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**Iron as a therapeutic target in chronic liver disease**

Kouroumalis E *et al*. Iron and the liver

Elias Kouroumalis, Ioannis Tsomidis, Argyro Voumvouraki

**Elias Kouroumalis,** Liver Research Laboratory, University of Crete Medical School, Heraklion 71003, Greece

**Ioannis Tsomidis, Argyro Voumvouraki,** First Department of Internal Medicine, AHEPA University Hospital, Thessaloniki 54621, Greece

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**Corresponding author: Elias Kouroumalis, MD, PhD, Emeritus Professor,** Liver Research Laboratory, University of Crete Medical School, 13 Kalokerinou Street, Voutes, Heraklion 71003, Greece. kouroumi@uoc.gr

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**Abstract**

It was clearly realized more than 50 years ago that iron deposition in the liver may be a critical factor in the development and progression of liver disease. The recent clarification of ferroptosis as a specific form of regulated hepatocyte death different from apoptosis and the description of ferritinophagy as a specific variation of autophagy prompted detailed investigations on the association of iron and the liver. In this review, we will present a brief discussion of iron absorption and handling by the liver with emphasis on the role of liver macrophages and the significance of the iron regulators hepcidin, transferrin, and ferritin in iron homeostasis. The regulation of ferroptosis by endogenous and exogenous modulators will be examined. Furthermore, the involvement of iron and ferroptosis in various liver diseases including alcoholic and non-alcoholic liver disease, chronic hepatitis B and C, liver fibrosis, and hepatocellular carcinoma (HCC) will be analyzed. Finally, experimental and clinical results following interventions to reduce iron deposition and the promising manipulation of ferroptosis will be presented. Most liver diseases will be benefited by ferroptosis inhibition using exogenous inhibitors with the notable exception of HCC, where induction of ferroptosis is the desired effect. Current evidence mostly stems from *in vitro* and *in vivo* experimental studies and the need for well-designed future clinical trials is warranted.

**Key Words:** Iron overload; Liver disease; Ferroptosis; Ferritinophagy; Ferroptosis modulators

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**Core Tip:** Iron overload may damage the liver in a variety of liver diseases such as cirrhosis and hepatocellular carcinoma affecting patient survival. In this review, we present the evidence, both experimental and clinical, of the detrimental effects of iron deposition in hepatocytes and other liver sinusoidal cells. Moreover, we examine the mechanism and implications of the recently described ferroptosis in the evolution of liver disease. Ferroptosis is a form of regulated hepatocyte death caused by excess iron and lipid peroxidation. Inhibition or induction of ferroptosis may profoundly improve the course of many liver diseases as demonstrated by a large number of experimental studies as well as a small number of clinical trials.

**INTRODUCTION**

The major suppliers of plasma iron are duodenal enterocytes and iron-recycling macrophages[1-3]. Duodenal cytochrome B reductase reduces inorganic trivalent iron reaching the duodenum to form divalent iron (Fe2+), and surface divalent metal transporter 1 (DMT1) imports Fe2+ into the cytoplasm. The gene *SLC11A2* encoding DMT1 is activated in cases of iron deficiency or hypoxia as it interacts with the hypoxia-inducible factors (HIF1α and HIF2α) overexpressed in these situations[4-7]. The cytoplasmic iron sensor iron-responsive element (IRE) and iron regulatory proteins (IRP1 and IRP2) also participate in iron absorption control as they stabilize the *SLC11A2* transcript in iron deficiency or dissociate and degrade in iron overload[8]. Then, the cytoplasmic divalent iron is bound to ferroportin, the only known iron exporter protein, and exported to the portal vein blood. Transportation is mediated by the chaperone protein poly (rC)-binding protein 2 encoded by the *SLC40A* gene[9]. The main regulator of ferroportin is hepcidin[10], but the IRP/IRE proteins and microRNAs are also involved[11]. Once in the portal vein, the divalent iron is oxidized back to trivalent by the ferroxidases hephestin and ceruloplasmin and then carried in different cells bound to transferrin. Peripheral cells import iron by the internalization of transferrin after it binds to its receptor TFR1[12] and is sorted into endosomes where iron is removed in the acidic environment, reduced again to Fe2+ by the ferrireductase STEAP3, and released into the cytosol by DMT1[1,3]. Iron is then either exported by ferroportin or stored in ferritin or in the labile iron pool (LIP).On the other hand, heme oxygenases (Hos) localized mainly in iron-recycling macrophages of liver and spleen, degrade heme to recover Fe2+[2,13].

The regulation of hepcidin is critical in iron metabolism as binding of hepcidin to ferroportin in hepatocytes, macrophages, or enterocytes leads to internalization and degradation of ferroportin, thus limiting iron export to the blood[2,3,10].A decrease in hepcidin when iron is needed leads to enhancement of ferroportin expression and increased iron absorption from the duodenum. In iron overload, ferroportin is downregulated and iron absorption is decreased[14]. In addition to iron deficiency, inflammatory molecules like interleukin (IL)-6 also upregulate hepcidin expression[15]. **The** *HAMP* gene encodes hepcidin, and its promoter is activated by the complex of bone morphogenic proteins (BMP2, BMP4, BMP6) and their receptor. This complex phosphorylates the SMAD pathway, which in turn activates *HAMP* expression[16,17]. Hemojuvelin (HJV) is a necessary co-factor for BMP-BMP receptor complex function[18]. BMP6 is mainly expressed in liver sinusoidal cells and induces hepcidin upregulation *via* paracrine signaling during iron overload[19-21].

The second receptor of transferrin (TFR2), a low-affinity receptor found in hepatocytes and erythroid precursors, is also an important inducer of hepcidin through the BMP/SMAD pathway[22-24] after forming a complex with HFE (the protein involved in hereditary hemochromatosis)[25]. Anomalies of either of the genes encoding these proteins will lead to hepcidin downregulation[26-28].

**Hepcidin inhibitors**

In contrast to iron overload, hypoxia, anemia, and erythropoiesis reduce hepcidin expression[29,30]. The main inhibitor of hepcidin expression is erythroferrone (ERFE)[31], which is produced by erythroid cells in response to erythropoietic stimuli. ERFE downregulates hepcidin, interfering with the BMP/SMAD pathway in hepatocytes[32-34].Three other hepcidin inhibitors have been described. PIEZO1 and the immunophilin FKBP reduce *HAMP* expression by inhibiting the BMP/SMAD pathway[35,36]. The third hepcidin inhibitor is theferritinophagy axis operating in both the enterocyte and the macrophage. Ferritinophagy is a specialized form of autophagy resulting in the lysosomal breakdown of ferritin and subsequent iron release to increase the LIP. It is controlled by the nuclear receptor coactivator 4 (NCOA4)[37,38] during transport of absorbed iron to ferritin. In increased iron demand, NCOA4 functions as a cargo receptor for lysosomal degradation of ferritin. Excess iron leads to lipid peroxidation-mediated ferroptosis[38]. NCOA4 is similarly involved in macrophage ferritinophagy and iron release for erythropoiesis[39].

Iron ions are dangerous to cells. In iron overload, redox-active iron increases and oxidative stress is induced through the formation of reactive oxygen species (ROS). Non-transferrin bound iron is mainly responsible for the redox-active iron when the capacity of iron binding proteins is not able to accommodate for the increased iron load. An additional dangerous form is the transit iron pool, which comprises iron that is not bound to ferritin or other chelating proteins. This iron may also induce the formation of ROS[40]. Iron is a double-edged sword[41], which even under normal conditions may cause pathological damage. Iron induces hydroxyl radical production through the Fenton reaction[42]. The Fenton-Haber-Weiss reaction is caused by the free donation and acceptance of electrons during the transition between Fe2+ and Fe3+ states. Iron-catalyzed generation of hydroxide ions and hydroperoxyl and hydroxyl radicals is the result of this exchange. Under normal conditions, free-radicals are quenched by cellular antioxidant mechanisms[43]. However, when overproduced, these free radicals promote the formation of other ROS such as thiyl and peroxyl radicals and a vicious circle is initiated leading to oxidation of lipids, proteins and nucleic acids[44]. Thus, in iron-loaded animals the products of lipid peroxidation such as malondialdehyde (MDA), isoprostanes, and 4-hydroxynonenal (4-HNE) can be detected in the liver[45]. MDA and 4-HNE form mutagenic adducts, reacting with amino groups and DNA bases[46,47] that target the p53 tumor suppressor gene initiating apoptotic resistance to the cells[48]. Levels of 4-HNE correlate well with hepatic iron levels[49]. Iron metabolism was recently reviewed in detail[50-53].

**Ferroptosis**

The most important mechanism of iron-induced liver damage is the recently described ferroptosis, a name derived from the Greek word “ptosis,” meaning a fall, and the Latin “ferrum” or iron[54]. It is an iron-dependent regulated cell death characterized by iron accumulation, lipid peroxidation, and the production of ROS that depends on the activity of NADPH oxidases[55,56]. The mitochondrial respiratory chain initiates lipid peroxidation by lipoxygenase (LOX) or cytochrome P450 reductase. The enzyme glutathione peroxidase 4 (GPX4), the antioxidant glutathione (GSH), the coenzyme Q10 (CoQ10), and the tetrahydrobiopterin (BH4) system are the defense mechanisms of the cell. They are further regulated by the nuclear factor erythroid 2-related factor (Nrf2)[57-59]. The process is controlled by multiple genes associated with iron uptake[60,61], lipotoxicity[62,63], and antioxidation responses[64,65].

Ferroptosis is regulated by several metabolic events such as lipogenesis and ferritinophagy. The mitochondrial tricarboxylic acid cycle fueled by glutaminolysis may promote ferroptosis induction. Phospholipid peroxidation is the critical event in ferroptosis. Production of ROS, iron, and phospholipids containing polyunsaturated fatty acids (PUFA-PLs) are the necessary requirements. The executioner of ferroptosis is phospholipid hydroperoxide (PLOOH) synthesized from its precursor, PUFA[66].

Both non-enzymatic/exogenous and enzymatic/endogenous pathways are implicated in lipid peroxidation. For the latter, LOXs and/or cytochrome P450 oxidoreductase mediate the induction of lipid peroxidation by the dioxygenation of lipids. Exogenous transporter mediated signaling pathways include the E cadherin-NF2-Hippo-YAP pathway, the glucose-regulated AMPK signaling pathway, and the p53 tumor suppressor pathway[67].

Mechanisms inhibiting ferroptosis are provided by three main biological pathways (Figure 1)[68,69]. The first is the GSH/GPX4 pathway, implicating the system Xc-, which is a membrane cystine/glutamate exchanger that imports cystine and exports glutamate. A critical mediator in this system is the cystine/glutamate antiporter SLC7A11, and GPX4 is the major protective system against lipid peroxidation[70]. In addition, ferroptosis suppressor protein 1 acts mainly on the plasma membrane, and dihydroorotate dehydrogenase is an important defense molecule in mitochondria[71-75]. The second comprises iron metabolism pathways, particularly the p62-Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 regulatory pathway[54]. Inhibition of ferritinophagy increases mitochondrial ferritin and protects from ferroptosis as evidenced in hypoxic macrophages. This is regulated by a hypoxia-induced decrease of *NCOA4* transcription, in combination with a microRNA 6862-5p-dependent degradation of NCOA4 mRNA[76]. Nrf2 is a transcription factor that protects cells against oxidative and toxic damage and plays a significant role in regulating ferroptosis[77-79]. In hepatocellular carcinoma (HCC) and other tumors, activation of the p62-Keap1-Nrf2 pathway leads to reduced Nrf2 degradation, the protection of tumor cells against ferroptosis, and resistance to anticancer drugs[80]. The third includes lipid metabolism pathways implicating p53 and various enzymes[54,66]. p53 is a tumor suppressor transcription factor that may prevent cancer by controlling the cell cycle, cellular senescence, and apoptosis. Ferroptosis is one of its antitumor mechanisms; p53 increases cell sensitivity to ferroptosis through repression of *SLC7A11*. The ferroptosis inhibitor fer-1 reverses this effect and induces *SLC7A11* overexpression[62,81-83]. Additional biological factors inhibiting ferroptosis were also recently identified: (1) GTP Cyclohydrolase-1 **(**the rate-limiting enzyme for biosynthesis of tetrahydrobiopterin (BH4), which counteracts ferroptosis[84]); (2) Transferrin and its cell surface TFR1 receptor[12]); and (3) CDGSH (iron sulfur domain 1, which negatively regulates ferroptosis protecting against lipid peroxidation in mitochondria)[85].

**Exogenous ferroptosis modulators**

Exogenous ferroptosis modulators discussed here are summarized in Table 1. Ferroptosis inhibitors are divided into two major groups: (1) Class I inhibitors, such asDeferoxamine (DFO) mesylate[86], which suppresses iron accumulation; and (2) Class II inhibitors, including ferrostatin-1, liproxstatin-1 and vitamin E, which react with chain free radicals and can inhibit lipid peroxidation[87-91]. The activity of drugs in the first generation of ferrostatin class specifically reduce the accumulation of lipid ROS. The second generation (SRS 11-92) and the third generation (SRS 16-86) ferrostatin drugs function through conferring increased metabolic stability[90].

The recently described inhibitor dynasore has characteristics of both classes, and prevents both iron accumulation and lipid peroxidation[92]. Other inhibitors of ferroptosis have been identified. For example, the cholesterol-reducing drug probucol was found to suppress ferroptosis[93]. The RIPK1 inhibitor necrostatin-1, which suppresses necroptosis, also has the additional effect of suppressing ferroptosis. Selenium administration has also been seen to suppress ferroptosis during stroke[94], and the nitroxide XJB-5-131 targets mitochondria and suppresses both apoptosis and ferroptosis[95]. However, it should be noted that these inhibitors have not been tested in the liver.

Interestingly, a recent experimental finding showed that the mechanism of action of bicyclol, a common hepatoprotectant in China, is *via* the prevention of ferroptosis. Furthermore, bicyclol attenuates cellular damage and lipid peroxidation induced by erastin. Additionally, Nrf2 inhibition and the subsequent reduction of GPX4 levels impedes the effects of bicyclol[96]. Finally, the anti-diabetic drug rosiglitazone inhibits ferroptosis and reduces hepatocyte death, acting as an ACSL4 inhibitor[97,98].

***Ferroptosis inducers***

Class I inducers such as erastin, sorafenib, sulfasalazine and glutamate, deplete cellular cysteine by inhibiting system Xc- and the biosynthesis of GSH, resulting in the loss of GPX4 activity[81,99-102]. The low water solubility and metabolic instability of erastin has limited its clinical application[103], but a metabolically stable erastin derivative has been tested[104].

Class II inducers, including RSL3 and DPI compounds, act by directly inhibiting GPX4[88,105-107], leading to the accumulation of lipid peroxides and eventual cell death. BSO and cisplatin also deplete GSH inducing ferroptosis. Cisplatin and erastin have a significant synergistic effect[108]. Interestingly, erastin promotes ferritinophagy and increased the free iron, lipid peroxidation, while RSL3 does not interfere with ferritinophagy, suggesting that RSL3 induction of ferroptosis is not dependent on ferritin degradation[109].

Class III inducers such as FIN56 act by both direct degradation of GPX4 and indirect inactivation of GPX4 *via* the squalene synthase-mevalonate pathway of the mitochondrial electron transport chain[103,110]. FIN56 also acts by depleting GPX4 and CoQ10. It seems that the cellular lethality of FIN56 is increased when cells are co-treated with statins and FIN56[110]. In addition, statins, such as simvastatin, enhance ferroptosis by inhibiting HMG-CoA reductase[110].

In class IV inducers, ferroptosis is induced by excess iron, omega-3 PUFAs, or peroxides, such as FINO2, that initiate lipid peroxidation and indirectly reduce GPX4 activity[111,112]. FINO2 is the only class IV ferroptosis inducer tested so far, but several other have been synthesized[103]. PUFAs show anticancer activity[113], but shortcomings such as reduced bioavailability, limited resistance to oxidative degradation, and lack of uptake specificity impede their use. However, the application of nanotechnology improves their therapeutic use[114]. Low density lipoproteins (LDLs) are taken up by LDL receptor expressed in tumor cells. LDL-based nanoparticles with docosahexaenoic acid (LDL-DHA NPs) were found to maintain their stability and specificity[115,116].

Experimental evidence suggests that there are additional biological inducers of ferroptosis, but their significance in human disease is still unknown. As mentioned above, ferritinophagy is a special recycling process of autophagy for the autophagic degradation of ferritin in lysosomes. It is mediated by the autophagic cargo receptor NCOA4, and leads to the initiation of ferroptosis[117]. Augmented ferritinophagy mediated by an increase of NCOA4 leads to induction of ferroptosis[64] (Table 1).

Reduction of iron-response element binding protein 2 significantly reduces erastin induced ferroptosis[55]. Increased activity of HO-1, the enzyme responsible for degradation of heme into ferrous iron, carbon monoxide, and biliverdin, increases LIP and initiated ferroptosis[118,119]. Artesunate (a derivative of artemisinin) is used in severe malaria[120] and induces hematopoietic stem cell (HSC) ferroptosis. However, the malaria drug chloroquine (a ferritinophagy inhibitor) reverses this effect, implying that artesunate induces HSC ferroptosis by activating ferritinophagy[121].

Finally, magnesium isoglycyrrhizinate (MgIG) is a natural product with anticancer activity[122] that has been shown to promote HSC ferroptosis. Inhibition of HO-1 reduces MgIG-induced HSC ferroptosis, suggesting that the promotion of HSC ferroptosis is mediated through upregulation of this enzyme[123].

**Liver macrophages in iron metabolism and ferroptosis**

Kupffer cells and other liver and spleen macrophages take up heme from damaged or senescent erythrocytes and either export the extracted Fe2+ using ferroportin or store it in ferritin in the cytoplasm[124]. It has been shown that intracellular iron regulates the differentiation of macrophages into M1 (pro-inflammatory) and M2 (anti-inflammatory) subtypes[125,126]. M1 macrophages have an iron storage capability with higher HAMP but lower FPN and IRP1/2 compared to M2 subtype[127]. M1 polarization is regulated by iron overload[128], but also by ROS production and p53 acetylation induced by iron overload[129]. Recently, experiments with cultured macrophages demonstrated that chronic iron overload may in fact downregulate M1 markers and show signs of M2 differentiation[130].

During infection, hepcidin blocks macrophage differentiation to reduce iron export that could increase the growth of pathogens[131], which is reversed in the case of intracellular pathogens. This is possibly achieved by an increased production of nitric oxide[132] and the expression of the phagolysosomal protein NRAMP1 both leading to induction of ferroportin and intracellular iron reduction[133].

Kupffer cells exhibit phagocytic dysfunction and impair iron homeostasis during the development of non-alcoholic fatty liver disease (NAFLD)[134-136]. In addition, they participate in the clearance of lipids in nonalcoholic steatohepatitis (NASH) through M1 differentiation with the help of invariant natural killer T cells[137-139]. This composite role indicates that Kupffer cells can influence the development of ferroptosis, providing a new target for therapy in NAFLD.

Moreover, acute iron deprivation led to changes in metabolic and immunoregulatory genes in human macrophages resulting in impaired cell proliferation and reduced inflammation[140]. This is in contrast to the pro-inflammatory production of leukotrienes by the enzyme 5-LOX mediated by ferric iron in human macrophages[141]. As expected, ferroptosis has been the subject of several detailed reviews[69,142-145], whichinclude descriptions of ferroptosis regulators[146,147], ferroptosis in viral disease[148], and the role of macrophages in ferroptosis[149].

**Iron in liver disease**

Patients with chronic liver disease may exhibit hepatic and splenic iron loading, usually inside Kupffer cells and splenic and bone marrow macrophages[150]. Sometimes, this is accompanied by low hemoglobin levels and other hemolysis indices, indicating that hemolysis may have a role in the development of secondary iron overload[151]. However, a recent review emphasized the role of low levels of hepcidin in various liver diseases as implicated in both iron deposition in hepatocytes and participation in stellate cell activation and liver fibrosis[152].

Excess free iron exerts a toxic effect on the liver, favoring the progression of liver disease[58,153], and indeed abnormalities of iron regulation are reported in various liver diseases apart from inherited hemochromatosis[154]. Hyperferritinemia has been the main manifestation of disturbed iron homeostasis in chronic liver disease[155,156].

Opposing views have also been expressed in the literature. Data from cell culture experiments and animal models suggest that iron overload is only a weak fibrosis inducer and rarely causes serious liver damage not supporting the concept that iron overload is an important cause of liver toxicity. Iron may co-exist with other causes of inflammation, and the resulting hepatocyte necrosis is the real driving force leading to fibrosis[157].

The role of iron overload and the significance of ferroptosis have been investigated in the context of several liver diseases. The most common liver diseases will be discussed as well as the common end points of all, namely cirrhosis sometimes followed by the development of HCC. The rather limited available information on other liver diseases will be presented.

**NAFLD/NASH**

The role of iron in liver damage has been extensively researched in the case of NAFLD. A new term was introduced, the dysmetabolic or insulin-resistance hepatic iron overload syndrome (DIOS or IR-HIO), which is characterized by high serum ferritin levels, unexplained iron overload, and is associated with metabolic abnormalities[158-161]. IR-HIO is detected in one third to half of patients with NAFLD[155,158,162,163]. The reason for the observed iron overload in NAFLD is still uncertain. A proposed mechanism is the redistribution of transferrin receptors (TfRs) to the cell surface, a process induced by insulin[158,163,164]. Tfr1 is upregulated in mice on a high fat diet, which may enhance hepatocellular iron uptake in NAFLD despite already increased hepatocellular iron[165]. The increase in serum ferritin may be due to increased iron stores, oxidative stress caused by lipid abnormalities, systemic inflammation, and genetics[166,167]. The implication of the presence of the Cys282Tyr *HFE* gene variant of hereditary hemochromatosis was also examined. A heterozygous mutation is associated with bridging fibrosis or cirrhosis in Caucasians[168-170]. By contrast, in knock out mouse models of hemochromatosis no progression to steatohepatitis or liver fibrosis was noted with a high-fat diet[171].

In addition, certain variants of ceruloplasmin are associated with increased liver iron stores and high ferritin in patients with NAFLD and advanced liver fibrosis[172,173]. Ceruloplasmin mutations have been associated with iron deposition in the liver of other chronic liver diseases as well[174]. Excess dietary iron causes hepatic oxidative stress, inflammation and hepatocellular ballooning injury leading to NASH[175,176]. Oxidative stress interferes with mitochondrial function, impairing fatty acid oxidation and producing different pro-inflammatory factors such as tumor necrosis factor (TNF)-α, IL-6, IL-8, MDA and nitric oxide[177-180], leading to NASH.Moreover, liver iron deposition increases cholesterol synthesis, lipid accumulation, and impairs cellular stress responses, which further exacerbate NAFLD[181-184].

The pattern of hepatic iron deposition is important in NAFLD patients, as iron deposition in macrophages is associated with more advanced disease[185]. An important observation was recently reported emphasizing the role of liver macrophages in the pathogenesis of NASH. A histological structure, the crown-like structure, has been described in NASH: Iron-rich Kupffer cells surround dead hepatocytes, take up debris, and induce inflammation and fibrosis. They have proinflammatory and profibrotic phenotypes, driving liver fibrosis[186]. Hepatic iron was significantly higher in patients with HCC associated with NASH and it was mostly localized in Kupffer cells[187]. Evidence suggests that iron may contribute to NAFLD pathogenesis and fuel the progression to NASH[178-180].

Red blood cell fragility and erythrophagocytosis may also explain iron deposition in NAFLD. It could be the result of insulin resistance and membrane lipid abnormalities[188]. Recently, aristolochic acid-associated drugs (atypical antipsychotic medications) were reported to induce NAFLD and link insulin resistance with iron metabolism dysregulation irrespective of drug-associated weight gain[189]. Regardless, whatever the etiology of the iron deposition in NAFLD and NASH, the clinical consequences are well documented.

Hyperferritinemia is also frequent in patients with NAFLD. Sometimes, it is the first laboratory abnormality leading to further clinical investigation[190]. In a large prospective population-based study from South Korea, serum ferritin was a strong early predictor of future development of steatosis, indicating that the ferritin association with NAFLD is not a simple consequence of the disease itself[191]. Patients with high ferritin have more severe steatosis[192,193], inflammation[194], advanced fibrosis[195], and increased mortality[196,197]. It has been suggested that serum ferritin could be used as a marker to identify NAFLD patients likely to have NASH and fibrosis[166]. However, a clear association between serum ferritin and fibrosis could not be verified in other studies that reported that ferritin could not accurately predict advanced fibrosis in NAFLD[198,199,200]. This discrepancy may be explained by the findings of a recent investigation in which hyperferritinemia was found in a quarter of NAFLD patients. In this study, stainable iron was present in hepatocytes, Kupffer cells, or more frequently, in both. Importantly, serum ferritin was not related to the presence of NASH, but it increased with worsening of fibrosis and decreased in the cirrhotic stage of the disease[201].

Iron measurement by magnetic resonance imaging (MRI) demonstrates that liver iron is the most important determinant of serum ferritin in NAFLD[202]. An important association of serum ferritin with the gut microbiome was also recently reported. In this study, ferritin levels were associated with differences in gut microbial composition. Both negative and positive associations with particular microbial species were found, and ferritin-related bacterial species correlated with hepatic iron-related genes. Moreover, the iron-associated microbiome was also linked to liver fat load. Fecal transplantation from high-ferritin mice to normal mice confirmed the human results and demonstrated an interplay among iron load, liver fat, and gut microbiome that could be exploited in future treatments[203].

***Hepcidin in NAFLD***

As in other liver diseases, extensive research has been conducted on the possible role of hepcidin in NAFLD. Investigations have tried to identify if the reported hepcidin abnormalities were the cause or the result of the iron overload observed in many cases of NAFLD. In various studies, hepcidin has been demonstrated to be either increased or decreased in NAFLD. In obese individuals, adipose tissue expression of hepcidin was upregulated, irrespective of steatosis and NASH. The contribution of adipose tissue hepcidin to the serum hepcidin is not well studied, but it may potentially explain the increased serum hepcidin in NAFLD[182,204-207].

Furthermore, leptin was found to correlate with hepcidin levels in obese children. Leptin also upregulates hepcidin expression in hepatocyte cultures, indicating that an increase in hepcidin may correlate to the leptin abnormalities in NAFLD[208,209]. Hepcidin downregulation, on the other hand, may be a consequence of oxidative stress secondary to iron overload[158-160,208,210]. Experimental evidence has demonstrated that hepcidin downregulation is a secondary phenomenon occurring after deposition of iron in the liver and the concomitant increase in oxidative stress[211]. Furthermore, an investigation on the relationship between iron stores and cardiovascular damage in patients with NAFLD showed that ferritin was associated with the components of the metabolic syndrome but not with liver inflammation and damage. In this study, hepcidin was increased due to the increased iron load[198], and fat in the liver of mice increased the expression of BMP-binding endothelial regulator, which was produced in sinusoidal endothelial cells and inhibited the BMP-SMAD pathway leading to a secondary inhibition of hepcidin. This is an additional explanation for the iron deposition in NAFLD[212].

Clinical data also indicate that hepcidin abnormalities are not the primary cause of the excess iron in the liver observed in NAFLD. HJV levels were low and hepcidin levels were high in iron-overloaded NAFLD patients. These findings support the suggestion that iron accumulation may be the primary inciting event in this disease[213].

Individuals with the metabolic syndrome preserve the iron regulatory control of hepcidin, and hepcidin progressively increases in response to the increase of iron stores[205,214-216]. In addition, serum hepcidin and HAMP mRNA in the liver correlate to body iron stores irrespective of the degree of iron deposition. Thus, the dysmetabolic iron overload syndrome (DIOS) syndrome seen in NAFLD is not related to altered hepcidin synthesis[217].

However, despite the elevated serum hepcidin, duodenal iron absorption is increased because DMT1 is upregulated by IRP1 activation, likely due to unidentified humoral factors in the sera of NASH patients[218]. It seems, therefore, that elevated hepcidin in NAFLD is either a reflection of hepatocellular inflammation in NASH, or that increased iron and the associated induction of hepcidin appears before the development of NAFLD or NASH[219].

So far, data suggest that the interplay between iron and lipid metabolism is multifaceted in NAFLD. Moreover, it could be suggested that iron is directly implicated in NAFLD pathogenesis. Reports that increased dietary iron from red meat may predispose individuals to type II diabetes and insulin resistance are supportive evidence for such an idea[220-222].

Contrasting results have also been reported. For example, inadequate hepcidin production in response to a given level of iron load in NAFLD patients compared to controls was found in one study[159]. An impairment in the ability of hepcidin to inhibit iron absorption was also demonstrated in DIOS, suggesting hepcidin resistance in this condition[223]. The recent description of ferroptosis has prompted new investigations on the effects of liver iron load in NAFLD, although its exact role in this disease process has not been fully clarified.

Ferroptosis was recently related to the induction of inflammation in the early stages of NASH, making it a possible the “first hit” in its pathogenesis[98]. Further studies indicated that ferroptosis plays a critical role in the progression of NASH, making it a promising treatment target[224,225]. The enzyme arachidonate 12-LOX is known to promote the progression of NASH[226,227], and arachidonic acid metabolism has been shown to trigger ferroptosis in a diet-induced NASH mouse model[224]. Furthermore, the levels of the central regulator of ferroptosis ACSL4 were increased in a rat NASH model, and inhibition of the Mfn2/IRE1αACSL4 pathway was found to prevent incidence and development of NASH[228]. However, the connection between NAFLD and ferroptosis is still debatable, and many reviews of iron and NAFLD pathogenesis have been presented[229-231].

**Alcoholic Liver Disease**

Early reports showed thatstainable iron is present in the livers of alcoholics[232,233]. Hepatocyte iron deposition is considered an important feature of alcoholic liver disease (ALD), although stainable iron in Kupffer cells is more prominent, particularly in the advanced stages of disease[234].Ethanol consumption triggers iron overload[235]; it has been shown in patients with ALD that ethanol increases iron uptake from circulating de-sialylated transferrin by hepatocytes[236].

Almost half of patients with ALD have hepatic iron overload (HIO)[237] with high values of plasma ferritin and transferrin saturation[238,239]. Drinkers, from an early age, have increased iron markers[208,240]. High liver iron was found to be predictive of HCC development or death in patients with alcoholic cirrhosis[241,242], often acting synergistically with diabetes mellitus and viral hepatitis[243,244]. Ethanol is metabolized into acetaldehyde, forming DNA and protein adducts that predispose individuals to HCC[103]. Iron is directly implicated in HCC development, since it accumulates in lysosomes through ferritinophagy and reaches the cytoplasm as free iron[245]. The resultant production of free radicals through the Fenton reaction initially activates Kupffer and stellate cells, ultimately leading to ferroptosis[246]. Additional significant production of ROS is mediated by cytochrome P450 2E1 (CYP2E1), which is directly induced by alcohol[247]. Alcohol consumption results in up to 20 folds increase of CYP2E1[248]. Additional mechanisms of alcohol-induced HCC have also been reviewed[249].

The question of increased iron load in the liver of patients with ALD has prompted research on hepcidin regulation in ALD. Suppression of hepcidin expression by ethanol has been reported in cell culture and experimental animal models, possibly *via* the inhibition of CCAAT enhancer binding protein-α (C/EBP-α)[250-253]. Iron induces activation of C/EBP-α, but ethanol inhibits this action and leads to inadequate hepcidin expression[254]. Suppression of the BMP6/SMAD pathway by alcohol has also been reported[255]. Hepcidin downregulation is also mediated by the induction of oxidative stress caused by either the effects of ethanol itself or free iron. As such, antioxidant treatment attenuates hepcidin downregulation[citation]. Ethanol may also increase hepatocyte iron uptake by upregulating the expression of TfR[246], even in habitual drinkers[256]. Additionally, ethanol may reduce hepcidin through proteins involved in liver regeneration; however, this requires further investigation[257].

Ethanol exposure simultaneously increases the expression of DMT1 and FPN in the duodenum[254], which has been linked to liver fibrosis[254,258]. Iron absorption is increased two-fold in chronic alcoholics[259], and ethanol administration in a mouse model overexpressing adipose tissue lipin-1 accelerated iron accumulation followed by lipid peroxidation, reduction of GSH, and induction of ferroptotic liver damage[260].

The effect of ethanol on hepcidin seems to be more complex than previously thought[261]. Ethanol has been shown to increase transforming growth factor (TGF)-β expression and phosphorylation of SMAD2[262]. Increased activation of SMAD2/3 can abrogate the TGF-β-induced hepcidin upregulation[263]. Hepcidin is also suppressed by ethanol through the toll-like receptor 4 (TLR4) pathway, and ethanol does not suppress hepcidin in TLR4 receptor mutant mice[264]. Interestingly, TLR4 deficiency has been shown to protect animals from liver fibrosis[265,266]. Further evidence suggests that ethanol action on TLR4 involves HSCs, as TLR4 on Kupffer cells or mature hepatocytes are unlikely targets of the effects of ethanol[267,268].

Both serum transferrin and serum hepcidin have been used as prognostic markers in ALD. To this end, low transferrin levels[269,270] have been associated with worse prognosis[197,270-272]. Importantly, the prognostic value of serum transferrin is similar to other traditional prognostic scores, such as the model of end-stage liver disease (MELD) and the Glasgow alcoholic hepatitis scores[273].

The recent identification of ferroptosis has allowed for a better understanding of the connection between lipid and iron abnormalities observed in ALD[274]. Ferroptosis is downregulated during the repair of ethanol-induced liver damage, while ferroptosis inhibition or activation of the Nfr2 pathway reversed ROS accumulation and lipid peroxidation induced by ethanol[275,276]. Excessive ethanol activates genes like frataxin that promote liver injury[277]. More importantly, ferroptosis provides a strong link for the recently demonstrated crosstalk between the liver and the gut[278]. Lack of intestinal sirtuin 1 has been shown to limit ferroptosis, normalize iron overload, and ameliorate ethanol-induced liver damage[279]. Ferroptosis is also implicated in adipose-liver axis abnormalities observed in alcoholic steatohepatitis[260]. Moreover, the overexpression of adipose-specific lipin-1 aggravates alcoholic steatohepatitis and iron deposition, increasing hepatic MDA levels[153,260].

Finally, an additional mechanism of ethanol-induced liver damage has been identified in severe alcoholic hepatitis patients. Iron overload triggers activation of the metallopeptidase ADAM17, which leads to the increase of TNF-α and soluble CD163, resulting in macrophage activation and promotion of hepatic inflammation[280]. Detailed reviews on iron and ALD were recently published[143,281,282].

**Chronic Hepatitis C**

The effect of iron on the activity and infection cycle of the hepatitis C virus (HCV) has been controversial. Inhibition of viral replication by iron due to the suppression of the nonstructural protein 5B has been reported[283],but enhancement of viral replication has also been observed[284]. HCV alters the expression of hepcidin and therefore cellular iron metabolism[285,286]. Experimental evidence in early HCV infection has demonstrated increased hepcidin expression followed by enhanced viral translation and replication. In this study, iron loading of macrophages accompanied hepcidin upregulation and resulted in increased viral transmission to naïve cells[287]. Other experimental studies, however, have shown that hepcidin levels are low in HCV-infected cell lines[288,289].

Inhibition of hepcidin expression has been attributed to HCV-induced oxidative stress[290,291]. Experiments in chimpanzees on high iron diets have demonstrated that liver damage is observed only in animals infected with HCV, indicating a harmful effect of iron in HCV infection[292]. In chronic infection, HCV interferes with the expression of the iron uptake receptor TfR1, a known mediator of HCV internalization[293,294]. The observed downregulation of hepcidin despite hepatic inflammation in chronic HCV[295] may be related to impairment of the BMP6/HJV pathway by TNF-α, which would suppress the transcription of HJV[296].

Clinical studies have verified that HCV infection downregulates hepcidin[297-299], and serum hepcidin has been correlated with severity of liver disease[300]. More than 40% of patients have iron overload associated with a high rate of liver damage and inflammatory activity, as well as an increased risk of hepatocarcinogenesis[301-303]. Hepatic iron and HCV proteins in combination produce a toxic hydroxyl radical (·OH) that forms mutagenic bases such as 8-hydroxy-2-deoxyguanosine (8-oxodG)[304,305]. HCV patients have been shown to have an approximately 10-fold increase of 8-oxodG in liver tissue compared to non-HCV control patients[306].

The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial has convincingly demonstrated that iron in hepatocytes and portal tract cells predicts progression to decompensated cirrhosis, HCC, and death[307]. Almost all liver tissue from HCV patients had some lysosomal iron deposits detected by electron microscopy and X-ray microanalysis, despite negative results with classical Prussian Blue staining[308]. Moreover, increased serum aminotransferases were found only in HCV patients with stainable iron in Kupffer cells but not in those with hepatocellular iron[309].

Even minor increases in iron load in heterozygous carriers of C282Y or H63D gene mutations for hemochromatosis were found to induce more fibrosis in chronic HCV infection[310,311]. Genotype 3-infected patients have more frequently elevated liver iron, which has been associated with hepatic steatosis in this type of HCV infection[312]. Evidence from thalassemia patients further indicates that iron adversely affects the disease course of HCV, increasing morbidity and mortality due to more severe liver disease[313].

Liver iron also adversely affects the response to interferon (IFN)-based treatments[314]. In studies involving IFN treatment, ferritin levels increased regardless of sustained virologic response (SVR) and decreased at about 3 years post-treatment. This is not the case with direct-acting antivirals (DAAs)[315,316], where SVR is achieved irrespective of iron status[317-320]. A recent study demonstrated that pre-treatment elevated serum ferritin and ERFE levels were restored after treatment with DAAs and correlated with changes in LDL cholesterol levels, but only in men[321].

Plasma ferritin, liver iron, and transferrin saturation are also increased in HCV infection[322] and elevated serum ferritin has been related to liver fibrosis[323]. An additional reason for increased liver iron in HCV patients is the reported increased hemolysis particularly in advanced stages of the disease[151]. Despite the evidence presented above, different results in relation to the role of HCV-induced iron overload have been presented[324,325]. In several studies, elevated serum ferritin and hepatic iron played no significant role in the progression of liver damage[326,327]. Moreover, the significance of hemochromatosis mutations has been questioned as a risk factor in the progression of HCV-related disease[328].

Recently, it has been suggested that ferroptosismay be implicated in the natural course of HCV[58]. Importantly, HCV replication is inhibited by an iron-dependent mechanism like ferroptosis, which is mediated by the desaturation of oleate to highly unsaturated fatty acids by the enzyme fatty acid desaturase 2 (FADS2). This is a key determinant of cellular sensitivity to ferroptosis; FADS2 suppression significantly enhances HCV replication, whereas the ferroptosis inducer erastin sensitizes HCV to DAAs, altering the conformation of HCV replicase[329].

**Chronic Hepatitis B**

Iron favors hepatitis B virus (HBV) mRNA expression in HepG2 cells[330]. Increased serum and cellular iron uptake and decreased hepcidin expression have been reported in HBV infection[297,331]. Hepatitis B-infected patients frequently show iron deposition in hepatocytes and elevated liver iron concentration (LIC) leading to increased disease severity[332,333]. Serum ferritin levels are also increased in patients with chronic HBV[332].

Levels of hepcidin are increased in early stages of HBV and reduced in the cirrhotic stage[334,335]. Co-infection with hepatitis D increases the iron load[332]. However, results of studies regarding serum hepcidin in HBV infection are not uniform. Reduced serum hepcidin has been reported in HBV patients with or without cirrhosis[336],while another report found that hepcidin is slightly increased in HBV patients without cirrhosis and in those with HCC[335]. The reason for this discrepancy is not clear. Nonetheless, decreased hepcidin levels and elevated transferrin saturation and ferritin levels have been associated with fibrosis severity in patients with chronic HBV[337].

It should be noted that iron deposition in the liver has been considered a secondary phenomenon. Damaged hepatocytes in viral hepatitis undergo necrosis and the released iron is scavenged by Kupffer cells[240,338]. However, this mechanism cannot entirely account for the deposition of iron in hepatocytes. The implication of HBV in iron deposition is exemplified in a case report in which a female patient with symptoms of iron overload had highly increased serum ferritin and transferrin saturation. In this case, all of the patient’s symptoms resolved and her iron abnormalities normalized after HBV antiviral monotherapy[339].

**Liver fibrosis and cirrhosis**

Nearly 6 decades ago, it was shown that iron on liver biopsy is associated with manifestations of advanced disease compared to that in non-iron overloaded cirrhotic patients[340]. Cirrhotic patients with hemosiderosis are more likely to be classified as Child Pugh class B or C with higher MELD scores than those without stainable iron[341,342].

As mentioned before, hyperferritinemia and high liver iron predict the risk of advanced liver fibrosis in NAFLD[166,179,343]. A recent study of a large number of NAFLD patients with a long follow-up (mean 8.4 years) emphasized the fact that it is the non-parenchymal iron deposition that leads to serious liver disease[344].

Fibrosis is increased by the presence of iron throughincreased HSC proliferation and selectively increased collagen synthesis without interference by non-collagen proteins[345,346]. Experiments with cultured HSCs have shown that incubation with either ferritin or transferrin increases nuclear factor kappa-B translocation and HSC activation[347,348], and enhances α-smooth muscle actin, collagen, and vimentin synthesis[349]. Isoprostanes, products of arachidonic acid peroxidation produced during iron-induced oxidative stress, increase HSC-collagen-production and TGF-β release from Kupffer cells[350]. Furthermore, 4-HNE upregulates the expression of collagen and the TIMP-1 inhibitor of metalloproteases in HSCs[351].

Elastin, another component of the extracellular matrix, is also affected by iron. Elastogenesis is modulated in cultured human skin fibroblasts by iron, as evidenced by the levels of both elastin protein and elastin mRNA are increasing 3-fold[194]. Liver iron load also induces both TGF-β[352] and BMP-6[353,354]. The connection between fibrosis and hepcidin pathways and the significance of SMAD4 as their common link has been demonstrated[353]. Other signaling pathways related to fibrosis are also modulated by iron. For example, iron deficiency stimulates Notch signaling[355], and recently, iron-loading revealed a protective role of β-catenin (a component of the cadherin complex that stimulates Wnt signaling) against liver fibrosis[356]. Hepcidin also has a protective role in liver fibrosis by suppressing HSC activation[357]. BMP6, the main hepcidin inducer, has a similar protective role in fibrosis inhibiting HSCs activation[358]. Evidence regarding the role of ferroportin in liver fibrosis is limited. However, ferroportin has been shown to be increased in activated HSCs and the anti-fibrotic action of hepcidin in HSCs mentioned above may be mediated by degradation of ferroportin[357].

Clinical evidence confirms the importance of iron metabolism in the development of fibrosis. For example, ferritin levels have been associated with decompensation and increased mortality in cirrhosis[359]. However, ferritin concentration has poor sensitivity as a marker of liver fibrosis, since it also increases as a result of inflammation[360]. Transferrin also has clinical significance in HCV- and HBV-related cirrhosis; it has been associated with advanced fibrosis and is a predictor of survival in cirrhotic patients[269,301,338]. Additionally, low hepcidin levels can cause iron overload and increased oxidative stress in the liver[361], which in combination with other factors such as genetic variables, viral infections, and alcohol use, can eventually lead to liver fibrosis[362].

Low hepcidin has also been demonstrated as a predictor of mortality and development of HCC in alcoholic cirrhosis[258,363]. Similarly, in HBV cirrhosis, hepcidin is low compared to patients without cirrhosis[335,364], where values are similar to healthy controls[335,365]. In HCV-related cirrhosis and alcoholic cirrhosis, hepcidin is significantly lower than in HBV cirrhosis[365-367].

Hepcidin levels are not reduced in the early stages of NAFLD, but eventually drop in advanced fibrosis, similar to what has been observed in other liver diseases[368]. Unlike ferritin[369], serum hepcidin is a reliable marker of severity of fibrosis in NAFLD[368,370]. A low hepcidin/ferritin ratio can differentiate between cirrhosis and non-cirrhosis in patients with HBV, HCV and NAFLD[367], but not in ALD patients, possibly because ethanol directly inhibits hepcidin expression as mentioned above.

***Ferroptosis***

The role of ferroptosis in liver fibrosis was recently investigated. Its role is debatable as both induction and attenuation of liver fibrosis by ferroptosis has been reported. Ferroptosis increased susceptibility to fibrosis in mice on a high-iron diet, an effect reversed by a ferroptosis inhibitor[12]. However, other studies have shown that ferroptosis attenuates HSC activation and reduces liver fibrosis. Moreover, the ferroptosis inducers erastin and sorafenib reduce liver fibrosis increasing ferritinophagy[371], and MgIG increases ferroptosis, leading to reversion of fibrosis[123]. The anti-malarial agent artemether increases the p53-dependent ferroptosis and inhibits HSC activation[372] and artesunate, a derivative of artemisinin with immunomodulating properties, induced ferroptosis of activated HSCs possibly triggering ferritinophagy[121]. The role of iron in liver fibrosis has been recently reviewed[152,373].

**HCC**

Hepatic iron overload has long been linked to HCC tumorigenesis and tumor growth[147,374-376]. Iron incubation of an HCC cell line has been shown to increase mesenchymal and metastatic markers, representing a fundamental defect in cancer development[377]. Patients with hereditary hemochromatosis show a 20-200-fold increase risk of HCC development[378,379]. Additionally, iron score has been demonstrated to be significantly higher in HCC-NASH patients than in NASH controls[343]. In HCC patients, iron localization is mainly sinusoidal[187], and iron deposition in the portal tract has been associated with poor survival after tumor resection[380]. Similar findings have been reported in prospective studies of HCC in alcoholic cirrhosis[241] and in HCV-associated cirrhosis[381].

Several studies suggest an association between HCC and dietary iron overload from beer fermented in steel drums in black Africans[382-385]. Furthermore, experimental evidence has identified several mechanisms of iron involvement in HCC development. Namely, HCC cells, like many other cancer cells, upregulate iron uptake and intracellular iron accumulation since they are dependent on iron[386,387]. The generation of ROS by this iron favors carcinogenesis through promotion of genomic instability and generation of DNA repair defects[388,389]; in other words,, this generation of ROS maintains the oncogenic phenotype of cancer cells[390,391]. The direct hepatocarcinogenic effect of free iron in the pathogenesis of HCC has also been demonstrated in an animal model of iron-rich diet where the tumor developed without fibrosis or cirrhosis[392,393]. Additionally, iron deposition directly decreases p53 protein level and its activity in the liver, facilitating the development of HCC[394]. An important mediator of intracellular iron is the protein leucine-rich repeat protein 5 (FBXL5); exposure of FBXL5 knockout animals to chemical or viral carcinogens has been shown to result in increased liver tumor formation. More importantly, low levels of FBXL5 in HCC patients are associated with a poor prognosis[395]. Ferritin heavy chain (FTH) acts as a protector of HCC cells, increasing their cellular resistance to ferroptosis, thereby acting as an oncogene in the pathogenesis and progression of HCC[396].

HCC patients in contrast to those with other cancers have low hepcidin levels[397-399]. Many mechanisms lead to the final decrease of hepcidin in HCC, including downregulation of inducers such as HAMP, TfR and HJV, and upregulation of suppressors such as matriptase 2 and GDF15[400]. Hepcidin downregulation increases cellular proliferation and HCC risk *via* reduction of the hepcidin protection against HSC activation. The downregulation of hepcidin in HCC has been attributed to the effects of cirrhosis rather than to HCC itself. Cirrhotic patients also show decreased hepcidin expression irrespective of disease etiology[152,336,399], while the hepcidin:ferritin ratio has been reported to decrease with fibrosis progression[373].

Ferroptosis and its inducers have been extensively investigated in HCC as it is considered an effective tumor suppression mechanism[81,401-403]. On the other hand, genes negatively regulating ferroptosis increase HCC drug resistance[404]. Sorafenib, a drug used for treatment of advanced HCC, is one example. This drug can induce the expression of metallothionein-1G (MT-1G), and upregulation of MT-1G has been demonstrated to serve as a negative regulator of ferroptosis, conferring resistance to sorafenib[405]. Some studies have also found that haloperidol can facilitate the cascade of ferroptosis induced by sorafenib in HCC[406].

In contrast to the negative regulators of ferroptosis, ACSL4 can positively regulate ferroptosis in HCC[97]. Inhibition of ACSL4 protects sorafenib-induced ferroptosis in HCC cells. A human study demonstrated an upregulation of the ACSL4 protein in HCC tissue from surgical specimens with a good response to sorafenib as a postsurgical adjunct treatment[407]. ACSL4 may therefore serve as a prognostic factor for survival and disease-free survival time[407,408].

Natural omega-3 PUFAs are the main peroxide substrates in ferroptosis and have anti-tumor activity[409], a fact that has been therapeutically exploited[410]. PUFAs consumed in the form of fish can reduce the risk of HCC development[411]. Ceruloplasmin has also been shown to inhibit ferroptosis in HCC cells, interfering with iron metabolism. Moreover, inhibition of ceruloplasmin increases the accumulation of iron and ROS production, facilitating erastin-induced ferroptosis in HCC cells[412].

Additional regulators of ferroptosis in HCC are the long non coding RNA molecules (lncRNAs), but their role has not been fully elucidated[413]. Erastin-induced ferroptosis upregulates the lncRNA GABPB1-AS1 in HepG2 cells, silencing the gene encoding peroxiredoxin-5 peroxidase and eventually leading to a reduction in cellular antioxidant capacity[414]. The predictive value of lncRNAs associated with ferroptosis in HCC has been recently addressed. Nine and five ferroptosis signature models have been established, which identified two groups of patients; the high-risk group in this study was shown to have enhanced tumorigenesis and worse prognosis[415,416].

Equally, the non-coding circular RNAs (circRNAs) seem to play a role in the development of HCC through ferroptosis. The circ0097009 endogenous RNA regulates the expression of SLC7A11, a key regulator of cancer cell ferroptosis in HCC. Circ0097009 therefore may be used as a potential target for HCC treatment[417].

Ferroptosis-related genes (FRGs) have also been identified and found to be upregulated in HCC tissue. In one study, three clusters have been determined, and a high expression of cluster 3 has been associated with worse prognosis and a higher histological stage[418]. Another approach regarding the use of ferroptosis as a prognostic marker in HCC has also recently been presented in which a novel ferroptosis-related 10-gene signature stratified HCC patients into two risk groups[419]. Those in the high-risk group have significantly reduced survival. The role of ferroptosis in HCC generation and progress has been recently reviewed[420].

**Cholestatic diseases**

Hepcidin is significantly lower in patients with primary biliary cholangitis and primary sclerosing cholangitis compared to patients with other chronic viral and metabolic liver diseases. In one study, low hepcidin was maintained even after two years of treatment[421]. The reason for low hepcidin may be the suppression of STAT3 phosphorylation by accumulated bile acids. Furthermore, hepcidin remains lower in cholestatic cirrhosis compared to non-cholestatic cirrhosis, suggesting the critical role of cholestasis in maintaining low values of hepcidin[422].

**Autoimmune hepatitis**

There is experimental evidence suggesting that iron is implicated in autoimmune hepatitis (AIH) through ferroptosis involvement. The classical AIH-inducer Concanavalin A (ConA) has been linked to an overproduction of reactive nitrogen species (RNS) such as nitric oxide and peroxynitrite in a mouse model of AIH. This effect is attenuated by Fer-1, indicating that ConA induces ferroptosis in the liver. Moreover, gadolinium chloride (a Kupffer cell depleting agent) inhibits RNS and hepatocyte ferroptosis[423]. Indoleamine 2,3-dioxygenase 1 (IDO1) is an intracellular heme enzyme involved in autoimmune diseases[424]. Upregulation of IDO1 has also been shown to be involved in ConA-induced hepatocyte ferroptosis through RNS accumulation and hepatocyte ferroptosis. An IDO1 inhibitor and an IDO1 knockout were shown to induce this effect, indicating that IDO1 promotes hepatocyte ferroptosis by triggering nitrative stress[425].

Clinical evidence also supports the detrimental effect of iron in AIH. Ferritin and iron are increased in serum of 65% and 58% of naïve patients with AIH respectively, which is resolved after successful treatment[426]. Increased serum ferritin has been independently associated with advanced fibrosis in patients with untreated AIH[427]. Moreover, serum hepcidin is low in patients with liver autoimmune disease[367,421]. Interestingly, in AIH, low serum hepcidin levels remain after 2 years of treatment, a finding similar to observations in autoimmune cholestasis. A plausible explanation could be that hepcidin is involved in hepatic autoimmune processes[428].

**Ischemia-reperfusion injury**

Although ischemia-reperfusion injury (IRI) is not strictly a liver disease as it also occurs with other organ transplantations, iron is clearly involved in the pathogenesis of IRI-related hepatic abnormalities. Ferroptosis is implicated in the pathogenesis of IRI through GPX4 inactivation[59,429]. Iron overload and upregulation of the ferroptosis indicator PTGS2 are prominent characteristics of IRI in the liver[59]. An analysis of 202 live-donor liver transplantation patients showed a high serum ferritin level indicating iron overload[430]. In this study, use of ferroptosis inhibitors such as Fer-1, α-tocopherol, and DFO prevented hepatic IRI.

**Acute Liver Failure**

Ferroptosis is also involved in the development of acute liver failure (ALF). In sepsis-induced ALF, analysis of the liver infiltrate has shown that FRGs may be responsible for the development of liver failure through the activities of B cells and natural killer cells[431]. The most common reason for ALF, however, is acetaminophen (APAP) toxicity in which lipid peroxidation leads to hepatocyte ferroptosis[432].

GSH is important for the inactivation of the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) responsible for APAP toxicity. GSH reduction and GPX4 inhibition are common in APAP-induced cell death[433]. The viability of mouse hepatocytes in the presence of APAP is improved by fer-1 without restoring the cellular GSH level, suggesting that suppression of the conversion of APAP to NAPQI is not the reason for the protective effect of fer-1[434]. Consistently, other experiments have confirmed the role of ferroptosis in APAP-induced hepatocyte cell death[432,435-437]. An additional mechanism of APAP-induced ferroptosis is the significant hepcidin reduction, likely *via* activation of HIF1[434,438-440].

However, the role of ferroptosis in APAP toxicity and other drug-induced liver injury is disputed. An earlier report showed that α-tocopherol does not improve APAP-induced liver injury and that lipid peroxidation is not involved in APAP hepatotoxicity[441]. A recent review suggests that APAP-induced hepatotoxicity should be identified as programmed necrosis and not ferroptosis or other types of cell death[442]. Therefore, more research is required before ferroptosis inhibitors are recommended as treatments for APAP toxicity.

**Sickle Cell liver disease**

Sickle cell liver disease (SCD) is an inherited disease caused by the presence of hemoglobin S. Under hypoxic conditions, red blood cells are dehydrated and form the characteristic sickle cells[443,444]. The formation of hemoglobin S is due to a single substitution of an amino (glutamic acid to valine) in the beta globin chain[444]. Viral hepatitis and iron overload are two major reasons for the development of liver disease in SCD, both of which are typically related to patients receiving multiple blood transfusions[445]. Sources of hepatic iron in SCD include these multiple blood transfusions and chronic intravascular hemolysis[446]. Liver iron deposition occurs mainly in Kupffer cells[447]. Liver iron deposition can also occur in non-transfusion dependent patients[448], and there is a single case described in a patient who never received any blood transfusion[449]. Hemosiderosis in SCD may lead to fibrosis and overt cirrhosis[445,448,449].

**coronavirus disease 2019**

There is considerable evidence to suggest an association between ferroptosis and coronavirus disease 2019. Cytokines produced during the infection have been shown to upregulate hepcidin expression, which leads to ferroportin suppression and iron accumulation. In addition, severe acute respiratory disease coronavirus 2 downregulates the expression of GPX4, contributing further to the initiation of the Fenton reaction and production of massive amounts of ROS and associated ferroptosis[450].

**Targeting iron**

There have been many attempts to reduce iron overload, which is uniformly considered detrimental in liver disease irrespective of etiology. However, it should be remembered that iron loading is not always similar between patients and between stages of various diseases[152]. Dietary iron restriction has been shown to be effective in reducing liver fibrosis and steatosis in diet-induced NAFLD animal models[451,452].

Phlebotomy is the traditional treatment in hereditary hemochromatosis, as it increases erythropoiesis, partially reverses liver fibrosis, and increases life expectancy[453,454]. Phlebotomy has been used to treat NASH patients, but the clinical benefit is unclear[455]. Phlebotomy improves liver enzymes, insulin resistance, and liver histology in the majority of NAFLD patients, but it is not fully successful in DIOS insulin resistant patients with slight ferritin increase[182,456-458]. Insulin sensitivity is improved by phlebotomy in type II diabetics with a high serum ferritin[459]. Moreover, in patients with the metabolic syndrome, phlebotomy improves metabolic parameters, including glycosylated hemoglobin A1c and LDL/high-density lipoprotein ratio[460]. In a meta-analysis of four interventional studies with more than 400 patients, phlebotomy was shown to improve liver enzymes, insulin resistance, and lipid abnormalities[461].

In contrast, no effect was reported in two prospective randomized controlled trials. The first, which is the largest series so far, was conducted in NAFLD patients[462], and the second in DIOS patients with insulin resistance[463]. To this end, the benefit of phlebotomy in patients with NASH remains unclear until more extensive studies are available[464].

Phlebotomy reduces the marker of oxidative stress 8-hydroxy-2’-deoxyguanosine in HCV patients who have failed IFN therapy. Fibrosis and inflammation are also reduced, but HCV titers are unaffected. None of the patients in these studies were shown to develop HCC at the six year follow-up point[306,465]. Reduction of HCC development in HCV patients after phlebotomy has been verified in additional studies[466,467]. Phlebotomy has also been reported to improve the response to IFN in chronic HCV[468].

Iron chelation is an additional intervention to reduce liver iron. DFO has been successfully used to control fibrosis in hemochromatosis[469]. Studies in several animal models have revealed that iron chelation decreases the stability of procollagen mRNA[470] and reduces elastin mRNA[194]. DFO has also been shown to reverse HSC activation and induces apoptosis of activated murine HSCs[471]. More recently, a study of the combination of DFO with pegylated IFN-α showed a synergistic anti-fibrotic effect in rats[472]. ROS degrade the apolipoprotein B100 (apoB100) component of VLDL, thereby enhancing hepatocyte steatosis in rodents. In another study, DFO restored apoB100 and increased VLDL secretion[473]. No firm conclusions can be drawn, however, without the results of clinical trials. It should be noted that inhibition of hemoxygenase-1 decreases hepatic iron deposition and attenuates liver fibrosis in rats[474].

Interestingly, commonly used drugs like the calcium channel blockers have been found to induce HSC apoptosis and reduce DMT1 expression, hepatic iron deposition, and liver collagen in mouse and cellular experiments[475]. Hepcidin may be a promising agent for the treatment of liver iron overload, ashepcidin administration has been shown to attenuate iron deposition in mouse models of hemochromatosis[476-478], while its overexpression ameliorates fibrosis severity. This is due to the inhibition by hepcidin of the TGFβ1-induced SMAD3 phosphorylation in HSCs, a pathway that requires the presence of ferroportin in stellate cells[357]. Similar reduction of liver fibrosis has been observed with BMP6 overexpression in murine and human NAFLD[358].

Hepcidin responds to iron conditions in HCV patients, but the response is impaired. Thus, correction of hepcidin regulation may improve the clinical progress in iron-overloaded HCV patients[479]. Hepcidin manipulation may be beneficial in the management of HCC as well. The iron chelator deferasirox induces apoptosis in hepatoma cells lines and decreases liver tumor development in mice, increasing HAMP mRNA expression. However, toxicity and the lack of response in some patients may be a problem in human trials[480]. Additionally, some HCC patients have increased hepcidin expression and downregulation of hepcidin may be required. In a murine HCC model with high liver hepcidin, the traditional Chinese medicinal herb dandelion polysaccharide has been shown to reduce hepcidin expression, arrest the cell cycle, and suppress the HCC proliferation[481]. Hepcidin, therefore, is a logical candidate target for clinical trials in HCC. Indeed, both hepcidin agonists and inhibitors have been tested *in vitro* and in laboratory animals[482]. It should be noted that synthetic mini-hepcidins have also been tested in Hamp -/- mice; in one study, serum iron was reduced after chronic administration of the drug[476].

Ferroptosis is the current therapeutic target in the treatment of iron overload diseases. It should be stressed, however, that the effects of ferroptosis in chronic liver disease depends on the cell type and the specific environment. In liver fibrosis, for example, ferroptosis has different effects on hepatocytes and HSCs as will be detailed later[483]. A future challenge is to develop drug delivery systems targeting ferroptosis in specific cell types. In ALD and in NAFLD, ferroptosis is implicated in liver damage, and ferroptosis inhibition would theoretically be beneficial[225,276,432]. For example, ferroptosis-induced liver injury could be reversed by sestrin 2, an antioxidant protein increased by ferroptosis inducers[484].

***Ferroptosis inducers***

In contrast to other liver diseases where ferroptosis is detrimental and therapies are directed towards inhibition of ferroptosis, HCC is benefited by enhancement of ferroptosis. Thus, ferroptosis inducers are used in advanced HCC. Sorafenib, a multi-kinase inhibitor, is the most extensively studied ferroptosis inducer[103,485]. In HCC, this drug acts by inhibiting cellular proliferation and neo-angiogenesis. Additionally, it induces ferroptosis in HCC cells[486]. It has been reported that sorafenib decreases the uptake of cystine in the Xc- system and starts the chain of events leading to ferroptosis induction through the accumulation of ROS, which is the result of GSH depletion and loss of GXP4 activity[487]. Excessive ROS production also results in the inhibition of the retinoblastoma protein Rb, an important negative regulator of cell proliferation[488].

Prolonged administration increases the resistance of HCC cells to sorafenib. ABCC5, a recently described regulator of ferroptosis, increases the generation of GSH and reduces the production of ROS through stabilization of SLCA11 and subsequent inhibition of ferroptosis. Accordingly, downregulation of ACCC5 reduces resistance to sorafenib[489]. Other proteins reducing the sorafenib-induced ferroptosis through stabilization of SLCA11 have also been recently described[490,491].

Haloperidol has also been shown to promote erastin- and sorafenib-induced ferroptosis, suggesting that it could be used in combination with sorafenib to achieve either dosage or resistance reduction[404,406,492]. An upregulation of Nrf2 through activation of the p62-Keap1-Nrf2 pathway inhibits sorafenib-induced ferroptosis in HCC cell lines[63,493]. Interestingly, trigonelline, the active ingredient of the traditional Chinese medicine fenugreek, increases ferroptosis by acting on Nrf2, therefore reducing sorafenib resistance[494]. Overexpression of the leukemia inhibitory factor receptor (LIFR) has also been shown to increase sorafenib-induced ferroptosis of HCC cell lines, whereas reduced LIFR expression increases resistance to ferroptosis[495].

A recent study reported an another target for HCC treatment. In this study, lactate-rich hepatoma cells were shown to exhibit increased resistance to the ferroptosis generated by common ferroptosis inducers. Moreover, lactate uptake was shown to be mediated by monocarboxylate transporter 1 (MCT1), which enhances the production of monounsaturated fatty acids, blocking ferroptosis. Inhibition of MCT1-mediated lactate uptake enhances ferroptosis[496]. In contrast to the presented evidence, a recent report indicated that sorafenib may not be an inducer of ferroptosis at least in many cancer cell lines[497]. Other drugs that could be used in the treatment of HCC based on increased ferroptosis have also been recently described[498,499]. Heteronemin, a marine terpenoid, induces ferroptosis in HCC cells by reducing GPX4[500]. IFN-γ has also been confirmed to inhibit system Xc- activity and increase ferroptosis[501]. Lenvatinib, another kinase inhibitor used in advanced HCC treatment, also acts through the inhibition of the system Xc-. Fibroblast growth factor receptor-4 (FGFR4) increases the activity of the system Xc- and lenvatinib inhibited FGFR4 increasing ferroptosis. Interestingly, patients with HCC positive for FGFR4 have a longer progression-free survival compared to those with FGFR4-negative HCC. Nrf2 upregulation has also been shown to decrease the sensitivity of HCC to lenvatinib[502]. Moreover, low-density lipoprotein nanoparticles (LDL-DHA NPs), selectively induce HCC cell death in mouse models, and LDL-DHA NPs enhance lipid peroxidation due to both GSH depletion (leading to GPX4 inactivation) and direct degradation[410].

Ferroptosis can be used for stratification of HCC patients to predict both prognosis and suitability for immunotherapy. For that purpose, a ferroptosis-related prognosis risk score model has been developed to stratify patients into two subgroups based on six FRGs (FRGs)[503].

Ferroptosis inhibitors are promising drugs in the treatment of various liver diseases, although evidence is mainly based on laboratory data. NAFLD and NASH progress is worsened by induction of ferroptosis[98,224,504]. Alleviation of NASH can be achieved by ferroptosis inhibitors, such as liproxstatin-1 or ferrostatin-1[225,505]. In one study, administration of the ferroptosis inducer RSL3 aggravated hepatic steatosis and inflammation in diet-induced NASH mice, while administration of liproxstatin-1 ameliorated NASH severity and rescued animals from cell death[225].

Other drugs, such as Ginkgolide B and dehydroabietic acid, alleviate NASH severity by inhibiting ferroptosis *via* upregulation of the p62-Keap1-Nrf2 pathway[506-508]. Thymosin β4 (Tβ4) improves liver lipid metabolism markers in NAFLD rat models and inhibits the palmitic acid-induced hepatocyte death in the LO2 cell line. Ferrostatin-1 increases the effect of Tβ4, which is attenuated by erastin, indicating that the protection of hepatocytes is mediated by ferroptosis reduction[509]. The enzyme enoyl coenzyme A hydratase 1 (ECH1) is an important component of mitochondrial fatty acid β-oxidation. ECH1 knockdown aggravates liver inflammation and fibrosis in mouse NAFLD models while fer-1 administration alleviates liver damage, again suggesting that the beneficial effect of ECH1 may be due to inhibition of ferroptosis[505].

Liver fibrosis is another disease that may be treated by ferroptosis regulators[510]. Inhibition of ferroptosis by ferrostatin 1 reverses liver fibrosis induced by a high-iron diet or and carbon tetrachloride[511], while induction of ferroptosis by liver iron overload aggravates APAP-induced fibrosis in mice[483]. However, ferroptosis is a double-edged sword in liver fibrosis. When ferroptosis is targeting activated HSCs, the induction of ferroptosis is beneficial. The cystine/glutamate antiporter SLCA11 has been shown to increase ferroptosis as mentioned before[55]. Inhibition of SLC7A11 enhances ferroptosis in HSCs and attenuates liver fibrosis[512]. Likewise, erastin and sorafenib induce ferroptosis in HSCs, and reduced liver fibrosis in mice[371,513].

There is growing evidence that natural products may effectively be used in the treatment of liver fibrosis. Artesunate can attenuate liver fibrosis by triggering ferritinophagy-mediated ferroptosis in HSCs[121]. Artemether can also induce ferroptosis in HSCs by increasing iron and ROS in HSCs[514] and promoting p53-dependent ferroptosis[372]. MgIG can also induce ferroptosis in HSCs by increasing the activity of the enzyme HO-1[123].

Chrysophanol isolated from the rhizome of rhubarb can inhibit the HBV x protein-induced activation of HSCs through ferroptosis and alleviate HBV-related fibrosis[515]. Additionally, wild bitter melon extracts can downregulate GPX4 and SLC7A11 in activated HSCs by inducing ferroptosis[516]. Two other proteins regulating ferroptosis in HSCs could be the future targets in the treatment of liver fibrosis: ZFP36/TTP and ELAVL1/HuR. These are critical regulators of HSCs ferroptosis[371,513]; ZFP36 protects against ferroptosis and ELAVL1 contributes to ferroptotic cell death.

Three more diseases may be benefited from ferroptosis inhibitors. Fer-1 improves I/R-mediated liver disease[59,224,276]. ALF is also a candidate for similar treatment based on experimental data. Glycyrrhizin, an active constituent of the licorice root, reduces ferroptosis during ALF, inhibiting oxidative stress through the Nrf2/HO-1/high mobility group box 1 pathway[517]. Finally, reduction of liver iron load will most certainly benefit ALD. Phlebotomy, however, is not recommended in patients with ALD.

An interesting approach to reduce iron load in ALD is the stabilization of erythrocytes and associated reduction in hemolysis. Administration of N-acetylcysteine or protective heme carriers like haptoglobin and hemopexin has been tested. Erythrocyte stabilizers include vitamins such as B12 or folate[281]. Ferrostatin-1 can also reduce alcoholic liver damage[276], indicating participation of ferroptosis in ALD progression. Dimethylfumarate reduces lipid peroxidation and alleviates liver cell ferroptosis leading to ALD improvement in a murine model[275]. Currently, no effective treatment can be recommended for ethanol-induced iron overload. Modulation of ferroptosis for the treatment of chronic liver diseases has been recently reviewed[282].

**Nutrients as treatment options of liver iron overload**

***Vitamin A***

Retinoid signaling is decreased in the livers of humans and mice with NAFLD[518,519], and is epigenetically silenced in HCC[520]. Administration of the synthetic retinoid tamibarotene improved oxidative stress and iron deposition in iron-fed mice. Retinoids downregulate the hepatic expression of HJV, leading to liver hepcidin downregulation and ferroportin upregulation[521,522]. Retinoids also attenuate insulin resistance and hepatic steatosis in a murine model of NAFLD[523,524]. Attenuation of hyperinsulinemia may prevent the development of HCC in NAFLD[525].

***Vitamin C***

A very large observational study with more than 8000 participants demonstrated that dietary vitamin C supplementation decreases plasma ferritin levels[526], indicating that vitamin C limits iron deposition and thereby increases iron mobilization. In a murine model of ALD, vitamin C administration was shown to restore hepatic hepcidin and downregulate intestinal ferroportin, leading to HIO amelioration[527]. Therefore, it is reasonable to supplement vitamin C in ALD and chronic HCV patients with hepatic iron deposition.

***Vitamin D***

Evidence from patients with thalassemia major and hereditary hemochromatosis indicates that iron overload suppresses vitamin D, as there is a negative correlation between liver iron and 25-hydroxyvitamin D levels[528-530]. In hereditary hemochromatosis, levels of vitamin D are partially restored after phlebotomy[531]. Moreover, vitamin D depletion exacerbates HIO in HJV knockout mice, an effect that is corrected by the administration of the calcium channel blocker verapamil but not by vitamin D supplementation[475,532]. These results indicate a link between iron and calcium and justify the use of calcium channel blockers as a treatment modality for iron deposition in patients with decreased levels of vitamin D, as is frequently observed in ALD, NAFLD, and chronic HCV[533-536].

***Zinc***

Zinc-deficient diet has been shown to lead to increased plasma ferritin and development of HIO in rats, while zinc supplementation returns liver iron to normal[537]. Clinical studies also indicate that iron deficiency anemia is frequently associated with zinc deficiency[538,539], implying a physiological crosstalk between iron and zinc. For example, zinc plus iron administration in rats has been demonstrated to ameliorate anemia more efficiently than iron alone[540]. The therapeutic effects of zinc on chronic liver diseases have been reviewed[541].

***Folate***

The Solute Carrier Family 46 Member 1 (SLC46A1) is the major importer of heme‑iron in the duodenum, and it is also present in the liver. In murine liver-specific SLC46A1 knockdowns, its role in liver iron deposition has been investigated. In these studies, SLC46A1 was found to take up heme in the liver and contribute to hepatic iron deposition. Interestingly, heme inhibited folate uptake after downregulation of SLC46A1 expression, but folate supplementation had no effect in heme uptake and SLC46A1 expression indicating that folate deficiency was the result of secondary liver heme uptake excess[542]. Accordingly, the combined administration of iron and folate in rats also significantly reduced liver iron compared with iron alone[543].

***Riboflavin***

Contrary to the agonistic use of the previously discussed nutrients in the treatment of liver iron deposition, riboflavin antagonists, such as galactoflavin, may be used in HIO[544]. This is because riboflavin deficiency leads to a decrease in iron absorption[544,545]. A detailed discussion on the role of nutrients in chronic liver diseases was recently published[546].

**CONCLUSION**

It is well documented, that iron in the liver is a double-edged sword. It is a necessary element in many metabolic pathways, but it is equally harmful if either the amount or its cellular localization are unbalanced. Increased iron deposition negatively affects most chronic liver diseases. The interplay with lipid metabolism prompted an extensive investigation for the role of iron in NAFLD/NASH. Moreover, the description of ferroptosis as a discrete form of regulated hepatocyte death opened the way for the therapeutic modulation of iron overload in many diseases. Interestingly, most liver diseases are benefited by ferroptosis inhibition. A notable exception is HCC, where the therapeutic target is ferroptosis induction.

The current evidence involves the integration of information from experimental models and less so, from patient findings. Further experimental *in vitro* and *in vivo* investigations are warranted to find more suitable molecules with wider availability and better specificity that could regulate ferroptosis. In this context, it is interesting to note that many natural products may influence iron metabolism and ferroptosis. Furthermore, it should be stressed that clinical trials involving ferroptosis regulation are scarce and sometimes inconclusive. Therefore, to draw valid conclusions, further well-designed randomized trials in humans are urgently required.

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**Footnotes**

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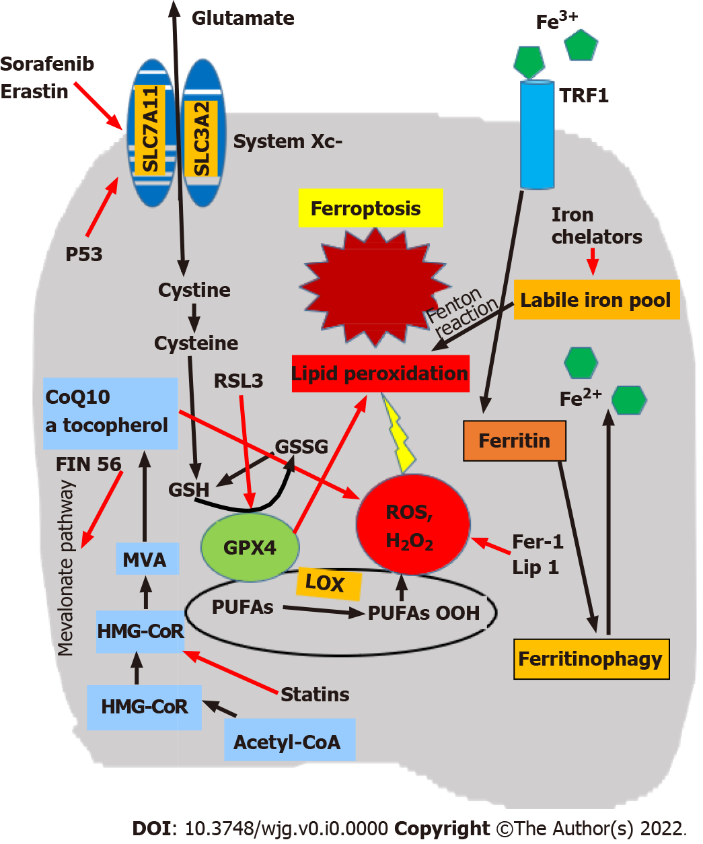
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**Figure Legends**



**Figure 1 Simplified pathways of ferroptosis and site of action of the main ferroptosis modulators.** Ferroptosisis mediated through excess intracellular iron in the labile iron pool (LIP). Ferritinophagy is a major source of LIP, leading to the production of reactive oxygen species (ROS) by mitochondria and lipid peroxidation. Deranged function of the system Xc- causes reduction of glutathione (GSH) and glutathione peroxidase 4 (GPX4) and an increased activity of lipoxygenases (LOXs), augmenting lipid peroxidation. Ferroptosis modulators act by interfering with components of this complicated pathway. Red arrows indicate inhibition. CoQ10: Coenzyme Q10; GSSG: Glutathione disulfide; MVA: Modified vaccinia virus Ankara; PUFAs: Polyunsaturated fatty acids; SLC3A2: Solute carrier family 3 member 2; SLC7A11: Solute carrier family 7 member 11; TRF1: Transferrin receptor 1.

**Table 1 Exogenous modulators of ferroptosis**

|  |  |  |
| --- | --- | --- |
| **Inducers** | **Mechanisms** | **Compounds** |
| Class 1 | Inhibition of system Xc- | Erastin, sorafenib, sulfasalazin |
| Prevention of cystine import | Glutamate |
| Class 2 | Inhibition of GPX4 | RLS3, DPIs (DPI7, DPI10) |
| Class 3 | Degradation of GPX4 | FIN56 |
| Depletion of CoQ10 |
| Class 4 | Initiation of lipid peroxidation | FINO2, PUFAs |
| Indirect reduction of GPX4 activity |
| Inhibitors |  |  |
| Class 1 | Suppression of iron accumulation | Deferoxamine |
| Class 2 | Inhibition of lipid peroxidation | Ferrostatin-1, liproxstatin-1, vitamin E |
| Unclassified |  | Dynasore, probucol, selenium, nitroxide XJB-5-131 |
| Bicyclol, **r**osiglitazone |

CoQ10: Coenzyme Q10; FIN: Ferroptosis inducing compounds; GPX4: Glutathione peroxidase 4; PUFAs: Polyunsaturated fatty acids.