH patients [21, 22].

The regulation of iron storage, release, import, and export significantly influence cellular sensitivity to ferroptosis. For instance, transferrin in serum and its receptor TfR1 play a critical role in ferroptosis by facilitating iron import into cells, both of which were upregulated in MASLD patients [13, 22]. While solute carrier family 39A14 (SLC39A14) mediates the uptake of non-transferrin-bound iron (NTBI) by the liver, the deletion of hepatic SLC39A14 attenuates liver fibrosis by suppressing ferroptosis [23–25]. Iron export is regulated through ferroportin (FPN), or the prominin2-multivesicular bodies (MVB)-exosome-ferritin pathway, which contributes to the mitigation of ferroptosis [26, 27]. A recent study found that metformin upregulates FPN expression through the adenosine-monophosphate-activated protein kinase (AMPK)-dependent lysosome degradation pathway, resulting in the alleviation of ferroptosis and preventing the progression of MASLD [28]. The intracellular iron storage mainly relies on a key protein complex, ferritin. Ferritin can be degraded by ATG5-mediated autophagy, a process regulated by nuclear receptor coactivator 4 (NCOA4), and consequently leads to iron overload, ferroptosis, and MASH aggravation [29, 30]. Moreover, CDGSH iron-sulfur domain1 (CISD1) has been shown to inhibit mitochondrial iron accumulation to suppress ferroptosis, and the genetic ablation of CISD1 contributes to lipid peroxidation and ferroptosis [31, 32]. The cytosolic iron chaperone Poly(rC)-binding protein 1 (PCBP1) binds iron as a Fe–glutathione complex, regulating the distribution of cellular labile iron. Restoring PCBP1-dependent iron homeostasis could suppress lipid peroxidation and ameliorate MASH progression [33].

Lipid peroxidation

Ferroptosis is driven by the lethal peroxidation of specific membrane lipids, which triggers fatal ion imbalances and

membrane permeabilization, thus leading to cell death [34]. Free polyunsaturated fatty acids (PUFAs) are the substrate of lipid signal transduction but must be incorporated into membrane phospholipids and require the removal of bis-allylic hydrogen atoms [18, 35]. Studies have revealed that lipid metabolic genes acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are key regulators of lipid peroxidation [36–38].

ACSL4 mediates the binding reaction of PUFAs and CoA, and LPCAT3 subsequently catalyzes the incorporation of these intermediates into membrane phospholipids (PL) to form PUFA-PLs [37, 39]. Hepatic ACSL4 level was found to be elevated in MASLD patients [40]. For one thing, ACSL4 catalyzed the production of acyl-CoA, the substrate of triglycerides (TG) synthesis, which may further exacerbate hepatic steatosis. For another, ACSL4 may deprive GPX4 activation by upregulating the p38-MAPK pathway to aggravate lipid peroxidation and ferroptosis to promote MASH progression [41]. Thus, selectively inhibiting ACSL4 indicates a promising therapeutic target. After incorporation into membrane phospholipids, the PUFAs-PL species are then either enzymatically autoxidized by LOXs or non-enzymatically attacked by ROS generated from the Fenton reaction, which will ultimately lead to lipid peroxidation and ferroptotic cell death [42]. The LOX enzyme family, particularly arachidonate lipoxygenase 12 (ALOX12) and ALOX15, was demonstrated as an important ferroptosis driver. ALOX12 is dispensable for p53-mediated ferroptosis and also acts as a downstream target for SLC7A11-mediated ferroptosis resistance [43, 44]. Moreover, ALOX15 initiates specific redox reactions in PUFA-phospholipids by binding with phosphatidylethanolamine binding protein 1 (PEBP1) to generate peroxides and enhance cellular sensitivity to ferroptosis [45, 46]. Inhibiting the ACSL4/LPCAT3/ALOX15 pathway may alleviate MASLD by suppressing ferroptosis execution [47]. In addition, the Hippo-YAP pathway has recently been uncovered as a ferroptosis regulator, as its transcriptional modulation on ACSL4, TFRC, and GPX4 exhibited its possible participation in MASH pathogenesis [48–50].

The uptake and storage of lipids and the metabolism of PUFA and monounsaturated fatty acid (MUFA) crucially shape cellular sensitivity to ferroptosis [34]. For instance, the cell-surface protein CD36 mediates the uptake of fatty acids by tumor-infiltrating CD8⁺ T cells in the tumor microenvironment (TME), thereby inducing lipid peroxidation and ferroptosis of CD8⁺ T cells and impairing their antitumor ability [51]. The fatty acid transport protein (FATP) family also mediates hepatic lipid uptake. Our recent work has revealed that hepatic FATP5 knockdown reshapes the balance between PUFA and MUFA, suppressing ferroptosis to alleviate MASH

[52]. Studies have also shown that in some cells, certain proteins like TPD52, PGRMC1, and HIF-2 α can alter ferroptosis sensitivity through modulating lipid storage [53–55]. ACSL3 is required for the incorporation of MUFAs into membrane phospholipids, which are less susceptible to oxidation compared to PUFA-PLs due to the absence of bis-allylic positions. Exogenous supplementation of MUFAs or activation of stearoyl-CoA desaturase 1 (SCD1), the key enzyme in MUFAs biosynthesis, has been shown to reduce cellular susceptibility to ferroptosis [56]. Our recent study found that FATP5 deficiency could activate SCD1 to promote MUFA de novo synthesis, subsequently suppress ferroptosis and reduce liver injury, inflammation, and fibrosis in MASH mice models [52]. The effects of PUFAs and MUFAs on ferroptosis have been widely explored, while the outcomes vary significantly due to context-dependent mechanisms. Given that individuals obtain fatty acids (FAs) from diets closely linked to metabolic syndrome, it is urgent to elucidate the specific effects of different FAs on ferroptosis in various contexts.

Mechanisms involved in the regulation of ferroptosis

System Xc⁻-GSH-GPX4 axis

The system Xc⁻-GSH-GPX4 axis is indispensable because of its antioxidant capacity to defend against ferroptosis. The system Xc⁻ is a cystine-glutamate antiporter composed of a light-chain subunit SLC7A11(xCT) and a heavy-chain subunit SLC3A2 linked by a disulfide bond. Through SLC7A11, cystine can be transported into cells and reduced into two cysteine molecules rapidly [57]. As a semi-essential amino acid, cysteine is required for the formation of GSH, the key antioxidant compound. With the assistance of GPX4, the toxic phospholipid hydroperoxide will be converted into non-toxic phospholipid alcohol [58, 59].

Multiple studies suggested that the upregulation of SLC7A11 decreased ROS levels, inhibited ferroptosis, and impeded MASLD/MASH progression [60, 61]. Under conditions of endoplasmic reticulum (ER) stress induced by amino acid starvation, oxidative stress, or other factors, the general control nonderepressible 2 (GCN2) is activated and phosphorylates eukaryotic initiation factor 2 α (eIF2 α) to induce the integrated stress response (ISR). This leads to increased translation of the downstream activating transcription factor 4 (ATF4), which modulates the expression of SLC7A11 to mitigate ferroptosis-dependent inflammatory cell death [62–64]. Intriguingly, the ablation of ATF4 showed both prevention of hepatic steatosis and promotion of ferroptosis susceptibility by decreasing SLC7A11 activity, which indicated the potential multifaceted role of ATF4 in simple steatosis and

steatohepatitis in MASH progression. In addition, given that GPX4 has been established as one of the most important guardians of ferroptosis, studies have identified the protective role of GPX4 in MASLD/MASH by decreasing ROS-mediated ferroptosis [65–67].

FSP1-CoQ-NADPH axis

Independent of the system Xc⁻-GSH-GPX4 axis, the ferroptosis suppressor protein1 (FSP1)-ubiquinol 10 (CoQ)-NADPH pathway is a plasma membrane-localized radical-trapping antioxidant system that suppresses lipid peroxidation to confer ferroptosis resistance [68, 69].

FSP1, also known as apoptosis-inducing factor mitochondria-associated 2 (AIFM2), which typically induces apoptosis in mitochondria, has been identified as a potent ferroptosis-resistant factor [69, 70]. FSP1 is recruited by N-myristylation to the cell membrane where it catalyzes the reduction of CoQ10, thereby trapping lipid peroxidation to inhibit ferroptosis [69]. Besides, FSP1 is also required for the endosomal sorting complexes required for transport (ESCRT)-III recruitment in the plasma membrane to resist ferroptosis [71]. Moreover, FSP1 can reduce vitamin K to its hydroquinone, which acts as a robust radical-trapping antioxidant to suppress ferroptosis [72]. ACSL1 can increase the myristylated FSP1, thereby inhibiting its degradation and promoting its translocation to the cell membrane, while a drug-like compound iFSP1 can inhibit FSP1 to increase ferroptosis [73]. Recent research has revealed that some molecular compounds, such as baicalein and diosgenin, may inhibit hepatic ferroptosis by activating FSP1 to effectively treat MASLD/MASH in mice models [47, 74]. These findings demonstrated that the FSP1-CoQ-NADPH pathway may become a potential target for MASH treatment.

Recently, Mao et al. demonstrated that dihydroorotate dehydrogenase (DHODH) operates independently of cytosolic GPX4 or FSP1 to inhibit ferroptosis in the mitochondrial inner membrane by reducing CoQ10 to ubiquinol [75]. However, Mishima et al. challenged this view, arguing that the sensitizing effect of the inactivation of DHODH is modest and primarily mediated by FSP1 inhibition [76]. Thus, further studies are required to clarify the anti-ferroptosis mechanism involved in DHODH and its interplay with other pathways.

GCH1-BH4-DHFR axis

The GTP cyclohydrolase-1 (GCH1)-tetrahydrobiopterin (BH4)-dihydrofolate reductase (DHFR) axis is another GPX4-independent mechanism to regulate the sensitivity of ferroptosis. Genome-wide CRISPR screening identified GCH1, the rate-limiting enzyme of BH4 biosynthesis, as an effective antagonist of ferroptosis via its downstream

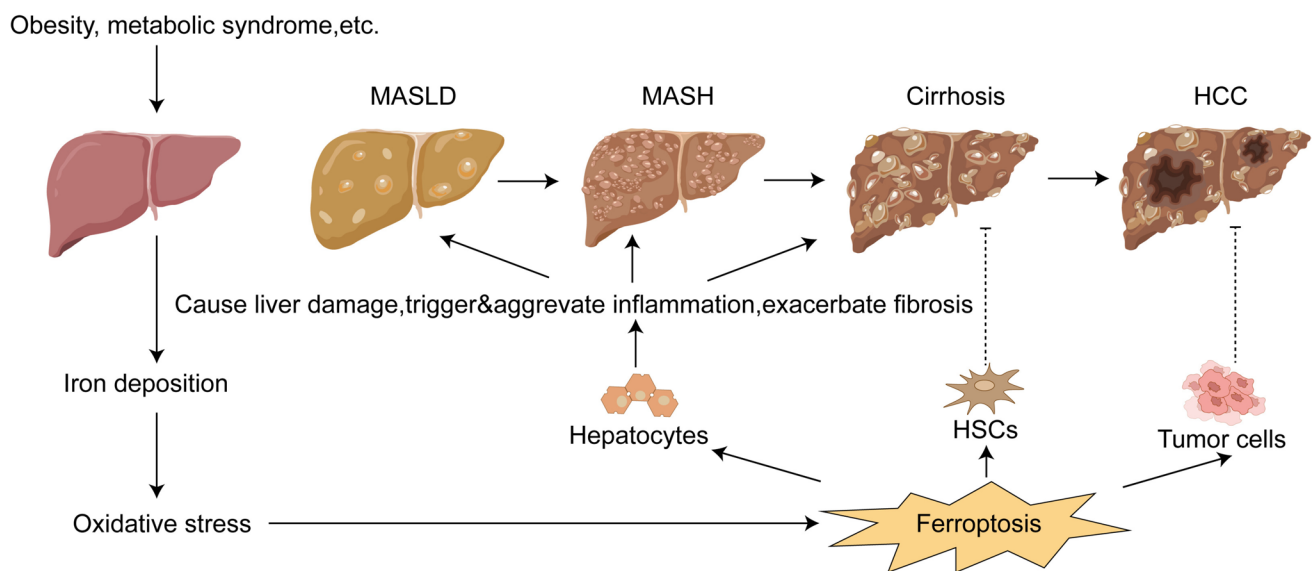


Fig. 2 The role of ferroptosis in MASLD/MASH and related liver diseases. Risk factors such as obesity and metabolic syndrome disrupt hepatic iron metabolism, leading to oxidative stress and ferroptosis. However, the role of ferroptosis varies depending on the cell type involved in the progression of MASLD/MASH and related liver diseases. Ferroptotic cell death in hepatocytes can cause liver damage, promote inflammation, and exacerbate fibrosis. In contrast, ferroptosis in HSCs inhibits their activation, thereby alleviating fibrosis. Furthermore, targeting ferroptosis in HCC cells has shown significant anti-tumor potential, offering a promising therapeutic strategy for advanced HCC patients. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HSC, hepatic stellate cell; HCC, hepatocellular carcinoma

metabolites BH4 [77, 78]. DHFR catalyzes the regeneration of BH4 from BH2, reinforcing this protective pathway [78]. As a potent radical-trapping antioxidant, BH4 produced by GCH1 can selectively protect the PUFA-PLs against peroxidation to resist ferroptosis and also serves as a critical regulator of CoQ10 synthesis [77]. Moreover, BH4 acts as a cofactor for several key enzymes involved in neurotransmitter synthesis, such as dopamine, which contributes to ferroptosis resistance [19, 79]. The relationship between this pathway and MASLD/MASH has not been explored yet. Given its role in lipid peroxidation resistance, future investigations could focus on this aspect.

Ferroptosis in MASH-related liver diseases

MASLD/MASH

MASLD is the most common cause of chronic liver disease. The spectrum of MASLD ranges from simple hepatic steatosis, steatohepatitis, cirrhosis, and even hepatocellular carcinoma. MASH is characterized by lipid droplet accumulation, inflammatory cell infiltration, hepatocellular injury, and fibrosis, representing a progression from simple steatosis. Given that MASH is a significant risk factor for cirrhosis and carcinoma, elucidating the mechanisms underlying its progression is crucial [80] (Fig. 2).

roptosis in HSCs inhibits their activation, thereby alleviating fibrosis. Furthermore, targeting ferroptosis in HCC cells has shown significant anti-tumor potential, offering a promising therapeutic strategy for advanced HCC patients. MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; HSC, hepatic stellate cell; HCC, hepatocellular carcinoma

In MASLD, hepatocytes take up FFAs and convert them into neutral triglycerides (TGs) for storage in lipid droplets. When FFA uptake exceeds the metabolic capacity of the liver, it leads to lipotoxicity, the central driver of the progression from simple steatosis to steatohepatitis. For one thing, the overload of saturated fatty acids (SFAs) will trigger ER stress and subsequently activate the unfolded protein reaction (UPR), which induces lipid metabolism reprogramming and promotes lipid peroxidation [81–83]. For another, the increased mitochondrial β -oxidation of FFA drives energy metabolism dysregulation, leading to mass mitochondrial ROS (mtROS) accumulation and mitochondrial dysfunction, which promotes lipid peroxidation, thereby inducing ferroptosis and contributing to MASH lesion formation [84, 85].

Under lipotoxicity, the lipid peroxidation products such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and the mitochondrial dysfunction products like mtRNA and ATP all behave as damage-associated molecular patterns (DAMPs). DAMPs are a series of potent pro-inflammatory mediators. Hepatic stellate cells (HSCs) can identify DAMPs and be activated, thereby promoting liver fibrogenesis [86]. Moreover, DAMPs will activate Kupffer cells to promote NF- κ B/NLRP3 signaling, amplifying the secretion of inflammatory cytokines to exacerbate inflammation [87, 88]. These interactions will further aggravate cell death and liver injury, establishing a vicious cycle. Despite that multiple

forms of cell death participate in this process, Tsurusaki et al. proved that hepatic ferroptosis, rather than necroptosis, triggers the initiation of inflammation in MASH [10]. Notably, Cui et al. identified hyperoxidized PRDX3 as a specific biomarker of ferroptosis and confirmed that hepatic damage in MASLD mice models is mediated by ferroptosis [89]. Our recent study found that the deficiency of FATP5, a long-chain fatty acid (LCFA) transporter that is specifically localized on the hepatocytes, reduces intrahepatic PUFA-lipids, thus leading to the activation of the SREBP1/SCD1 axis to promote MUFA biosynthesis, thereby ultimately suppressing ferroptosis and alleviating MASH [52]. As the key enzymes for fatty acids de novo synthesis, SREBP1 and SCD1 were previously identified as the risk genes for MASLD/MASH [90, 91]. However, under the context of FATP5 knockdown, the synthesis of MUFA mediated by SREBP1/SCD1 exhibited potent anti-inflammatory and anti-ferroptotic capacity in MASH [52]. Future study of MASLD/MASH should focus on the therapeutic modulation of lipotoxic lipids to modulate fatty acid homeostasis.

Furthermore, ferroptosis also participates in the aggravation of MASH. A recent study revealed that lipid peroxidation markers such as 4-HNE and MDA were elevated in MASH patients, and vitamin E effectively reduced these markers, thereby improving liver injury in MASH [80, 92]. Furthermore, several ferroptosis-related genes, including ACSL3, ACSL4, AKR1C2, and FADS2, were identified as closely associated with both the hepatic steatosis grade and MASLD activity score [93]. In experimental models, ferroptosis inhibitors such as Trolox, Liproxstatin 1 (Lip-1), and deferoxamine mesylate reduced MASH severity [10, 94]. Besides, Enolase 3 (ENO3) was shown to promote MASH progression by negatively regulating ferroptosis through elevated GPX4 expression and lipid accumulation in MCD-induced mice [95]. Similarly, ECH1 overexpression significantly alleviated hepatic steatosis, inflammation, fibrogenesis, apoptosis, and oxidative stress in MCD mice models by suppressing hepatic ferroptosis [96].

Taken together, these findings strongly implicated ferroptosis as a key player in MASLD/MASH pathogenesis, suggesting its potential as a therapeutic target for MASH. However, further studies are needed to elucidate the specific molecular mechanism by which ferroptosis contributes to MASH progression.

MASH-related liver fibrosis

Liver fibrosis, an intermediate stage of many chronic liver diseases including MASLD/MASH, is characterized by the excess deposition of extracellular matrix (ECM) and sustained by the activation of myofibroblasts (MFs). The activation of HSCs is a key event in this process [97].

Currently, liver transplantation is the only effective therapy for advanced fibrosis, but organ availability is limited. Therefore, there is an urgent need to identify new ways to interfere with liver fibrosis.

Recent studies have revealed that ferroptosis exerts double effects on fibrosis progression. On one hand, since HSC activation is central to fibrosis pathology, inducing ferroptosis in HSCs may have a protective effect. For example, in a mouse model, artesunate alleviates liver fibrosis by mediating HSCs' ferroptosis [98]. Similarly, simvastatin was shown to inhibit HSCs' activation by regulating the ferroptosis signaling pathway [99]. On the other hand, ferroptosis in hepatocytes, rather than HSCs, may exacerbate liver fibrosis. Some hepatocyte-specific anti-ferroptotic targets exhibited the potential to resist fibrosis. For example, Salvianolic acid B attenuates liver fibrosis by specifically targeting the upregulation of *Ecm1* in hepatocytes and inhibiting ferroptosis [100]. A recent study demonstrated that AGE receptor 1 (AGER1) deficiency triggers hepatocyte ferroptosis, driving fibrosis progression, and AAV-mediated AGER1 overexpression effectively relieved liver fibrosis in a murine model [101]. This finding suggests a potential strategy to selectively regulate ferroptosis.

Taken together, these findings indicate that inducing ferroptosis in HSCs will alleviate liver fibrosis, while in hepatocytes, it exacerbates the condition. Thereby, selectively triggering ferroptosis in HSCs while protecting hepatocytes from ferroptotic damage could offer a novel therapeutic approach for liver fibrosis.

MASH-related HCC

HCC, one of the leading causes of cancer-related death, is associated with viral hepatitis, MASH, and alcohol-related steatohepatitis [64]. The prevalence of MASH-related HCC (MASH-HCC) is increasing globally and is projected to become the leading cause of HCC in developed countries. The mechanism underlying MASH-HCC development remains incompletely understood, while emerging evidence indicates a bidirectional and complex relationship between ferroptosis and MASH-HCC.

For one thing, ferroptosis plays a critical role in accelerating the DNA mutations, thus inducing MASH-HCC. Both ROS and the lipid peroxidation products like MDA and 4-HNE generated from ferroptosis lead to hepatic DNA damage and mutations [84, 102]. For another, the mutations in numerous genes activate the cellular antioxidant programs, thereby conferring ferroptotic resistance to HCC cancer cells. Under sustained oxidative stress, the activation of key antioxidative Nrf2 signaling will upregulate anti-ferroptotic proteins and mediate iron deficiency, thus ultimately leading to tumorigenesis and

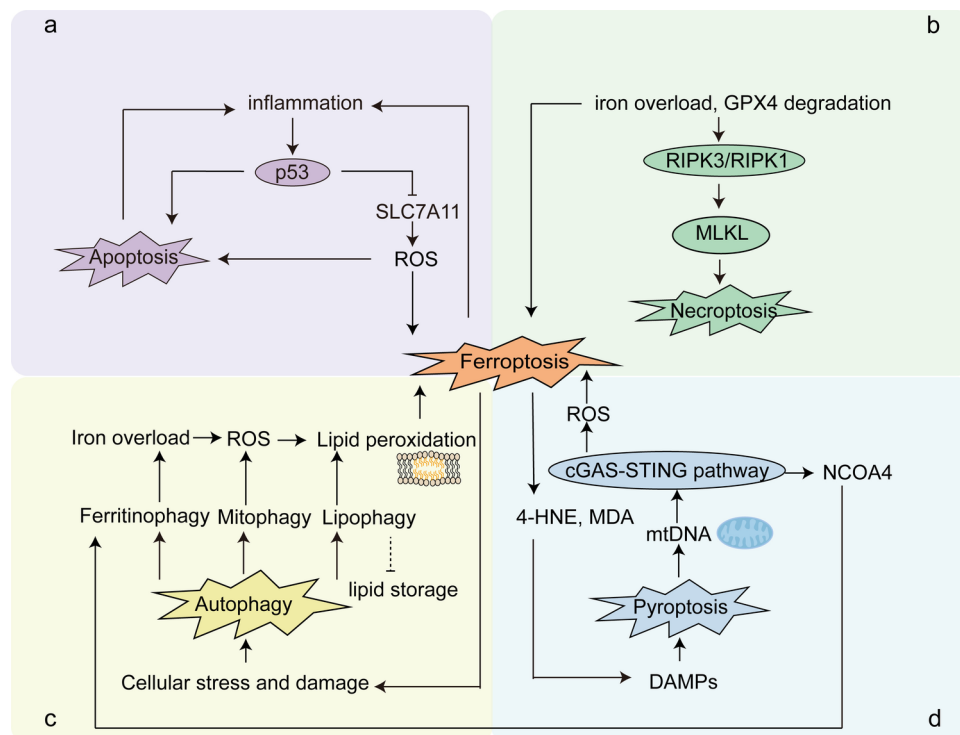


Fig. 3 Crosstalk between ferroptosis and apoptosis, necroptosis, autophagy, and pyroptosis in MASLD/MASH. (a) Apoptosis. The amplification loop of liver damage induced by the interplay between ferroptosis and apoptosis. (b) Necroptosis. Iron overload and GPX4 degradation can regulate both necroptosis and ferroptosis. (c) Autophagy. Dysregulated autophagy, including ferritinophagy, mitophagy, and lipophagy, mediates iron overload, ROS generation, and lipid peroxidation to induce ferroptosis in MASH/MASLD. (d)

Pyroptosis. The DAMPs generated from pyroptosis activate the cGAS-STING pathway to induce ferroptosis, which in turn generates more DAMPs. RIPK, receptor-interacting protein kinase; MLKL, mixed-lineage-like kinase; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; DAMP, damage-associated molecular pattern; mtDNA, mitochondrial DNA; NCOA4, nuclear receptor coactivator 4; ROS, reactive oxygen species

therapy resistance [103–105]. Therefore, some ferroptosis-related long non-coding RNAs (lncRNAs) were identified as novel risk-prognostic model for HCC [106].

Inducing ferroptosis in HCC has emerged as a promising therapeutic strategy to inhibit tumor proliferation and metastasis. Sorafenib, the first-line drug for HCC treatment, was demonstrated to exert its effect by trapping ferroptosis. Studies have revealed that sorafenib triggers ferroptosis by suppressing SLC7A11 or inhibiting hepatitis B X-interacting protein/stearoyl-CoA desaturase (HBXIP/SCD) to increase MDA production and GSH depletion, thereby killing HCC cells [107, 108]. Although inducing ferroptosis may prevent HCC progression, studies also uncovered that blocking ferroptosis can suppress hepatocarcinogenesis. A recent study found that ATF4 can suppress hepatocarcinogenesis by upregulating SLC7A11 to block ferroptosis. This suggests that activating ATF4 or inhibiting ferroptosis might blunt HCC onset in patients with benign MASLD/MASH [64].

Taken together, these findings highlight the complex role of ferroptosis in cancer biology: (i) ferroptosis accelerates DNA mutations to induce MASH-HCC, with its suppression

may be protective in tumorigenesis; (ii) while inducing ferroptosis can be therapeutic in tumor progression, the antioxidant mechanisms may reduce HCC susceptibility to ferroptosis and lead to therapy resistance. Therefore, further studies should focus on elucidating the distinct effects of ferroptosis during the onset and progression of HCC to develop precise anti-tumor therapy.

Crosstalk between ferroptosis and other cell deaths in MASH

Accumulating evidence has demonstrated that cell death plays a fundamental role in the pathogenesis from benign liver steatosis to advanced steatohepatitis. Therefore, understanding the crosstalk between ferroptosis and other forms of cell death is crucial for elucidating the pathogenesis of MASH and developing effective therapeutic strategies (Fig. 3).

Apoptosis

Apoptosis, a programmed cell death, is biochemically characterized by the activation of caspase. During apoptosis, cytoplasmic Ca^{2+} concentration and pH levels increase, and endonuclease is activated, leading to nuclear DNA fragmentation [109]. Apoptosis plays a significant role in MASH pathogenesis. The soluble cytokeratin-18 (CK-18) fragment, a caspase-cleaved molecule released from apoptotic hepatocytes, is identified as the most reliable single blood marker for the diagnosis of MASH, which is usually elevated in MASH patients and can predict disease presence [110, 111].

During MASLD/MASH progression, emerging evidence has revealed the pathogenetic interplay between apoptosis and ferroptosis. For one thing, the inflammation in MASLD upregulates the pro-apoptotic protein p53 while downregulating the anti-apoptotic protein Bcl-2 [112]. Notably, p53 was shown to repress SLC7A11 expression and promote cellular sensitivity to ferroptosis [113]. For another, ferroptosis-derived ROS products can disrupt mitochondrial membranes, activate caspase-9-dependent apoptosis, and amplify liver damage [114].

Necroptosis

Necroptosis, a receptor-interacting protein kinase (RIPK)-dependent programmed cell death mode, is recognized as an important role in cell development, inflammation, and disease. RIPK3 is a key regulator of necroptosis execution and an emerging metabolism regulator. Gautheron et al. demonstrated that RIPK3 deficiency leads to an obvious reduction in liver injury, inflammation, and fibrosis in the MCD-diet-induced MASH mice model, suggesting that necroptosis contributes to MASH pathogenesis [115]. Notably, RIPK3 overexpression does not necessarily indicate necroptosis execution [116]. Instead, increased circulating levels of RIPK1 and phosphorylated mixed-lineage-like kinase (p-MLKL), the terminal executor of the necroptosis signaling pathway downstream of RIPK3, were observed in MASLD patients' serum and correlated with ALT levels and histologic activity [117]. Taken together, these findings suggest that targeting RIPK3/RIPK1/MLKL represents a promising strategy for MASH treatment.

Previous studies have suggested that iron overload can activate the RIPK3/RIPK1/MLKL pathway to induce necroptosis by regulating redox balance [118]. Besides, chaperone-mediated autophagy (CMA) degrades GPX4 while upregulating RIPK3, compromising antioxidant defense and potentiating necroptotic signaling [119]. Although there is currently no evidence indicating that ferroptosis and necroptosis share distinct regulatory

pathways, these findings still suggest the existence of interactions between ferroptosis and necroptosis in MASH.

Autophagy-dependent cell death (ADCD)

Autophagy is a critical intracellular degradation mechanism that maintains cellular homeostasis. In the liver, autophagy regulates diverse metabolism pathways, removes damaged organelles, and protects hepatocytes from injury, thereby playing a key role in hepatic homeostasis. While dysregulated autophagy may lead to ADCD and exhibits a complex role in MASLD/MASH [120], for one thing, impaired autophagy leads to the accumulation of p62, a protein involved in the oxidative stress response of the liver [121]. Accordingly, restoring impaired autophagy flux might prevent the progression of MASLD [122]. For another, extensive evidence demonstrates that selective autophagy, which targets specific receptors, is closely linked to ferroptosis, the key driver of MASH inflammation [123].

The selective autophagy plays multiple roles during MASLD/MASH progression. First, hepatic lipophagy facilitated lipid droplets (LD) degradation for fueling β -oxidation to alleviate steatosis at the early stage of MASLD [124]. However, overwhelmed LD breakdown conversely offers abundant substrates for lipid peroxidation to induce autophagy-dependent ferroptosis [125]. Second, the NCOA4-mediated ferrotinophagy leads to an increase in intracellular ferrous ions and ROS generation, which subsequently triggers ferroptosis [29, 126, 127]. A recent study revealed that iron overload promotes the autophagic degradation of ferritin and lipid droplets via nuclear translocation of transcription factor EB (TREB), aggravating MASH pathology through ferroptosis [30]. Thirdly, mitophagy represents a selective autophagic process that degrades dysfunctional mitochondria and eliminates mitochondrial ROS (mtROS) to maintain cellular homeostasis [128]. Emerging evidence has demonstrated the impaired mitophagy as a feature of MASLD/MASH hepatocytes, leading to the accumulation of excessive mtROS and ultimately aggravating steatosis, lipid peroxidation, and inflammation [129, 130].

Beyond the autophagy subtypes mentioned above, other forms such as clockophagy and GPX4 degradation have been mechanistically linked to ferroptosis [123]. Future studies may focus on the crosstalk between selective autophagy and ferroptosis to further elucidate the pathogenesis of MASLD/MASH.

Pyroptosis

Pyroptosis, a programmed inflammatory cell death, is initiated by inflammasome and caspase activation, leading

to the cleavage of inflammatory cytokines and gasdermins and subsequent pore formation on the cell membrane.

Pyroptosis is regulated through canonical and non-canonical pathways. In the canonical pathway, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), or ATP activate the NLRP3 and AIM2 inflammasomes via the NF- κ B pathway, leading to caspase-1 maturation. This promotes the release of pro-inflammatory cytokines (IL-1 β and IL-18) and gasdermin D (GSDMD) cleavage, triggering an inflammatory response and pyroptosis, which contribute to the progression of MASH [131, 132]. In the non-canonical pathway, human caspase-4/5 or mouse caspase-11 is activated by intracellular bacteria lipopolysaccharide (LPS) to cleave GSDMD. This pathway was also proven to aggravate MASH [133].

During pyroptosis, the impaired mitochondria will generate excessive mtDNA and mtROS. As a typical DAMP, the mtDNA can subsequently activate the cGAS-STING pathway [134]. Intriguingly, the activation of cGAS-STING signaling was demonstrated to upregulate NCOA4, thereby activating ferritinophagy and inducing ferroptosis [135]. In addition, the ROS generated from the cGAS-STING pathway will also lead to ferroptosis and apoptosis [136]. While DAMPs from ferroptotic cells, such as 4-HNE and MDA, will in turn aggravate pyroptosis. In MASH, the crosstalk between pyroptosis and ferroptosis may establish a positive feedback loop to exacerbate inflammation and liver injury.

Potential clinical applications by targeting ferroptosis in MASH

Although targeting ferroptosis has not yet been incorporated into clinical practice for the diagnosis or treatment of MASH, it remains an active and promising area of investigation. Numerous ferroptosis-related biomarkers and therapeutic agents are currently under preclinical evaluation. Given the instrumental role of ferroptosis in the initiation and progression of MASH, targeting this pathway may offer novel opportunities to improve the management and outcomes of MASH patients.

Utilizing ferroptosis-related biomarkers in MASLD/MASH diagnosis

The current diagnosis of MASH has several limitations. For one thing, the invasive histological assessment carries the risk of serious complications, coupled with substantial interpretative variability and limited reliability [137, 138]. For another, while non-invasive imaging can detect steatosis and fibrosis, it lacks sensitivity in identifying inflammation and disease activity of MASH [139, 140]. Emerging studies suggest that ferroptosis-related biomarkers may assist in the

diagnosis and the assessment of drug efficacy of MASLD/MASH.

Previous studies have demonstrated that MASLD patients with hyperferritinemia and iron overload are associated with a higher risk for MASH [141, 142]. At present, the serum ferritin level is identified as a predictive biomarker for long-term outcomes and iron chelator-targeted MASH therapy [14, 143]. In addition, the serum lipid peroxidation products may also reflect the hepatic oxidative stress [144]. A recent study suggested that the plasma levels of free PUFA and oxylipins characterized different stages of MASLD/MASH [145]. Moreover, the immunohistochemical detection of 4-HNE is validated in MASLD patients, while its circulating level is not hepatic-specific but reflects the systemic redox states [146, 147]. To solve this problem, recent clinical trials and analysis indicated that vitamin E supplementation reduces liver redox biomarkers; thus, the combination of vitamin E supplementation and serum 4-HNE detection may serve as a valuable tool for monitoring MASLD/MASH pathological progress [148, 149].

Suppressing ferroptosis in MASLD/MASH treatment

Targeting ferroptosis represents a potential method to alleviate MASLD/MASH progression (Table 1). Several iron chelators have been demonstrated as potential drugs to suppress ferroptosis and treat MASH. Deferoxamine (DFO), an FDA-approved iron chelator, inhibits ferroptosis by binding Fe³⁺ and treating iron overload. However, DFO's poor oral bioavailability and rapid clearance limit its clinical application, highlighting the need for more stable delivery methods [94, 165]. Strikingly, compared to traditional iron chelators, FerroTerminator1 (FOT1) demonstrates superior liver-specific accumulation and is more efficacious for MASH, thereby minimizing its impact on iron metabolism in other organs. Long-term administration potentially alleviates severe MASH by blocking iron accumulation and suppressing ACSL4-induced ferroptosis [14]. To enhance safety and efficacy, further development of iron chelators should focus on (i) developing liver-targeted delivery systems and (ii) stratifying patients based on biomarkers such as serum ferritin.

Some marketed drugs are also proven to modulate lipid peroxidation, suppress ferroptosis, and alleviate MASH. Firstly, vitamin E has been shown to bolster the anti-ferroptotic capability in cooperation with GPX4 [150]. As a fatty-soluble antioxidant, the combination activity of vitamin E and hepatocellular membrane scavenges free radicals and prevents the peroxidation of PUFA-PLs [151, 152]. A clinical trial revealed that vitamin E therapy exerts a significantly higher rate of improvement in MASH patients compared to placebo treatment (43% vs. 19%, $P = 0.001$) [80]. However,

Table 1 Potential compounds/drugs that impede ferroptosis in MASLD/MASH

Compounds/drugs	Target	Mechanism	Reference(s)
DFO	Iron overload	Binds free iron and then inhibits iron overload	[94]
FOT1	Iron overload	Blocks iron accumulation and suppresses ACSL4-induced lipid peroxidation	[14]
Vitamin E	Free radicals	Scavenges free radicals to inhibit lipid peroxidation	[80, 150–152]
OCA	FXR	Activates FXR to upregulate ferroptosis gatekeepers, including GPX4, PPAR α , ACLS3, FSP1, and SCD1	[153, 154]
Fenofibrate	PPAR- α	Promotes β -oxidation, prevents lipid peroxidation, and alleviates iron overload	[155, 156]
Bezafibrate	PPAR- γ	Targets Nrf2 signaling to prevent lipid peroxidation	[80, 157, 158]
Rosiglitazone			
Pioglitazone			
Lanifibranor	Pan-PPAR	Activates PPAR- α , PPAR- γ , and PPAR- δ	[159, 160]
GB	Nrf2 pathway	Improves the tolerance to ferroptosis through up-regulating the expression of GPX4 and HO-1 by activating the Nrf2 pathway	[161]
DA	Nrf2 pathway	Binds with Keap1, activates the Nrf2-ARE signaling pathway, and induces its downstream target genes to inhibit ferroptosis	[162]
IMA-1	ALOX12	Binds to a pocket in ALOX12 to prevent ALOX12-ACC1 interaction, thereby inhibiting lipid peroxidation	[163]
Icariin	Nrf2 pathway	Activates Nrf2, then suppresses ferroptosis through Nrf2-xCT/GPX4 signaling pathway	[164]

vitamin E is currently only considered a second-line therapy for MASH due to its limited efficacy in reversing fibrosis and its restriction to use in non-diabetic patients [166, 167]. Secondly, a typical farnesoid-X-receptor (FXR) agonist, obeticholic acid (OCA), which was initially designed for primary biliary cholangitis (PBC), has shown its antifibrotic effect on patients with pre-cirrhotic liver due to MASH [153]. One of the possible mechanisms is the activation of FXR significantly reducing lipid peroxidation by upregulating ferroptosis defenders such as GPX4, peroxisome proliferator-activated receptor- α (PPAR- α), ACLS3, FSP1, and SCD1 [154]. Unfortunately, the FDA committee opposed OCA as the first MASH drug due to its side effects in 2023. Nevertheless, OCA still offers us a novel perspective on FXR-dependent MASH therapy. Thirdly, PPARs are a family of nuclear transcription factors that regulate the expression of genes involved in metabolic processes and inflammation. Activation of PPAR- α promotes hepatic lipid β -oxidation, reduces lipid accumulation and peroxidation, and alleviates iron overload-induced ferroptosis [155, 156]. PPAR agonists effectively address the key limitation of vitamin E by being suitable for diabetic patients. PPAR- α agonists fenofibrate and bezafibrate, drugs for hyperglyceridemia, have been shown to lower ALT, AST, and γ TG and reduce hepatocyte ballooning or steatosis in MASH patients, while their effects on inflammation or fibrosis remain limited [168, 169]. Type 2 diabetes (T2D) drugs, PPAR- γ agonists, were shown to alleviate ferroptosis by regulating Nrf2 to modulate lipid oxidation [157]. In a randomized controlled trial, the 48-week therapy of rosiglitazone in MASH patients exerted an obvious improvement on liver steatosis, inflammation, ballooning, and fibrosis [158]. Since MASH is closely related to lipid metabolism disorders and insulin resistance,

pan-PPAR agonists like lanifibranor are becoming a promising method for MASH treatment [159, 160].

Several compounds have also shown promise by targeting ferroptosis in preclinical MASH investigations. For instance, Ginkgolide B (GB) activates the NRF2 signaling pathway to scavenge radicals and reduce lipid accumulation, thereby suppressing ferroptosis and potentially treating MASLD [161]. Similarly, dehydroabietic acid (DA) binds Keap1 to activate the Nrf2-ARE pathway, inducing target gene expression and inhibiting ROS accumulation and lipid peroxidation, thus preventing ferroptosis in high-fat diet (HFD)-induced MASLD [162]. Moreover, small molecules like IMA-1 have been shown to ameliorate MASH by disrupting the ALOX12-ACC1 interaction [163]. Another promising compound, icariin, attenuates MASH by suppressing ferroptosis through the Nrf2-xCT/GPX4 pathway [164]. However, most preclinical studies on these compounds rely on intraperitoneal injection or intragastric gavage, whereas their efficacy via oral administration remains elusive [170]. Although these compounds demonstrate promising anti-ferroptotic and MASH-attenuating effects in animal models, their translation into clinical applications faces substantial challenges.

Conclusions and perspectives

Previous studies have highlighted the critical role of ferroptosis in MASH pathogenesis and its potential as a therapeutic target. Here, we emphasized some promising directions: (i) In the clinical domain, since MASH always occurred with metabolic syndromes such as T2DM and obesity, exploring the therapeutic effects of T2DM

medications, including PPAR agonists and GLP-1 receptor agonists, on MASH via ferroptosis regulation has also emerged as a research hotspot. (ii) in fundamental research, given that dysregulated lipid metabolism and ferroptosis are established hallmarks of MASH, investigating how lipotoxicity of lipids in varying saturation degrees contributes to MASH progression by modulating ferroptosis represents a highly promising direction.

Moreover, based on current progress and gaps in this field, we would like to discuss some speculative issues that need to be tackled in follow-up research. Firstly, although researchers have made great headway in ferroptosis in the pathological progression of MASH, it is still unclear what the physiological role of ferroptosis is in the liver. This knowledge gap thwarts the assessment of the side effects of the ferroptosis inhibitors. Secondly, ferroptosis appears to exert different effects depending on the pathological stage and cell type. As mentioned above, ferroptosis contributes to liver steatosis and triggers inflammation during the early stages of MASH, while in MASH-related cirrhosis, it has dual effects: ferroptotic cell death in hepatocytes exacerbates liver injury, whereas in hepatic stellate cells (HSCs), it attenuates fibrosis. Besides, the DAMPs released from ferroptotic cells will activate Kupffer cells to exacerbate inflammation, ultimately establishing a vicious cycle. Therefore, future research should determine the optimal timing and cell types for targeting ferroptosis. Lastly, different types of cell deaths often share similar upstream stress responses, initial signals, and molecular regulators. For example, the suppression of ferroptosis may cause cells to engage in other lethal subroutines, and the inhibition of apoptosis in MASH may shift cells to more inflammatory forms of cell death [19, 171]. Therefore, it is urgent to define the interaction and conversion between ferroptosis and other cell death pathways to develop effective therapeutic strategies.

Abbreviations *MASLD*: Metabolic dysfunction-associated steatotic liver disease; *MASH*: Metabolic dysfunction-associated steatohepatitis; *HCC*: Hepatocellular carcinoma; *GSH*: Glutathione; *GPX4*: Glutathione peroxidase 4; *FSP1*: Ferroptosis suppressor protein 1; *CoQ*: Coenzyme Q; *GCH1*: GTP cyclohydrolase 1; *BH4*: Tetrahydrobiopterin; *DHFR*: Dihydrofolate reductase; *ROS*: Reactive oxygen species; *LOX*: Lipoxygenase; *POR*: Cytochrome P450 oxidoreductase; *TfR1*: Transferrin receptor 1; *SLC*: Solute carrier family; *NTBI*: Non-transferrin bound iron; *MVB*: Multivesicular bodies; *ATG5*: Autophagy-related 5; *NCOA4*: Nuclear receptor coactivator 4; *CISD1*: CDGSH iron sulfur domain 1; *PCBP1*: Poly(rC)-binding protein 1; *HO-1*: Heme oxygenase-1; *PUFA*: Polyunsaturated fatty acid; *ACSL*: Acyl-CoA synthetase long-chain family member; *LPCAT3*: Lysophosphatidylcholine acyltransferase 3; *PL*: Phospholipids; *CYB5R1*: NADH-cytochrome b5 reductase; *NOX4*: NADPH oxidase 4; *MUFA*: Monounsaturated fatty acid; *FATP*: Fatty acid transport protein; *SCD1*: Stearoyl-CoA desaturase 1; *ACC*: Acetyl-CoA carboxylase; *AMPK*: Adenosine-monophosphate-activated protein kinase; *ER*: Endoplasmic reticulum; *GCN2*: General control nonderepressible 2; *eIF2 α* : Phosphorylate eukaryotic

initiation factor 2 α ; *ISR*: Integrated stress response; *ATF4*: Activating transcription factor 4; *CTNS*: Cystinosis; *AIFM2*: Apoptosis-inducing factor mitochondria-associated 2; *ESCRT*: Endosomal sorting complexes required for transport; *DHODH*: Dihydroorotate dehydrogenase; *PRDX3*: Peroxiredoxin 3; *mt DNA*: Mitochondrial DNA; *MCD*: Methionine-choline deficient diet; *4-HNE*: 4-Hydroxynonenal; *EMC*: Extracellular matrix; *MF*: Myofibroblast; *HSC*: Hepatic stellate cell; *Fer-1*: Ferrostatin-1; *AGER1*: AGE receptor 1; *HBXIP*: Hepatitis B X-interacting protein/stearoyl-CoA desaturase; *MDA*: Malondialdehyde; *CK-18*: Cytokeratin-18; *RIPK*: Receptor-interacting protein kinase; *p-MLKL*: Protein mixed-lineage-like kinase; *TREB*: Transcription factor EB; *GSDMD*: Gasdermin D; *NF- κ B*: Nuclear factor- κ B; *PAMP*: Pathogen-associated molecular patterns; *DAMP*: Damage-associated molecular patterns; *NLRP3*: NOD-like receptor protein 3; *AIM2*: Absent in melanoma 2; *Lip-1*: Liprostatin-1; *DFO*: Deferoxamine; *GB*: Ginkgolide B; *DA*: Dehydroabietic acid; *PPAR*: Peroxisome proliferator-activated receptor; *FOT1*: FerroTerminator1; *FXR*: Farnesoid X receptor; *OCA*: Obeticholic acid

Author contribution Yiran Liu and Suhong Xia designed the primary concept. Yiran Liu wrote the initial manuscript. Mingyu Zhang and Yiran Liu designed and prepared the figures and table. Mingyu Zhang, Yujie Huang, and Yu Zhang polished the language. Jialun Guan and Chen Zhu searched and collected related articles. Jiazhi Liao and Suhong Xia edited the primary manuscript and provided funding and overall supervision. All authors reviewed the manuscript.

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Declarations

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