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EDITORIAL

Ferroptosis in liver diseases: Fundamental mechanism and clinical implications

Ming-Shuang Lai, Xi-Peng Yan, Donald R Branch, Melika Loriamini, Li-Min Chen

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Abstract

This editorial discusses a recently published paper in the *World Journal of Gastroenterology*. Our research focuses on p53's regulatory mechanism for controlling ferroptosis, as well as the intricate connection between ferroptosis and liver diseases. Ferroptosis is a specific form of programmed cell death that is dependent on iron and displays unique features in terms of morphology, biology, and genetics, distinguishing it from other forms of cell death. Ferroptosis can affect the liver, which is a crucial organ responsible for iron storage and metabolism. Mounting evidence indicates a robust correlation between ferroptosis and the advancement of liver disorders. P53 has a dual effect on ferroptosis through various distinct signaling pathways. However, additional investigations are required to clarify the regulatory function of p53 metabolic targets in this complex association with ferroptosis. In the future, researchers should clarify the mechanisms by which ferroptosis and other forms of programmed cell death contribute to the progression of liver diseases. Identifying and controlling important regulatory factors associated with ferroptosis present a promising therapeutic strategy for liver disorders.

Key Words: Liver disease; P53; Programmed cell death; Ferroptosis; Therapeutic target

Core Tip: Ferroptosis is closely linked to the development and advancement of different liver diseases. A comprehensive examination of the fundamental processes and controlling factors that govern ferroptosis offer new perspectives and potential strategies for the prevention, diagnosis, and treatment of liver diseases. Recent studies have discovered that drugs that control ferroptosis, as well as interventions that focus on iron metabolism and oxidative stress, have the potential to be used in the prevention and treatment of liver diseases.

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INTRODUCTION

Various factors influence liver disease, which poses a substantial risk to global health[1,2]. Cell death is an essential mechanism of self-destruction that has a substantial impact on embryonic development, organ upkeep, and cellular aging [3]. Additionally, it has a crucial function in controlling immune responses and preventing the occurrence of autoimmunity by eliminating dysfunctional or excessive cells[4]. Genetically regulated mechanisms such as apoptosis, necroptosis, autophagy, and pyroptosis, as well as metabolic abnormalities like ferroptosis, can initiate this process of self-destruction. The occurrence and dysregulation of cell death have a significant impact on the development and prognosis of numerous liver diseases[5,6]. Consequently, conducting a comprehensive examination of the mechanisms that govern cell death in liver diseases may result in novel therapeutic concepts that enhance both prognosis and treatment efficacy[6]. We anticipate that continuous research endeavours in this domain will result in additional findings and advancements.

Ferroptosis has become a central focus in liver disease research in recent years. In 2012, the laboratory of Dixon *et al*[7] at Columbia University discovered ferroptosis, a distinct form of programmed cell death that relies on iron. As a specific form of cell death, ferroptosis is triggered by the combined effects of elevated iron levels, lipid oxidation, and damage to the plasma membrane[8]. Ferroptosis demonstrates unique molecular mechanisms that distinguish it from other forms of programmed cell death, including apoptosis, necroptosis, pyroptosis, and autophagy[9,10].

Ferroptosis is influenced by various processes, including the enzyme glutathione peroxidase 4 (GPX4), iron metabolism, lipid metabolism, and the regulation of specific genes[11]. Ferroptosis is strongly associated with a lack of cystine. Peptide bonds are responsible for the synthesis of glutathione (GSH), which is a vital antioxidant found within cells. Glycine, glutamate, and cysteine combine to produce GSH, which plays a crucial role in storing cysteine[12]. GPX4 functions as an antioxidant and plays a significant role in the cystine/glutamate antiporter system (system Xc^-). GPX4 plays a critical role in reducing phospholipid hydroperoxides in the cell membrane, which is necessary to prevent cell ferroptosis[12]. Conversely, GPX4 requires GSH to function. Decreased levels of GSH cause the enzyme GPX4 to cease its activity, resulting in the process of lipid peroxidation and leading to ferroptosis[13]. Reports have established a connection between iron metabolism and ferroptosis. Iron ions play an active role in generating free radicals, which subsequently induce the peroxidation of lipids in cell membranes. In addition, iron can engage in the Fenton reaction and promote the generation of free radicals, which in turn intensify lipid peroxidation and cellular harm.

Reactive oxygen species (ROS) are a wide range of oxygen derivatives that play a role in aging and disease processes [14,15]. An overabundance of ROS can trigger oxidative stress, resulting in the oxidation of lipids, denaturation of proteins, and damage to DNA[16]. An imbalance in iron metabolism results in elevated levels of ROS, which in turn induce oxidative stress. Excessive lipid-derived ROS have the potential to initiate ferroptosis[17]. Lipid metabolism can have an impact on iron metabolism, which in turn influences the occurrence of ferroptosis[18].

Research has demonstrated that phospholipidp hosphatidylethanolamine (PE) plays a crucial role in triggering ferroptosis[19]. The biosynthesis and remodeling of PE require the active involvement of Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3). These enzymes play a role in activating polyunsaturated fatty acids and adjusting their properties across cell membranes[20]. Consequently, the reduction of ACSL4 and LPCAT3 expression effectively inhibits the accumulation of lipid peroxide substrates within cells, thereby halting ferroptosis[21,22].

The regulation of certain crucial genes is of utmost importance in a wide range of fundamental biological processes, including cell differentiation, stress response, tissue homeostasis, and immune system function[23]. Specific genes encode proteins that play a role in iron metabolism, antioxidant systems, and lipid metabolism. Changes in the patterns of gene expression can then influence the way that cells respond to ferroptosis[24]. As an illustration, the tumor suppressor p53 inhibits the absorption of cystine and increases the likelihood of cells undergoing ferroptosis by reducing the expression of SLC7A11, a crucial component of system Xc^-[25]. In addition, ferroptosis is regulated by three antioxidant pathways, namely, the cyst(e)ine/GSH/GPX4 pathway, the GCH1/BH4/DHFR pathway, and the ferroptosis/coenzyme Q10 (CoQ10) pathway, all of which are supported by nicotinamide adenine dinucleotide phosphate[26].

The liver is a vital organ in the human body, serving as the primary site for anabolic processes and playing a critical role in regulating lipid and glucose metabolism[27]. In hepatocytes, ROS are primarily generated in the mitochondria and endoplasmic reticulum during cellular metabolism. The metabolism of both naturally occurring and exogenous

substances in hepatocytes play a role in the production of iron ions and ROS. The iron-mediated Fenton reaction and enzymatic oxygenation, which are unique features of ferroptosis, are accountable for lipid peroxidation and toxic ROS production[28]. Therefore, due to its crucial role in storing and processing iron, the liver is a key location for ferroptosis [29]. Consequently, the liver is susceptible to harm caused by oxidative stress and the occurrence of ferroptosis. Studies have established a connection between ferroptosis and the occurrence of different diseases, including cancer, cardiovascular disease, neurodegenerative disorders, kidney diseases, and specifically liver diseases[11]. Ferroptosis associated liver diseases include acute liver failure (ALF), alcohol-related liver disease, non-alcoholic steatohepatitis, and hepatocellular carcinoma[30].

In summary, the intricate correlation between the physiological and pathological impacts of ferroptosis suggests its potential as a therapeutic target for various liver diseases. The objective of this editorial is to provide a commentary on the study conducted by Zhou *et al*[31] and present a comprehensive overview of the mechanism, significance, and present state of research of ferroptosis as it relates to liver diseases. This will pave the way for future novel methods of diagnosing and treating these diseases.

ROLE OF FERROPTOSIS IN PATHOGENESIS OF LIVER DISEASES

Multiple reports have documented the role and mechanism of ferroptosis in the pathophysiology of liver disease. The latest edition of the *World Journal of Gastroenterology* features a noteworthy study by Zhou *et al*[31] titled "Silent information regulator sirtuin 1 ameliorates acute liver failure *via* the p53/glutathione peroxidase 4/gasdermin D axis". This study aimed to clarify the relationship between ferroptosis and pyroptosis as well as the regulatory mechanisms that control them in ALF. The authors conducted the study using a population-based approach. Initially, they noted elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and markers of inflammation in the blood of patients with ALF. In addition, liver tissue samples from patients with ALF exhibited iron accumulation. There was a concurrent reduction in the levels of GPX4 and SLC7A11, both of which function as suppressors of ferroptosis, along with elevated expression of the pyroptosis marker gasdermin D protein (GSDMD). The results show that ALF activates both ferroptosis and pyroptosis.

Huang *et al*[32] demonstrated the simultaneous occurrence of apoptosis and ferroptosis in a mouse model of ALF. Additionally, they discovered that inhibiting either apoptosis or ferroptosis can significantly decrease the occurrence of LPS/D-GalN-induced ALF. Acetaminophen (APAP) overdose is a common reason for drug-induced liver damage and ALF[33-35]. Liu *et al*[9] observed significant hepatocytic ferroptosis and pyroptosis in a mouse model of APAP-induced ALF. They discovered that 3,4-dihydroxyphenylethyl alcohol glycoside has the potential to treat APAP-induced ALF by inhibiting ferroptosis and pyroptosis in liver cells. Another study demonstrated that liproxstatin-1, a substance that inhibits ferroptosis, effectively reduced liver damage and fibrosis in a mouse model of metabolic dysfunction-associated fatty liver disease[36]. This could be attributed to its regulation of PANOptosis, a process that encompasses pyroptosis, apoptosis, and necroptosis[36]. These studies collectively presented convincing evidence that various forms of programmed cell death, such as ferroptosis and pyroptosis, play a significant role in liver diseases. Combined, these studies show that pharmacological substances that target ferroptosis can alleviate the advancement of hepatic diseases in *vitro* and in *vivo*.

The study conducted by Zhou *et al*[31] demonstrated an increase in the expression levels of p53 and acetylated p53 (Ac-p53) in human ALF liver tissues. The researchers observed a significant rise in animal survival, a reduction in inflammatory cytokines, and a decrease of p53 expression following the administration of inhibitors for ferroptosis and pyroptosis. The *p53* gene, an essential tumor suppressor, has a central role in cellular growth, differentiation, apoptosis, DNA repair, and metabolism[37]. Increasing evidence indicates that p53 utilizes ferroptosis as a mechanism to exert its anticancer effects[38,39].

There are reports indicating that p53 can regulate ferroptosis in two directions through various signaling pathways. As an illustration, p53 enhances the process of ferroptosis by increasing the levels of SLC25A28 and SAT1 (spermidine/spermine N1-acetyltransferase 1)[40,41] and reducing the activity of SLC7A11, thereby making cells more susceptible to ferroptosis[25]. Under stress and damage to DNA, p53 triggers cell death pathways like ferroptosis to eliminate damaged cells[42]. The deliberate promotion of ferroptosis plays a role in suppressing tumors and eliminating abnormal cells. Nevertheless, p53 can additionally inhibit ferroptosis by controlling metabolic pathways, triggering anti-oxidative stress mechanisms, and adjusting mitochondrial function. For instance, p53 can enhance the functionality of GPX4 by activating p21. This facilitates the elimination of toxic lipids and ROS, thereby halting the process of ferroptosis[43]. Xie *et al*[44] demonstrated that p53 inhibits the function of dipeptidyl peptidase-4, which is associated with its ability to halt erastin-induced ferroptosis.

The interaction between ferroptosis and the regulatory role of p53 in various liver disorders are complex. Zhou *et al*[31] observed elevated levels of p53 and Ac-p53 in human ALF liver tissues. Researchers discovered a negative correlation between the levels of p53 and the levels of SLC7A11 and GPX4. As a result, ferroptosis and pyroptosis ensued. Moreover, in an ALF mouse model, the use of drugs to block p53 activity and enhance GPX4 activity effectively reduced AST and ALT levels, as well as inflammatory reactions. This study demonstrated the crucial function of SIRT1 in protecting hepatocytes from cell death in ALF by specifically investigating the processes of ferroptosis and pyroptosis and modulating the p53/GPX4/GSDMD pathway. Moreover, it offered new perspectives on the dual regulatory role of SIRT1, which controls both the ferroptosis and pyroptosis processes. This discovery implies the possibility of targeting SIRT1 for therapeutic purposes.

It is important to recognize certain constraints in the present study. First, the research findings may lack generalizability due to the small sample size of only 30 ALF patients and control samples included in the study. Furthermore, the authors failed to examine the demographic and clinical traits of individuals with ALF and healthy controls, and they did not present any clinical proof of a connection between ferroptosis and ALF. Furthermore, this study did not examine or monitor the enduring consequences of ferroptosis inhibitors (pifithrin-α and liproxstatin 1) and pyrodeath inhibitors (GSDMD) on ALF.

Ferroptosis plays a dual role in liver disease. Under specific oxidative stress conditions, it can facilitate the elimination of impaired or anomalous cells, thereby halting inflammation and fibrosis. Conversely, an excessive amount of ferroptosis can result in liver damage, leading to an inflammatory reaction and accelerating the advancement of fibrosis. Additional research is required to investigate the following areas: (1) Understanding the mechanisms that cause and promote ferroptosis; (2) Examining the therapeutic impact of small molecules that target ferroptosis on liver diseases in a larger group of participants; and (3) Confirming the safety and effectiveness of drugs that target this condition. In the future, it is crucial to thoroughly examine the connections between alterations in ferroptosis mechanisms and the recurrence of diseases from different perspectives. Additionally, it is important to conduct prospective studies to explore the links between ferroptosis and the prognosis of diseases.

By possessing a comprehensive understanding of the intricate workings associated with ferroptosis, we can readily discern potential therapeutic targets for enhanced control of diverse liver ailments. Figure 1 depicts the interplay between GPX4, iron homeostasis, lipid peroxidation, and the modulation of specific genes in influencing ferroptosis.

IMPACTS OF FERROPTOSIS IN RELATION TO OTHER TYPES OF CELL DEATH IN LIVER DISEASES

Apoptosis is a form of cellular death that is regulated by genetic factors. The characteristic features of this condition include the shrinkage of cells, increased chromatin, the formation of apoptotic bodies, DNA fragmentation, and the absence of inflammation[45]. Necroptosis is a type of programmed cell death that occurs when receptor-interacting protein kinase 1 and receptor-interacting protein kinase 3 interact after the activation of death domain receptors[46]. This process is characterized by the swelling of cells, the disruption of the integrity of the cell membrane, the induction of inflammation, and the dependence on energy metabolism[47]. Pyroptosis, an inflammatory form of programmed cell death, facilitated by cysteine proteinease, is characterized by cellular swelling with multiple bubble-like protrusions, subsequent cell membrane rupture, and the consequent release of cellular contents, leading to a robust inflammatory reaction[48]. Autophagy is a cellular process that involves the degradation of damaged organelles, misfolded proteins, and other large molecules within lysosomes. This process is essential for maintaining cell homeostasis. The process involves the formation of bilayer membrane structures called autophagosomes, which surround and encapsulate degraded substances. These autophagosomes then fuse with lysosomes to complete the breakdown of these substances [49].

Cell death is a crucial physiological process in living organisms that is executed through intricate mechanisms, which mutually influence the development and prognosis of diseases[50]. While various cell death forms are classified according to their specific causes and distinct morphologies, the activation of signaling molecules in cell death pathways is typically interconnected, resulting in pleiotropic effects.

Research has demonstrated the existence of a reciprocal relationship between ferroptosis and pyroptosis. Zhou *et al*[31] determined the significance of ferroptosis and pyroptosis in the progression of ALF. In addition, they highlighted the involvement of SIRT1 in this process through its interaction with the p53/GPX4/GSDMD signaling pathway. Another study discovered that pyroptosis and ferroptosis collaborated in an ALF model induced by polystyrene microplastics [51]. Nevertheless, there exist antagonistic mechanisms between ferroptosis and pyroptosis. It was discovered that the breast cancer susceptibility gene 1/breast cancer susceptibility gene 2-containing complex subunit 36 uses an enzyme to remove ubiquitin from 3-hydroxy-3-methylglutaryl-coenzyme A reductase. This stopped ferroptosis and promoted pyroptosis[52].

Signal transduction involves the activation of common cell death triggers, resulting in both apoptosis and necroptosis. These two processes intersect at multiple points. An example of this is that when cells are exposed to signals that trigger programmed cell death, an enzyme called caspase-8 cleaves receptor-interacting protein 3 (RIP3). RIP3, in its complete form, plays a role in both caspase-dependent and -independent pathways of programmed cell death[53]. Ferroptosis and apoptosis have mutual regulatory mechanisms. Mitochondrial release of cytochrome c acts as a catalyst for apoptosis. Afterwards, interference with the mitochondrial electron transport chain produces ROS, which have the potential to cause ferroptosis[54]. Conversely, ROS generated during ferroptosis initiate the oxidation of polyunsaturated phospholipids, thereby facilitating mitochondrial apoptosis[55]. ALF establishes a close connection between ferroptosis and autophagy. The drug sulforaphane activates the nuclear factor erythroid 2-related factor 2 signaling pathway. This pathway controls cellular autophagy and can also mitigate ferroptosis and decrease liver damage[56].

In summary, ferroptosis and other types of cell death have a reciprocal influence on each other and have a substantial impact on the development of liver diseases. Together, they contribute to the initiation and progression of these diseases [57,58]. To gain a comprehensive understanding of the detrimental mechanisms responsible for liver diseases and develop efficacious therapies, it is crucial to thoroughly investigate their intricate interplay.

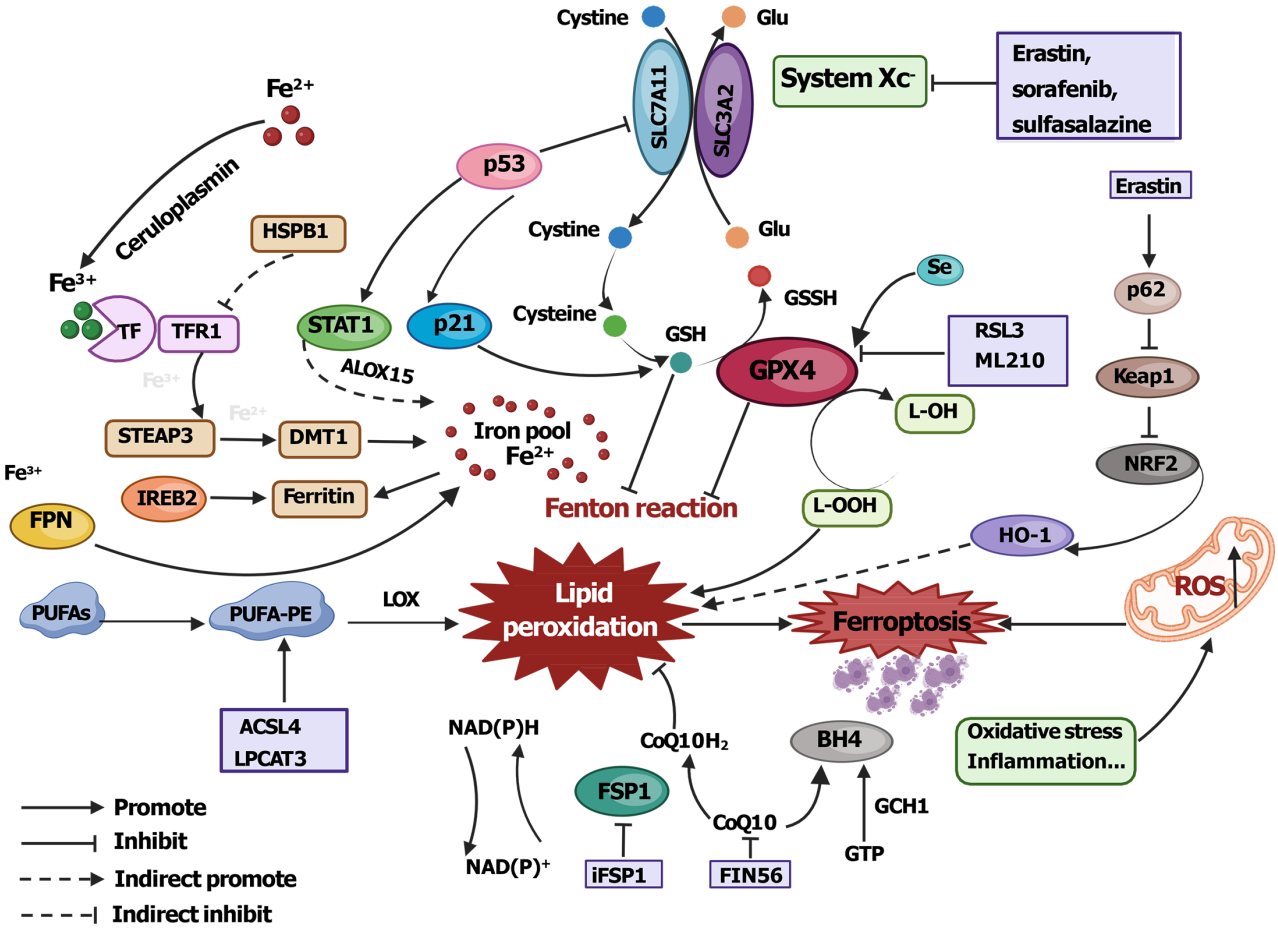

Figure 1 Mechanisms by which glutathione peroxidase 4, iron homeostasis, lipid peroxidation, and regulation of some key genes influence ferroptosis. The diagram illustrates the regulatory pathways of ferroptosis, which can be categorized into three main groups. The glutathione/glutathione peroxidase 4 pathway plays a role in regulating several processes, such as system Xc- inhibition, glutamine metabolism, and the p53 signaling axis. Furthermore, iron metabolism is influenced by regulatory mechanisms such as the p62-kelch like ECH associated protein 1-nuclear factor erythroid 2-related factor 2 pathway. Finally, the pathways associated with lipid metabolism, namely, p53-SAT1-arachidonate (15S)-lipoxygenase, acyl coenzyme a synthetase long chain family, member 4, and lysophosphatidylcholine acyltransferase 3, play an important role regulating lipids and enhancing the rate of ferroptosis. In addition, the ferroptosis-coenzyme Q10-nicotinamide adenine dinucleotide phosphate pathway prevents phospholipid peroxidation and inhibits ferroptosis. Glu: Glutamic acid; NRF2: Nuclear factor erythroid 2-related factor 2; SLC7A11: Solute carrier family 7 member 11; SLC3A2: Solute carrier family 3 member 2; System Xc-: Cystine/glutamate antiporter (Xc-) system; GSH: Glutathione; GSSH: Glutathione oxidized; GPX4: Glutathione peroxidase 4; ROS: Reactive oxygen species; GTP: Guanosine triphosphate; CoQ10: Coenzyme Q10; CoQ10H2: Reduced coenzyme Q-10; GCH1: GTP cyclohydrolase 1; BH4: Tetrahydrobiopterin; NADPH: Nicotinamide adenine dinucleotide phosphate; HO-1: Heme oxygenase-1; L-OH: Lipid hydrogen peroxide; L-OOH: Lipid peroxide; ALOX15: Arachidonate (15S)-lipoxygenase; LOX: Lysine oxidase; ACSL4: Acyl coenzyme a synthetase long chain family, member 4; LPCAT3: Lysophosphatidylcholine acyltransferase 3; iFSP1: Inhibitor of ferroptosis; FSP1: Ferroptosis; PUFAs: Polyunsaturated fatty acids; PUFA-PE: Polyunsaturated fatty acids-phosphatidylethanolamine; FPN: Ferroportin; STEAP3: Six transmembrane epithelial antigen of the prostate 3; DMT1: Divalent metal transporter 1; IREB2: Iron-regulated element binding protein 2; TF: Transferrin; TFR1: Transferrin receptor 1; HSPB1: Heat shock protein beta-1; Keap1: Kelch like ECH associated protein 1.

CLINICAL IMPLICATIONS

Ferroptosis has diverse clinical implications in liver diseases, encompassing a range of applications: (1) Assessment: Identifying biomarkers associated with ferroptosis aids in the diagnosis and staging of liver diseases. To illustrate, evaluating the levels of iron ions, lipid peroxidation products, antioxidant enzyme activity, and other indicators allows us to ascertain the condition of ferroptosis in liver cells; (2) Therapy: Therapeutic approaches that focus on targeting ferroptosis offer new strategies for managing liver disease. Examples involve the utilization of iron chelators to decrease the levels of iron ions within cells, the use of antioxidants to alleviate damage caused by lipid peroxidation, and the modulation of lipid metabolism to improve the treatment outcomes of liver diseases; (3) Pharmaceutical research and development: Studying the mechanisms that cause ferroptosis could provide valuable insights into new targets for intervening in liver disease. This encompasses medications that specifically target signaling pathways associated with ferroptosis or regulate the balance of iron ions within cells; and (4) Personalized targeted therapy: The processes of ferroptosis exhibit variability among individuals and across different liver diseases. Thus, evaluating the ferroptosis condition of patients allows for tailored treatments to enhance the effectiveness of therapy. Figure 2 provides an overview of the strategies used to specifically target ferroptosis to treat liver diseases.

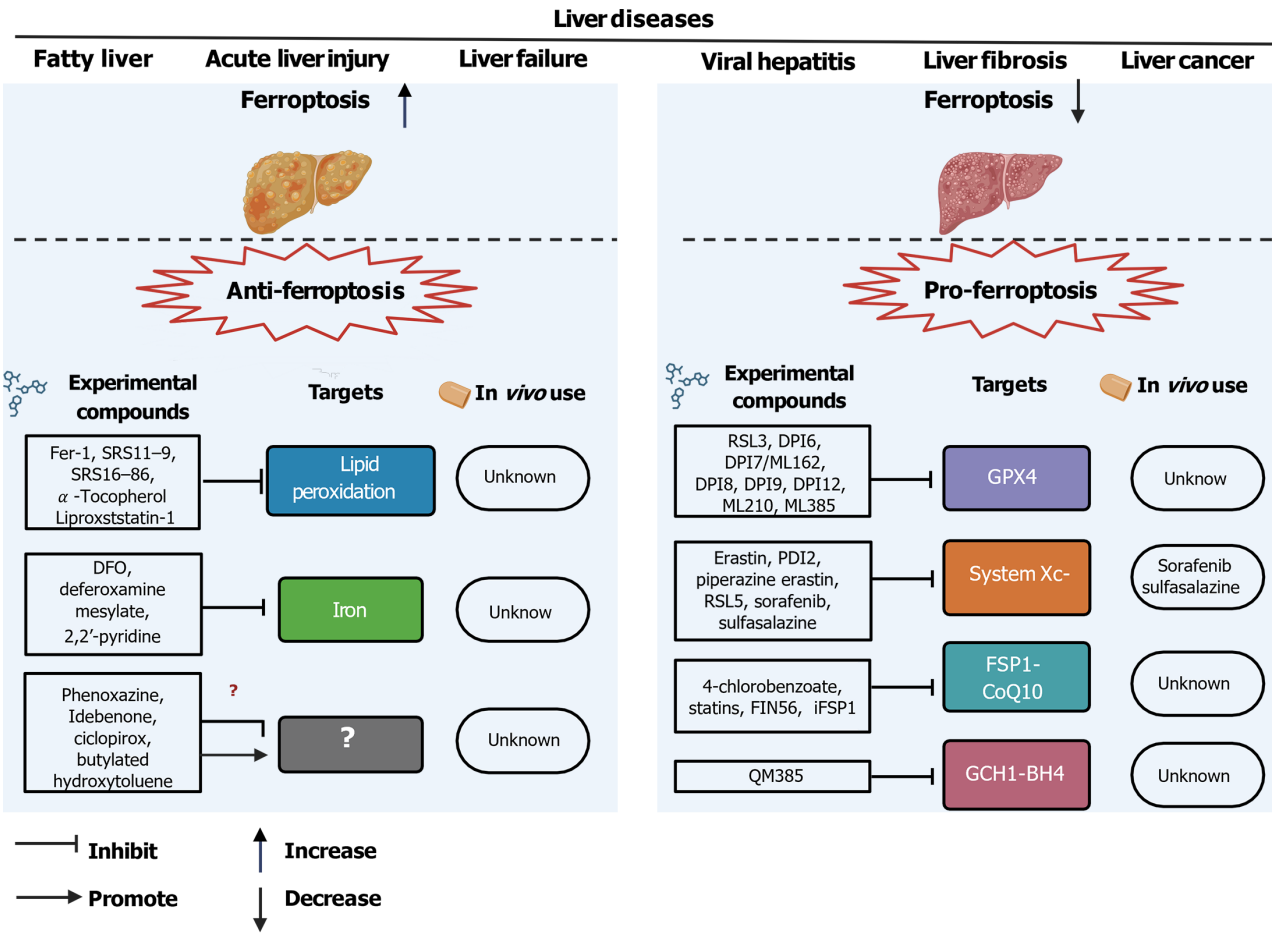

Figure 2 Strategies targeting ferroptosis for treatment of liver diseases. Ferroptosis has been associated with various liver diseases, including fatty liver disease, acute liver injury, chronic and acute liver failure, hepatitis, liver fibrosis/cirrhosis, and liver cancer. Compounds that inhibit or induce ferroptosis have the potential to impact the development of liver diseases. System Xc^-: Cystine/glutamate antiporter (Xc-) system; GPX4: Glutathione peroxidase 4; CoQ10: Coenzyme Q10; GCH1: Guanosine triphosphate cyclohydrolase 1; BH4: Tetrahydrobiopterin.

The clinical implementation of targeting ferroptosis for liver disorders is currently in the research stage. Additional clinical trials and studies are required to confirm its efficacy and safety profile. Furthermore, it is essential to conduct a comprehensive examination of the intricate interaction between ferroptosis and other types of cellular death in order to devise more comprehensive and individualized therapeutic strategies.

CONCLUSION

In summary, ferroptosis has a significant impact on the development and advancement of liver diseases. Further investigation into the mechanism that causes ferroptosis will provide new opportunities and ideas for more effective treatment of liver disorders.

FOOTNOTES

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