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REVIEW

Ferroptosis in liver fibrosis and its potential intervention strategy

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Abstract Liver fibrosis, a common manifestation in numerous hepatic diseases, is critical in the progression from mild injury to cirrhosis and ultimately to hepatocellular carcinoma. To date, there are no effective pharmacological therapies for liver fibrosis. Ferroptosis is a type of programmed cell death characterized by alterations in redox lipid metabolism and is associated with the pathological conditions in liver fibrosis. The induction of ferroptosis is considered a novel way to kill hepatic stellate cells (HSCs). However, some studies in recent years challenge the existing paradigm. In addition to promoting HSC death, ferroptosis sets in motion the activation of profibrogenic HSCs and causes the death of hepatocytes and immune cells. In this review, we discuss the dual role of ferroptosis in promoting and inhibiting fibrosis in the liver, and the ferroptosis-related mechanisms underlying liver fibrosis of distinct etiologies. Despite significant progress in understanding ferroptosis's pathological roles in liver fibrosis, we highlight several critical questions that need to be addressed for strategies based on ferroptosis-targeted therapies, taking into account its ambiguous role in liver fibrosis.

Keywords Liver fibrosis · Ferroptosis · Cell-specific ferroptosis · Hepatic stellate cells

Abbreviations

α-SMA	Alpha smooth muscle actin
AGER1	Advanced glycation endproduct receptor 1

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CCL4	Carbon tetrachloride
CCL2	Chemokine ligand 2
CCL7	Chemokine ligand 7
cGAS	Cyclic GMP-AMP synthase
DHODH	Dihydroorotate dehydrogenase
ECM	Extracellular matrix
FPN	Ferroportin
GSH	Glutathione
GSSG	Oxidized glutathione disulfide
GPX4	Glutathione peroxidase 4
HSC	Hepatic stellate cell
HBV	Hepatitis B virus
IL-6	Interleukin 6
IL-1β	Interleukin 1 beta
KC	Kupffer cells
LIP	Labile iron pool
MF	Myofibroblast
NCOA4	Nuclear receptor coactivator 4
PUFA	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SLC3A2	Solute carrier family 3 member 2
SLC7A11	Solute carrier family 7 member 11
SiNPs	Silica nanoparticles
TAK1	Transforming growth factor-beta- activated kinase 1
TGF-β	Transforming growth factor beta
TNF-α	Tumor Necrosis Factor Alpha
TFRC	Transferrin receptor
TUG1	Taurine upregulated 1

Introduction

Liver disease represents a significant contributor to deaths worldwide, primarily due to viral hepatitis infections, obesity, alcohol, drugs, and autoimmunity (Asrani et al. 2019). Hepatic fibrosis, a universal feature of chronic liver injury, plays a pivotal role in the progression from early liver injury to cirrhosis and ultimately to hepatocellular carcinoma (Friedman 2010). The hallmark of liver fibrosis is the activation of hepatic stellate cells (HSCs) and the overproduction of extracellular matrix (ECM) components. This evolving phenomenon is shaped by various fibrogenic mediators, such as cytokines, chemokines, growth factors, and reactive oxygen species (ROS) (Che et al. 2023). The strategies for inhibiting hepatic fibrosis encompass safeguarding liver vasculature, preventing the activation of HSCs, and modulating extracellular matrix evolution and immune responses (Fang et al. 2022; Hammoutene and Rautou 2019; Lin et al. 2022). Despite significant progress in understanding the mechanisms of liver fibrosis and developing therapies by pharmaceutical industries, there are still no FDA-approved pharmacotherapies targeting liver fibrosis (Lin et al. 2022). Exploring safe and effective high-value hepatic fibrosis treatment strategies is imperative.

The liver serves as the central regulator of systemic iron homeostasis and is the primary source of hepcidin. Extracellular iron bound to transferrin is recognized by transferrin receptor 1 (TfR1) on hepatocytes and internalized via endocytosis. Following internalization, iron is released into the labile iron pool (LIP) within the hepatocyte or stored in ferritin. When iron is required, ferritin is degraded through nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy to release iron. Excess Fe^{2+} can be exported into the circulation via the ferroportin (FPN). Cellular iron metabolism is precisely regulated by iron regulatory proteins (IRP1 and IRP2) in conjunction with iron-responsive elements (IREs). Furthermore, the hepcidin-FPN axis constitutes a critical systemic regulatory mechanism for maintaining iron homeostasis (Camaschella et al. 2020; Pan et al. 2021).

Clinically, it has been observed that four pivotal biomarkers of hepatic fibrosis demonstrate inverse correlations with transferrin receptor (TRFC) levels (Hamill et al. 1991). Described as a glycoprotein embedded in the membrane, the TRFC primarily facilitates iron absorption into cells (Ponka and Lok 1999). Nevertheless, the correlation of low transferrin receptor (TRF) levels with poor outcomes may likely result from worsening disease. Liver biopsy samples from patients with congenital atransferrinemia are frequently characterized by hepatic iron deposition and signs of liver fibrosis (Bruns et al. 2017). This implies that fibrosis induced by ferroptosis, a form of cell death due to iron accumulation, could be a contributing factor in the development of hepatic disease. Actually, accumulating evidence suggests that ferroptosis plays a significant role in the pathogenesis of liver diseases, especially hepatic fibrosis (Chen et al. 2022; Gao et al. 2023; Pan et al. 2021).

In 2012, Dixon et al. first proposed the concept of ferroptosis, a distinct cell death modality marked by iron overload and antioxidant system disruption, which triggers massive lipid peroxide accumulation

and consequent cell membrane rupture (Dixon et al. 2012). The pathological mechanism of ferroptosis in the liver is primarily associated with dysfunction of system Xc−, dysregulated iron metabolism, and abnormal lipid metabolism. Elevated intracellular iron promotes the Fenton reaction, catalyzing the peroxidation of polyunsaturated fatty acids (PUFAs) within cellular membranes, a phenomenon known as lipid peroxidation. Consequently, antioxidant defenses are compromised, reactive oxygen species (ROS) accumulate, and cellular redox homeostasis is disrupted. These changes ultimately lead to hepatocyte death and serve as a significant role in the pathogenesis of liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), alcoholic liver disease (ALD), and hepatocellular carcinoma (Chen et al. 2022; He et al. 2025).

Increasing evidence suggests that ferroptosis plays a crucial role in the development of liver fibrosis. For example, the excessive accumulation of iron, crucial for the function of proline hydroxylase in the production of collagen, could potentially decrease the breakdown of collagen due to reduced collagenase activity (Zheng et al. 2022). However, while elevated iron levels in cells are linked to the activation of HSC, this increase also seems to heighten susceptibility to ferroptosis (Tang et al. 2023).

This review aims to synthesize current knowledge and the significance of ferroptosis in molecular events or alterations associated with liver fibrosis. We summarize the published studies to present evidence regarding the functions and management of ferroptosis in liver fibrosis in various pathophysiological contexts, particularly in hepatocytes, HSCs, and hepatic macrophages. We also review ferroptosis in various types of liver diseases, including viral hepatitis and steatotic liver diseases. While the induction of ferroptosis in HSCs is beneficial, it can also exert detrimental effects on hepatocytes and macrophages, potentially contributing to the activation of HSCs.

Cell-specific ferroptosis in liver fibrosis

Ferroptosis likely exhibits a dual role in liver fibrosis. During hepatic fibrosis, various cell types are involved in liver pathogenic alterations, encompassing the apoptosis and necrosis of hepatocytes, the infiltration of inflammatory cells, and the activation of HSCs (Tomita et al. 2014). On the other hand, various stresses lead to the ferroptosis of hepatocytes; ferroptotic hepatocytes can activate HSCs directly or be activated after being mediated by macrophages. Conversely, the inhibition of ferroptosis in activated HSCs may also aggravate liver fibrosis (Fig. 1).

Hepatocytes

Hepatocytes, the predominant liver cells, control the intermediate metabolic processes, neutralize endogenous and exogenous toxins, produce essential proteins for circulation, and initiate the production of bile flow (Malhi et al. 2010). Studies have demonstrated that hepatocyte injury is a crucial element in promoting the formation of liver fibrous scar tissue (Kisseleva and Brenner 2021). Hepatocyte apoptosis and necrosis play an important role in contributing to the pathogenesis of liver disease, while recent studies showed that hepatocyte ferroptosis is also closely associated with liver inflammation and fibrosis (Cho et al. 2022; Liang et al. 2023; Su et al. 2023). Ferroptotic hepatocytes act as the primary catalysts for liver fibrosis, initiating the excessive secretion of ROS and attractant cytokines, releasing damage-associated molecular patterns (DAMPs), inducing inflammatory cells to recruit leukocytes, activating HSCs, secreting ECM, and setting off the sequential process of inflammation and fibrotic development (Huang et al. 2022; Zou et al. 2018). Monitoring the progress of liver fibrosis through the early prevention of hepatocyte ferroptosis presents a sensible foundation for designing therapeutic approaches. It has been proposed that the fibrogenic impact caused by HSC, which is induced by hepatocyte death, is counterbalanced by a fibrosis-mitigating effect due to the death of HSCs (Mehal and Imaeda 2010) (Fig. 1). One study confirmed that long-term Silica nanoparticles (SiNPs) exposure can trigger ferritinophagy-cascaded ferroptosis in hepatocytes, subsequently leading to liver fibrosis (Liang et al. 2023).

In addition, ferroptosis-mediated hepatic fibrogenesis may result from crosstalk between hepatocytes, macrophages, and HSCs. Ferroptotic hepatocytes induce macrophage infiltration; particularly, Kupffer cells (KCs) secrete abundant pro-inflammatory and pro-fibrogenic mediators like TGF-β, thereby driving the activation of HSCs (Hernandez-Gea and Friedman 2011). Research shows that TAK1 deficiency in

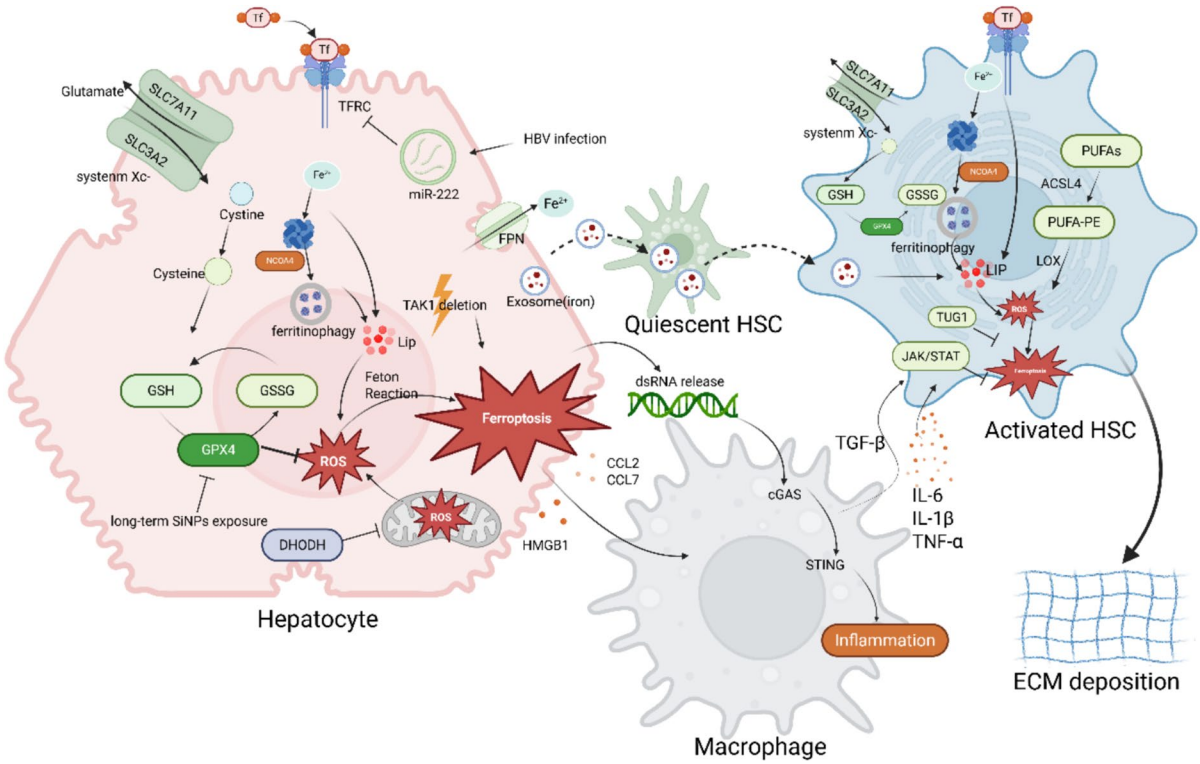

Fig. 1 Mechanisms of ferroptosis in liver fibrotic microenvironments and its function as a key mediator in intercellular communication among hepatic cells during fibrosis initiation and progression. Under pathological conditions in liver diseases, ferroptosis exhibits a dual role in liver fibrosis. Ferroptosis in hepatocytes under various stressors activates hepatic HSCs, prompting their transdifferentiation into myofibroblasts (MFs). Meanwhile, liver injury at the hepatic lobule induces the activation of resident KCs, which is also a significant way to induce the activation of HSCs. MFs represent the key cell population responsible for the majority of ECM collagen production and secretion. Created with BioRender

hepatocytes induces ferroptosis. The resulting oxidative DNA damage acts as a key signal that activates the cGAS-STING pathway in macrophages, which in turn drives the development of liver injury, fibrosis, and tumorigenesis (Su et al. 2023). On the other hand, hepatocytes play a key role in controlling iron metabolism and can also secrete exosomes containing iron that can be absorbed by HSCs, resulting in HSC activation (Gao et al. 2022). Additionally, intercellular communication can be promoted via the release of exosomes containing aberrant miRNAs from ferroptotic hepatocytes (Wu et al. 2024) (Fig. 1).

Macrophages and Kupffer cells

The complex interplay between the ferroptosis of liver parenchymal cells and inflammation driven by macrophages plays a vital role in the progression of liver fibrosis (Gao et al. 2022; Su et al. 2023). When hepatocytes undergo ferroptosis, they release damage-associated molecular patterns (DAMPs), including signaling molecules such as MCP-1, CCL2, CCL17, and HMGB1. The released HMGB1 can interact with the receptor for advanced glycation end products (RAGE/AGER) on macrophages, promoting their recruitment and activation (Jiang et al. 2025; Wen et al. 2019; Yang et al. 2022). Evidence from co-culture studies indicates that ferroptotic cells potently induce M1 macrophage polarization, resulting in the secretion of pro-inflammatory mediators, including IL-6, iNOS, and TNF-α (Yang et al. 2022). Cytokines such as IL-6 and TNF-α bind to their respective receptors, thereby inducing the activation of the JAK-STAT pathway. Phosphorylated STAT3 upregulates the expression of hepcidin, which in turn inhibits iron export, consequently promoting ferroptosis. Furthermore, activated STAT1 exerts a

pro-ferroptotic effect by suppressing the system Xc- and modulating IRF1 (Chen et al. 2023).

Liver macrophages are classified into two primary categories: liver-resident macrophages, also known as Kupffer cells, which originate from the yolk sac; and myeloid-derived macrophages, which develop in the bone marrow and subsequently migrate to the liver (Tacke 2017). Specifically, macrophages activated by ferroptotic cells exhibit a dual function in this process.

Activated Kupffer cells phagocytize dead red blood cells, resulting in iron deposition in the liver (Mehta et al. 2019). In a NASH model driven by a high-fat diet, Kupffer cells laden with iron, exhibiting a pro-inflammatory nature, stimulate MiT/TFE transcription factors, promoting NASH-related liver fibrosis (Kanamori et al. 2021). Another study shows that elevated secretion of iron-containing extracellular vesicles (EVs) causes hepatocyte iron deficiency; meanwhile, the reduced population of Kupffer cells in nonalcoholic steatohepatitis (NASH) livers results in HSCs absorbing an excessive amount of these hepatocyte EVs, causing an accumulation of iron, an increase in ROS, and a tendency towards a fibrosis-promoting state in HSCs. Conversely, depleting iron cargos from hepatocyte EVs mitigates these adverse effects (Gao et al. 2022). Iron overload also disrupts the M1/M2 macrophage polarization balance, induces a transition to the M1 phenotype, and leads to inflammation and fibrogenesis in high-fat diet mice (Handa et al. 2019).

In contrast, Kupffer cells can also phagocytize ferroptotic hepatocytes, mitigate inflammatory responses, and play a role in recruiting and activating monocyte-derived macrophages (MDMs) and natural killer cells to induce apoptosis in activated HSCs (Feng et al. 2018). Kupffer cells are instrumental in preventing the transfer of iron from hepatocytes to HSCs by clearing hepatocyte EVs, a vital process in maintaining the microenvironmental iron homeostasis in the liver. However, a marked reduction in Kupffer cell population is observed in MASLD/NASH conditions, both in humans and mice. Transcriptomic analyses reveal that the MASLD/NASH liver environment impairs Kupffer cell functions, including iron recycling and phagocytosis capabilities (Gao et al. 2022) (Fig. 1).

Furthermore, ferroptosis can promote macrophage polarization by perturbing iron metabolism or other metabolic reprogramming pathways within macrophages. Studies have demonstrated that iron overload elevates the levels of M1 macrophage markers, such as IL-6, TNF-α, and IL-1β, thereby inducing M1 polarization (Handa et al. 2019). In addition to inducing inflammatory factors, iron overload has also been found to promote the M1 phenotype by enhancing glycolysis in macrophages, thereby exacerbating the development of atherosclerosis (Hu et al. 2019). Furthermore, ROS accumulation driven by iron overload can also promote macrophage polarization toward the M1 subtype via the induction of p53 acetylation (Zhou et al. 2018). It has been found that iron overload exerts a stage-dependent, biphasic regulatory role on M2 macrophage polarization during liver fibrogenesis: it promotes M2 polarization in the initial phases, whereas it transitions to a suppressive role as the disease advances to middle and late stages (Yu et al. 2025).

Hepatic stellate cells (HSCs)

Residing in the space of Disse, HSCs are critical for the progression of liver fibrosis.. The transformation of these cells into actively dividing, myofibroblasts that promote fibrosis is a well-recognized and critical driver in the advancement of hepatic fibrosis (Tsuchida and Friedman 2017). Inducing ferroptosis in HSCs is gaining recognition as a potent treatment approach for liver fibrosis (Pan et al. 2021; Zhou et al. 2022). Nevertheless, the overall impact of ferroptosis on liver fibrosis, whether beneficial or detrimental, necessitates further exploration.

Previous studies have demonstrated that clearing activated HSCs by inducing ferroptosis effectively eliminates activated HSCs, a key strategy in combating hepatic fibrosis (Wang et al. 2019; Zhang et al. 2020, 2018). Caveolin-1 (Cav-1), a vital membrane protein, has been recognized as a vital controller in a range of liver-related disorders, including fibrosis (Gvaramia et al. 2013; Jiang et al. 2021). Recent research indicates that Cav-1 overexpression can trigger activated HSC ferroptosis and reduction of extracellular matrix (ECM) components, suggesting a protective role in liver fibrosis. Concurrently, increased alanine serine cysteine transporter 2 protein expression and Taurine up-regulated gene 1 (TUG1) expression have been observed in an advanced liver fibrosis study, contributing to disease progression by inhibiting HSC ferroptosis (Zhang et al. 2023b). Modulating autophagy pathways to trigger HSC ferroptosis has also shown promise in alleviating liver fibrosis (Zhang et al. 2020, 2018).

Conversely, there is evidence that ferroptosis induction may paradoxically promote HSC activation. While higher intracellular iron levels increase HSC susceptibility to ferroptosis, they also appear to facilitate HSC activation (Auguet et al. 2017). Ferroptotic hepatocytes can activate HSCs, which mediates the development of liver fibrosis (Hernandez-Gea and Friedman 2011). Another study indicated that ferroptosis could facilitate the induction of fibrogenesis-related genes, reinforcing its functional role during fibrotic progression. It was observed that the fibrogenic effects driven by ferroptosis rely on the activation of the AP-1 pathway, as opposed to the Smad signaling route (Cho et al. 2022). Furthermore, while extensive studies have affirmed the anti-fibrotic role of autophagy by promoting HSC ferroptosis, the potential pro-fibrotic properties of autophagy in liver fibrosis should not be overlooked (Hernandez-Gea and Friedman 2012; Li et al. 2018; Zhang et al. 2020).

In summary, the role of ferroptosis in HSCs within the context of liver fibrosis is complex and not fully understood. The determination of whether ferroptosis is beneficial or detrimental to HSCs necessitates further research. These findings highlight the complex characteristics of ferroptosis in liver fibrosis, suggesting that the current level of ferroptosis in eliminating overactivated HSCs might not be adequate or prolonged enough to completely halt the advancement of fibrosis.

The role of ferroptosis in liver fibrosis of different etiologies

Viral hepatitis

MiR-222, derived from HBV-infected hepatocytes, has been shown to promote the activation of LX-2 cells by suppressing the expression of transferrin receptor (TFRC), thereby inhibiting TFRC-induced ferroptosis (Zhang et al. 2023a). The core protein of the Hepatitis C Virus (HCV) has been found to decrease nitric oxide (NO) release from Liver sinusoidal endothelial cells (LSECs) via the inhibition of endothelial Nitric Oxide Synthase (eNOS) activity, which in turn induces functional impairment of LSECs (Sun et al. 2018).

Research has revealed that reduced NO bioavailability in LSECs exacerbates hepatic fibrosis (Shao et al. 2020). Furthermore, damaged LSECs release pro-inflammatory cytokines, which trigger an increased influx of immune cells. This process further activates HSCs, prompting them to secrete excessive amounts of collagen and other extracellular matrix components. This ultimately disrupts the normal liver architecture and thereby promotes the progression of liver fibrosis (Ford et al. 2015; Lafoz et al. 2020).

Simultaneously, the HCV core protein is associated with an increase in ROS production (Sun et al. 2018). ROS, as the executors of ferroptosis, can attack a wide range of organic molecules upon local production. This process is likely driven by a Fenton reaction, which uses iron as a catalyst. However, the specific relationship between ferroptosis and liver fibrosis, particularly in the context of HBx protein from HBV, remains unclear. Further investigation is critical to clarify this relationship. Additionally, the precise roles of ROS in this context require more in-depth investigation (Kuo et al. 2020) (Fig. 2).

Metabolically-dysfunction-associated steatotic liver disease (MASLD)

In patients with MASLD, the concentrations of biomarkers indicative of lipid peroxidation and oxidative DNA damage, such as 4-Hydroxynonenal (HNE), 8- Hydroxydeoxyguanosine (8-OHdG) have increased (Takaki et al. 2013). The accumulation of cholesterol within HSCs is known to not only trigger their activation but also shield them against ferroptosis by maintaining elevated levels of glutathione peroxidase 4 (GPX4) (Liu et al. 2021; Teratani et al. 2012). Research has demonstrated that simvastatin induces ferroptosis in HSCs by downregulating GPX4 expression, an effect mediated through the suppression of the mevalonate pathway (Kitsugi et al. 2023). Moreover, hyperglycemia is identified as a separate risk factor for the rapid transition from Metabolic Steatohepatitis (MASH) to liver fibrosis. Characteristic features of ferroptosis, including excessive iron accumulation, reduced antioxidant abilities, elevated levels of reactive oxygen species, and heightened lipid peroxidation, have been validated in both in vivo and in vitro models. A notable decrease in both gene and protein levels of Advanced Glycosylation End Product- Specific Receptor 1 (AGER1) was observed throughout the progression from NASH to liver fibrosis. Advanced glycation

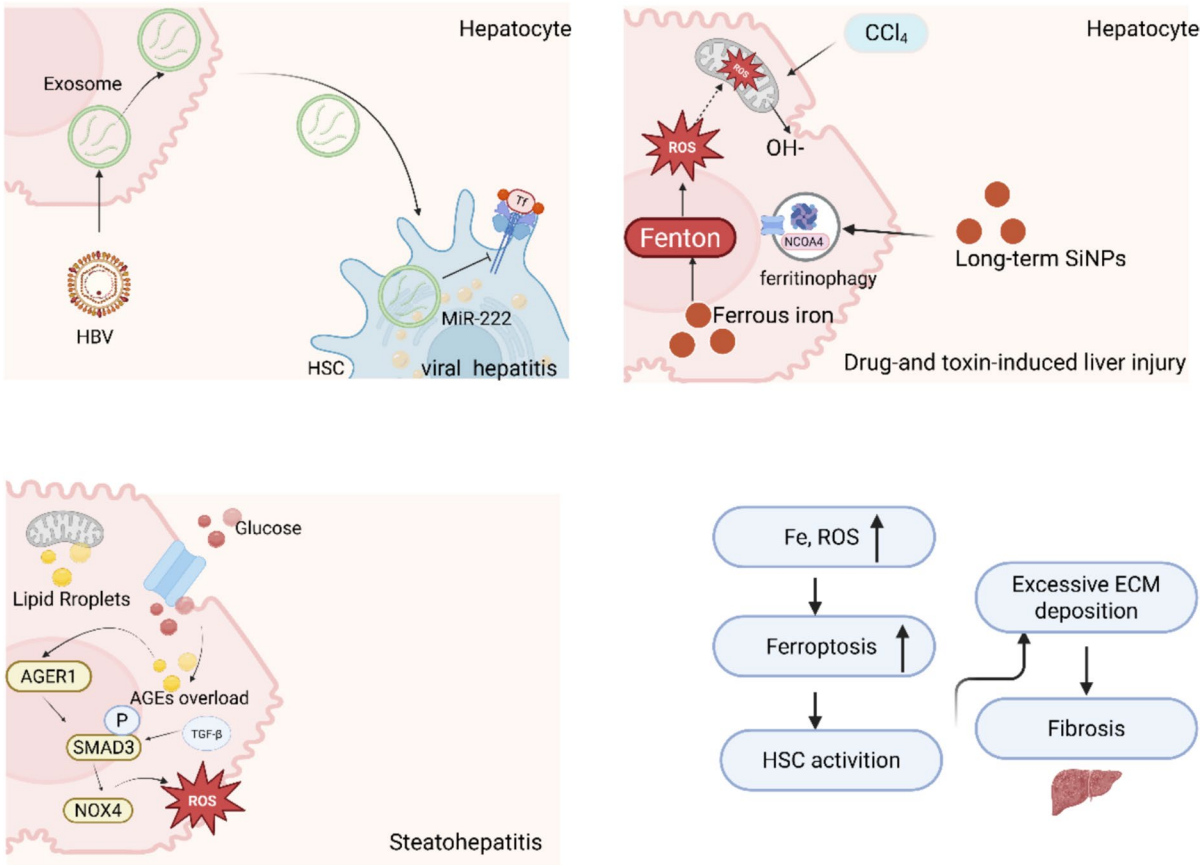

Fig. 2 Pathogenic contributions of ferroptosis in the development and progression of liver fibrosis of diverse etiologies, including viral hepatitis, steatohepatitis, and drug- and toxin-induced liver injury. Liver fibrosis of distinct etiologies, such as NASH, viral infection, and long-term SiNPs exposure, induces ferroptosis in injured hepatocytes and results in the activation of HSCs, followed by their transdifferentiation into myofibroblasts that cause excessive accumulation of ECM. Finally, Fibrous scars accumulate in the liver. Created with BioRender

end products (AGEs) accumulate during prolonged hyperglycemia, and the impaired balance of AGER1/RAGE targets NOX4 through the SMAD3-dependent pathway, thereby promoting redox imbalance, inflammatory responses, and fibrotic activity in NASH (Dehnad et al. 2020). Glucose can undergo oxidation by iron enediol radical anion, leading to the formation of ketoaldehydes and superoxide anion radicals, which further dismutate into hydrogen peroxide (Maritim et al. 2003). Additionally, abnormalities in hepatocyte iron export are considered a contributing factor to disorders in iron allocation and the development of metabolic liver conditions. Hepcidin, a hepatic hormone, is known to hinder Ferroportin (FPN) activity through the facilitation of its internalization and subsequent degradation (Drakesmith et al. 2015). Elevated levels of Transferrin receptor protein 1 (TfR1) and reduced levels of FPN1 contribute to increased Labile Iron Pool (LIP) in the liver. Excess Fe^{2+} can exacerbate lipid ROS generation through Fenton reactions (Fig. 2).

Furthermore, an imbalance in the Cystine/Glutamate Antiporter System Xc- leads to restricted glutathione exchange, reduced GSH synthesis, and decreased GPX4, culminating in ferroptosis. (Fig. 1) Nuclear factor erythroid 2-related factor 2 (Nrf2) can enhance Heme Oxygenase-1 (HO-1) expression, thereby elevating GPX4 and offering protection against lipid ROS damage (Song et al. 2022).

Alcohol-associated liver disease (ALD)

The United States witnessed a marked rise in the proportion of ALD patients with stage ≥ 3 fibrosis, from 2.2% in 2001–2002 to 6.6% by 2015–2016 (Dang et al. 2020). Previous studies have reported ferroptosis-related features in patients with ALD, including oxidative stress, increased TfR expression in hepatocytes, and iron overload (Kohgo et al. 2005; Suzuki et al. 2002). Several laboratory and clinical outcomes have highlighted that iron overload may promote the progression of ALD (Ganne-Carrie et al. 2000; Harrison-Findik et al. 2006; Ioannou et al. 2004). For instance, iron overload may trigger the activation of KCs and HSCs, promoting inflammation and fibrosis in ALD (Li et al. 2022b).

Jiao Luo et al. found that long-term ethanol feeding induced labile iron accumulation and enhanced polyunsaturated lipid peroxidation. Among them, miR-214 helps sensitize hepatocytes to ferroptosis by upregulating the transcription of key ferroptosis-driver genes, including ACSL4, SLC38A1, and RPKAA2 (Luo et al. 2023). A study has demonstrated that ablation of SIRT1 in the intestine protects against steatosis, inflammation, and fibrosis in mice after ethanol consumption (Zhou et al. 2020). In addition, numerous studies showed that IL-1β expedites ALD progression by amplifying the production of pro-inflammatory cytokines, upregulating fatty acid synthesis, inducing liver steatosis, and promoting liver fibrosis (Canali et al. 2017).

Drug- and toxin-induced liver injury

Acute and chronic hepatic damage induced by Carbon Tetrachloride (CCl4) is manifested through liver lipid peroxidation, impaired function, inflammation, and fibrotic development. These consequences are intimately linked with the development of cirrhosis and oxidative damage (Nakayama et al. 1989). FUN14 domain-containing 1 (FUNDC1) emerges as a primary factor in a series of pathological events, highlighting its potential as a therapeutic target in ferroptosis and CCl4-induced liver fibrosis. Research has shown that FUNDC1 forms a direct connection with GPx4, an essential inhibitor of ferroptosis, through its 96–133 aa domain. This interaction leads to the decreased expression of GPx4. The findings indicate that the movement of GPx4 into mitochondria driven by FUNDC1, followed by its mitophagic breakdown, could play a vital role in the ferroptotic outcomes observed in liver fibrosis. This indicates a potential therapeutic target in GPx4 for liver damage caused by CCl4 exposure. However, Gene Expression Omnibus (GEO) analysis has indicated a decrease in the mRNA level of GPx4, suggesting the involvement of transcriptional factors in GPx4 transcription during liver fibrosis (Bi et al. 2024).

SiNPs are extensively utilized in biomedicine, food, cosmetics, the chemical industry, and textiles (Wang et al. 2018). They are primarily introduced into the human body through inhalation(Sun et al. 2021). Once inhaled, these particles build up in the pulmonary system and gain entry into the bloodstream via gas-blood exchange in the interalveolar capillaries (Duan et al. 2018; Wu and Tang 2018). hey subsequently access the liver through blood-liver molecular exchange, leading to elevated plasma Alanine Aminotransferase (ALT) levels (Wu and Tang 2018). The process of NCOA4-mediated ferritinophagy in response to nanoparticles or fine particulate matter is implicated in inducing hepatocyte dysfunction (Fig. 2).

Therapies for liver fibrosis by targeting ferroptosis

Since the initial demonstration of ferroptosis's pathophysiological relevance in vivo, particularly in ischemia/reperfusion injury (IRI) of the liver in 2014, there has been a substantial increase in research efforts aimed at developing ferroptosis-related therapeutics for liver diseases (Friedmann Angeli et al. 2014). These efforts have led to the discovery of numerous inducers and inhibitors of ferroptosis. Identifying and characterizing these compounds has not only expanded our understanding of the ferroptotic process but also opened new avenues for treating liver pathologies where ferroptosis plays a critical role. Ferroptosis, as a unique form of iron-dependent programmed cell death, involves multiple key molecular targets in its regulatory network. Table 1 summarizes the main targets and their specific roles, validated through gene knockdown or knockout experiments in animal models.

Table 1 Key targets of ferroptosis

Target	Type	Model	Refs
GPX4	Liver-Specific Knockout	CCl_4-induced acute liver injury	Colyn et al. 2025
SLC7A11	Global Knockout	MCD-induced MASLD	Shen et al. 2024
NCOA4	Liver-Specific Knockdown	HFD-induced fatty liver mouse	Li et al. 2022c
ACSL4	Liver-Specific Knockout	HFD-induced fatty liver mice	Duan et al. 2022

HFD, high-fat diet; *MCD*, Methionine and Choline Deficient

Ferroptosis inducers

Drugs designed to trigger ferroptosis are primarily classified according to their mechanism of action into three groups: (i) those that deplete intracellular GSH by inhibiting system Xc–, (ii) compounds that inhibit GPX4, and (iii) agents that induce lipid peroxidation (Li et al. 2020a). Simvastatin, known as a specific HMG CoA reductase inhibitor and commonly used for treating hypercholesterolemia (Stancu and Sima 2001), has recently been shown to promote ferroptosis in HSCs. This effect is attributed to iron accumulation, oxidative stress, lipid peroxidation, and reduced GPX4 protein expression (Kitsugi et al. 2023). Within the class of ferroptosis-inducing compounds, several agents like doxofylline deplete intracellular GSH by inhibiting system Xc-. These small-molecule drugs are currently undergoing relevant preclinical studies (Xu et al. 2023). Similarly, sorafenib, a clinically approved anti-tumor drug, has been found to trigger HSC ferroptosis via HIF-1α/SLC7A11 signaling, thereby attenuating liver injury and fibrosis (Yuan et al. 2022). Berberine, a major bioactive compound of Rhizoma Coptidis (commonly known as Huanglian in Chinese), inhibits HSC proliferation by impairing the autophagy-lysosome pathway and increasing cell ROS., thereby leading to ferroptosis and attenuating liver fibrosis (Yi et al. 2021). Nuclear receptor co-activator 4 (NCOA4) is a crucial regulator of ferritinophagy, targeting ferritin for lysosomal degradation and thereby releasing free iron. This NCOA4-mediated ferritinophagy plays a significant role in iron metabolism (Santana-Codina and Mancias 2018) (Fig. 1). Overexpression of NCOA4 in HSCs activates iron autophagy, degrades intracellular ferritin, increases intracellular free iron, and consequently leads to ferroptosis (Zheng et al. 2022). However, the role of autophagy in liver fibrosis is multifaceted and remains a subject of debate. Notably, the pro-fibrotic properties of autophagy during HSC activation should also be fully considered (Hernandez-Gea and Friedman 2012; Thoen et al. 2012; Wu et al. 2017). Additionally, there are several other preclinical small-molecule ferroptosis inducers, such as wogonoside and isoliquiritigenin, which are currently under investigation (Huang et al. 2022; Que et al. 2022; Thoen et al. 2012) (Table 2).

Ferroptosis inhibitors

Several clinically approved agents exhibit potential antiferroptosis activity. These agents inhibit ferroptosis through three primary mechanisms: preventing peroxidation, upregulating System Xc-, and enhancing the expression of ACSL4 and ALOX15 (Table 3). The Nrf2-Keap1 pathway is a critical regulator of cellular antioxidant response (Liu et al. 2019). Liraglutide, identified as a potential Nrf2 inducer, has been shown to protect against liver fibrosis. This protection is achieved by reducing oxidative stress, diminishing lipid peroxidation, and alleviating iron overload, thereby inhibiting ferroptosis (Song et al. 2022). Similarly, natural compounds such as Mori Fructus aqueous extracts, sulforaphane, and Gandankang aqueous extracts can ameliorate acute and chronic liver injury. These effects are mediated through the promotion of Nrf2 nuclear transport (Wei et al. 2023a).

Targeting ferroptosis inducers of HSCs

As described above, ferroptosis is like a double-edged sword in liver fibrosis because it can instigate liver damage or drive activated HSC death. Nevertheless, strategies such as curtailing HSC proliferation, encouraging HSC apoptosis (Sun et al. 2016b), senescence (Sun et al. 2016a), and autophagy (Sun et al. 2015) are being explored as methods to reverse liver fibrosis. It is crucial to consider that agents inducing ferroptosis might adversely affect hepatocytes and macrophages. Consequently, the challenge lies in selectively inducing ferroptosis in HSCs without harming healthy liver cells and macrophages. In the realm of liver fibrosis,

Table 2 Preclinical-induced agents used to target ferroptosis

Drug/molecule candidates	Mode of action	Mechanism of action	Model	Refs
Simvastatin	inducer	Block GPX4; induce peroxidation	CCl4-induced fibrosis	Kitsugi et al. 2023
PZH	inducer	Inhibit system xc–	DEN-induced fibrosis	Yan et al. 2023
Sorafenib	inducer	Inhibit system xc–	CCl4-induced fibrosis	Yuan et al. 2022
DOX	inducer	Inhibit system xc–	CCl4-induced fibrosis	Xu et al. 2023
BBR	inducer	Induce peroxidation	TAA and CCl4-induced fibrosis	Yi et al. 2021
WG	inducer	Inhibit system xc–	CCl4-induced fibrosis	Liu et al. 2022
ISL	inducer	Block GPX4	CCl4-induced fibrosis	Huang et al. 2022
Decursin	inducer	Block GPX4	CCl4-induced fibrosis	Que et al. 2022
Curcumo	inducer	Up-regulate NCOA4	HSC-T6 cells	Zheng et al. 2022
Celstrol	inducer	Induce peroxidation	CCl4-induced fibrosis	Luo et al. 2022
Artesunate	inducer	Induce peroxidation	CCl4-induced fibrosis	Kong et al. 2019
MgIG	inducer	Induce peroxidation	CCl4-induced fibrosis	Sui et al. 2018
GRh2	inducer	Inhibit system xc–;Up-regulates IRF	CCl4-induced fibrosis	Lang et al. 2023
Dan	inducer	Inhibit system xc–	lipopolysaccharide-induced LX-2 and T6 cells	Wang et al. 2023a
ART	inducer	Induce peroxidation	CCl4-induced fibrosis	Wang et al. 2019
EA	inducer	Induce peroxidation	CCl4-induced fibrosis	Li et al. 2022a
Sch B	inducer	NCOA4-mediated ferritinophagy	CCl4-induced fibrosis	Ma et al. 2023

CCl4, carbon tetrachloride; *BBR*, Berberine; *WG*, Wogonoside; *ISL*, Isoliquiritigenin; *MgIG*, Magnesium isoglycyrrhizinate; *GRh2*, Ginsenoside Rh2; *Dan*, Danshensu; *ART*, artemether; *EA*, Ellagic acid; *Sch B*, Schisandrin B

Table 3 Preclinical inhibitory agents used to target ferroptosis

Drug/molecule candidates	Mode of action	Mechanism of action	Model	Refs
Liraglutide	inhibitor	Prevents peroxidation	T2DM-induced fibrosis	Song et al. 2022
MFAEs	inhibitor	Prevents peroxidation	CCl4-induced fibrosis	Wei et al. 2023a
AAEO	inhibitor	Upregulate System XC-	BPA-induced fibrosis	Cui et al. 2023
LPT1	inhibitor	Block ACSL4 and ALOX15	HFHF-induced fibrosis	Tong et al. 2023
SFN	inhibitor	Up-regulate System XC-; prevents peroxidation	LPS/D-Gal induced fibrosis	Zhang et al. 2023c
GDK	inhibitor	Up-regulate GPX4	CCl4-induced fibrosis	Wei et al. 2023b
Sal B	inhibitor	Up-regulate xCT/Gpx4	CCl4-induced fibrosis	Fu et al. 2024

T2DM, Type 2 diabetes mellitus; *MFAEs*, Mori fructus aqueous extracts; *AAEO*, Artemisia argyi essential oil; *BPA*, bisphenol A; *LPT1*, liproxstatin-1; *HFHF*, a high-fat diet with 30% fructose in water; *SFN*, sulforaphane; *LPS*, Lipopolysaccharide; *D-Gal*, D-galactosamine; *GDK*, Gandankang; *CCl4*, carbon tetrachloride; *Sal B*, Salvianolic acid B

Ji et al. discovered that nanoparticles loaded with Germacrone and miR-29b, specifically designed to target HSCs, show promise for clinical application in treating liver fibrosis (Ji et al. 2020). Mesenchymal stem cell-derived exosomes (MSC-ex) could intensify ferroptosis in HSCs. However, their effects on ROS production enhancement and GPX4 expression reduction were not observed in the human hepatocyte cell line L-02 (Jiang et al. 2018; Tan et al. 2022). The xCT membrane antiporter, which exchanges intracellular glutamate for extracellular cysteine, plays a role in defending cells against oxidative stress and ferroptosis (Zhang et al. 2022). Recent studies indicate significantly lower xCT mRNA levels in primary mouse hepatocytes compared to primary mouse HSCs, suggesting that MSC-ex-mediated xCT inhibition might selectively induce

Table 4 Preclinical inducers of ferroptosis targeting HSCs

Drug/molecule/particle	Target	Effector/reagent	Refs
Simvastatin	GPX4	mevalonate pathway	Kitsugi et al. 2023
Sorafenib	SLC7A11	HIF-1α	Yuan et al. 2022
MSC-ex	GPX4	xCT	Tan et al. 2022
Sal B	GPX4	xCT	Fu et al. 2024
GRh2	SLC7A11	IRF1	Lang et al. 2023

ferroptosis in HSCs, but not in hepatocytes. Resistance to MSC-ex treatment was observed in hepatocytes, while HSCs showed sensitivity (Fu et al. 2024; Tan et al. 2022). Furthermore, some studies have noted that certain molecules trigger ferroptosis in HSCs but have minimal impact on hepatocytes and macrophages (Ieda et al. 2021; Kitsugi et al. 2023; Yuan et al. 2022) (Table 4).

DHA: dihydroartemisinin; siRNA: small interfering RNA; MSC-ex: exosomes secreted by human umbilical cord mesenchymal stem cells; Sal B: Salvianolic acid B; xCT: Solute carrier family 7 member 11; GRh2: Ginsenoside Rh2; IRF1: interferon regulatory factor 1.

Non-coding RNAs and epigenetics

Beyond the classical metabolic pathways, emerging evidence indicates that diverse non-coding RNAs (ncRNAs), including microRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), contribute to ferroptosis, which subsequently modulates the progression of multiple pathologies such as liver fibrosis (Zhang et al. 2024). One study has demonstrated that miR-214 selectively binds to the AGO2 protein in the nucleus and transcriptionally activates ferroptosis driver genes, thereby enhancing hepatocyte ferroptosis and exacerbating alcoholic liver injury (Luo et al. 2023). The overexpression of LncRNA-MEG3 promotes ferroptosis in liver cancer cells, leading to the inhibition of cellular proliferation and migration (Zhu et al. 2024).

Accumulating evidence indicates that epigenetic modifications (e.g., ubiquitination, phosphorylation) regulate ferroptosis in liver diseases (Wang et al. 2023b). TRIM26 suppresses liver fibrosis by promoting ferroptosis in hepatic stellate cells through mediating SLC7A11 ubiquitination (Zhu et al. 2021). Artemether alleviates liver fibrosis both in vitro and in vivo by inhibiting the ubiquitination of IRP2, which induces ferroptosis in HSCs through promoting intracellular iron accumulation (Li et al. 2020b).

Conclusion and future perspectives

In summary, the impact of ferroptosis on liver fibrosis represents a double-edged sword. Ferroptosis does not invariably lead to the remission of fibrotic conditions. Therefore, its exact role in liver fibrosis must be carefully examined, taking into account different etiologies and cell types, including hepatocytes, Kupffer cells, and HSCs. The core strategy of antifibrotic therapy lies in the selective induction of ferroptosis in HSCs. The development of drugs that selectively induce ferroptosis in HSCs, while sparing hepatocytes, LSECs, and macrophages, is an emerging trend in the treatment of liver fibrosis. There are effective strategies to selectively eliminate fibrogenic HSCs during liver injury (Lang et al. 2023).

On the other hand, although increased cytoplasmic iron levels contribute to HSC activation, they also increase sensitivity to ferroptosis. Appropriately designed drugs that induce iron-mediated lipid peroxidation can disrupt the membrane integrity of activated HSCs, thereby facilitating their removal (Zhang et al. 2021).

Although ferroptosis inducers and inhibitors have not been examined in clinical trials specifically for liver fibrosis, many ferroptosis inducers and inhibitors have shown efficacy in preclinical studies. Optimized Fer-1 molecules with improved ADME (absorption, distribution, metabolism, and excretion) profiles hold promise for advancing to clinical trials (Chen et al. 2022).

The most critical challenge is developing therapies with high cell-type specificity.. Future research should focus on developing more effective ferroptosis inducers and inhibitors, enhancing drug efficacy, and improving tissue and organ specificity. For instance, nanoparticle-based targeted drug delivery systems could enhance

drug safety and reduce adverse effects (Hong et al. 2023). Furthermore, as a potential therapeutic target for HCC, the application of bioactive substances combined with chemotherapeutic drugs in HCC treatment has garnered significant attention, providing new insights and foundations for developing more effective targeted therapies. Studies have demonstrated that the combination of NaB and Sora synergistically induces ferroptosis, thereby inhibiting the proliferation of liver cancer cells (He et al. 2024). Currently, most ferroptosis modulators remain in the preclinical stage, and their clinical translation requires addressing challenges related to safety and pharmacokinetic profiles.

There is a pressing clinical need for sensitive and reliable biomarkers to monitor ferroptosis. Research should prioritize the development of non-invasive biomarkers (e.g., specific circulating non-coding RNAs or lipid metabolites) for tracking disease progression and treatment response.

Ferroptosis-associated non-coding RNAs (ncRNAs) play a pivotal role in the progression of hepatic fibrosis, representing a promising therapeutic avenue for the treatment and prevention of this condition (Zhang et al. 2024).

The optimal timing and intensity for modulating ferroptosis remain elusive. Future studies must elucidate the therapeutic window across different liver conditions and disease stages, determining when to inhibit ferroptosis to protect hepatocytes and leveraging the therapeutic window for ferroptosis induction to eliminate HSCs or cancer cells. Drug resistance represents a critical challenge in liver cancer therapy. Targeting ferroptosis represents a viable therapeutic approach to eliminate tumor cells with chemotherapy-resistant traits (Chen et al. 2021). Multi-kinase inhibitors such as Lenvatinib suppress System Xc- expression, elevate lipid ROS levels, and cause ferroptosis induction in HCC cells (Iseda et al. 2022). Future studies should explore combination therapies, such as using ferroptosis inducers in conjunction with existing chemotherapeutic agents, to achieve synergistic anti-tumor effects.

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Declarations

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