J Appl Biol Chem (2023) 66:23, 159–164
https://doi.org/10.3839/jabc.2023.023

Online ISSN 2234-7941
Print ISSN 1976-0442

Review: Biochemistry/Molecular Biology

Mechanism of action of ferroptosis and its role in liver diseases

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Received: 20 February 2023 / Accepted: 5 April 2023 / Published Online: 10 April 2023

Abstract Ferroptosis is a type of regulated cell death recently discovered, characterized by the accumulation of iron-dependent lipid peroxides in the cell membrane, and it involves a complex network of signaling pathways, including iron metabolism, lipid peroxidation, and redox regulation. The dysregulation of these pathways can lead to the induction of ferroptosis and the development of liver diseases, such as alcoholic liver disease, non-alcoholic fatty liver disease, viral hepatitis, and liver cancer. Studies have demonstrated that targeting key molecules involved in iron metabolism, lipid peroxidation, and redox regulation can reduce liver injury and improve liver function in different liver diseases by inhibiting ferroptosis. Thus, modulation of ferroptosis presents a promising therapeutic target for treating liver diseases. However, further research is required to gain a more comprehensive understanding of the mechanisms underlying the role of ferroptosis in liver diseases and to develop more effective and targeted treatments.

Keywords Ferroptosis · Liver fibrosis

Introduction

Chronic liver diseases, such as viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and liver cancer, are frequently characterized by the presence of hepatic fibrosis as a pathological feature. The excessive deposition of extracellular matrix components, such as collagen and fibronectin, in the liver characterizes hepatic fibrosis, which can progress to cirrhosis, a life-threatening condition associated with significant morbidity and mortality. Recently, ferroptosis, a newly identified form of regulated cell death characterized by the iron-dependent accumulation of lipid peroxides in the cell membrane, has been proposed as a potential therapeutic target for hepatic fibrosis. In this review article, we will discuss the current understanding of ferroptosis and its role in liver diseases.

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Ferroptosis Inducing Mechanisms

Iron Metabolism

Ferroptosis is a recently discovered type of regulated cell death distinguished by the iron-dependent accumulation of lipid peroxides in the cell membrane [1]. Unlike apoptosis and necrosis, ferroptosis is a distinct form of cell death and contributes to several physiological and pathological processes. The mechanisms responsible for ferroptosis involve a complex network of signaling pathways, which include iron metabolism, lipid peroxidation, and redox regulation.

Iron is an essential mineral that is involved in numerous cellular processes, such as DNA synthesis, energy production, and oxygen transport. Nevertheless, excessive iron accumulation can lead to the buildup of reactive oxygen species (ROS) and lipid peroxides, which can lead to cell death. Transferrin receptor 1 (TfR1) and ferroportin 1 (FPN1) are crucial proteins in iron metabolism, with the former facilitating the entry of iron into cells while the latter exports it out of cells [2]. Ferritin, on the other hand, stores iron in a non-toxic form, and heme oxygenase 1 (HO-1) degrades heme, releasing iron, biliverdin, and carbon monoxide. Multiple studies have shown that the dysregulation of iron metabolism contributes to the development of ferroptosis. For example, a study by Stockwell et al. revealed that the inhibition of TfR1 reduced cancer cells' sensitivity to ferroptosis, while the overexpression of FPN1 protected cells from ferroptosis [3]. Iron chelators are compounds that bind to iron, reducing the accumulation of toxic

ROS and lipid peroxides. Several iron chelators, including deferoxamine and deferiprone, have been shown to inhibit the sensitivity of cells to ferroptosis [4]. On the other hand, overexpression of ferritin can protect against ferroptosis [5]. These findings suggest that dysregulation of iron homeostasis can lead to the induction of ferroptosis and the development of diseases.

Lipid Peroxidation

The accumulation of lipid peroxides resulting from the biochemical process of lipid peroxidation impairs the cell membrane, which is mainly caused by the oxidation of polyunsaturated fatty acids (PUFAs) in the membrane, resulting in cell death. Lipid peroxidation is initiated by key enzymes such as lipoxygenases, and it involves the accumulation of PUFA-CoA in the cell membrane, which is facilitated by acyl-CoA synthetase long-chain family member 4 (ACSL4) [6]. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) is an enzyme that plays a crucial role in the biosynthesis of phospholipids (PLs) by catalyzing the transfer of an acyl group from acyl-CoA to lysophosphatidylcholine, resulting in the formation of PLs [7]. Specifically, LPCAT3 has been shown to preferentially esterify PUFAs to produce PUFA-containing PLs, which are important in maintaining the fluidity and functionality of cellular membranes. Lipoxygenases (LOX) catalyzes oxidation of PUFA-containing PLs can also lead to the formation of oxidized phospholipids [8]. The most common free radical involved in lipid peroxidation is the hydroxyl radical (•OH), which can react with polyunsaturated fatty acids to form lipid radicals (L•). These lipid radicals can then react with molecular oxygen (O_2) to form lipid peroxyl radicals (LOO•), which can continue the chain reaction of lipid peroxidation. Once initiated, lipid peroxidation can propagate through a chain reaction of reactions that involve the interaction of lipid peroxyl radicals with other molecules. One important reaction in this chain is the interaction of lipid peroxyl radicals with other polyunsaturated fatty acids in cellular membranes, leading to the formation of new lipid radicals and the continuation of the chain reaction. A study by Dixon et al. demonstrated that ACSL4 inhibition reduces cancer cells' sensitivity to ferroptosis [9]. Additionally, the study showed that lipoxygenase overexpression increases lipid peroxide accumulation, promoting ferroptosis [10].

Several factors that can reduce lipid peroxidation, including the use of antioxidants to scavenge free radicals such as vitamin E, and the detoxification enzymes such as GPX4 and Nrf2. Research on the mechanism of action of vitamin E in ferroptosis has revealed that vitamin E acts as an antioxidant and prevents the accumulation of lipid peroxides in cell membranes, thereby inhibiting ferroptosis [11]. Vitamin E can also regulate the activity of various enzymes involved in ferroptosis. Another lipid peroxidation inhibitor is edaravone [12]. Edaravone is a small molecule that functions as a free radical scavenger, preventing lipid peroxidation in the cell membrane. It has been approved for the treatment of amyotrophic lateral sclerosis in Japan, where it has been demonstrated to slow disease progression and enhance the survival of some patients. Other compounds that have been investigated as lipid peroxidation inhibitors include resveratrol, curcumin, and melatonin.

GPX4 is a key regulator of ferroptosis and is responsible for the reduction of lipid peroxides in the cell membrane [13]. GPX4 utilizes glutathione (GSH) to reduce lipid peroxides to their nontoxic forms. Several studies have shown that the inhibition of GPX4 leads to the accumulation of lipid peroxides and the induction of ferroptosis [14]. Especially several GPX4 inhibitors, including RSL3 and ML162, have been shown to induce ferroptosis [15]. Glutathione reductase, on the other hand, is responsible for the regeneration of glutathione, which is a critical antioxidant that can scavenge ROS and protect against lipid peroxidation. Compounds that target these enzymes, such as RSL3 and ML162, have been shown to protect against ferroptosis in a variety of disease models [16]. The cellular antioxidant defenses are regulated by a transcription factor known as Nrf2, which has a crucial function in this process. Nrf2 induces the expression of various antioxidant enzymes, including GSH, heme oxygenase 1 (HO-1), and NAD(P)H:quinone oxidoreductase 1. Several studies have shown that the upregulation of Nrf2 protects cells from ferroptosis [17].

Redox Regulation

Redox balance regulation plays a crucial role in ferroptosis development. System xc^-, also known as the cystine/glutamate antiporter system, is a crucial transport system for regulating cystine and glutamate levels in cells. This system is composed of two proteins, xCT (SLC7A11) and 4F2hc (SLC3A2) [18,19]. System xc^- is responsible for transporting cystine into the cell, while exporting glutamate out of the cell. This exchange plays a critical role in maintaining cellular redox balance and protecting against oxidative stress. Dysregulation of the System xc^- system has been linked to a variety of diseases, such as cancer, neurodegenerative disorders, and immune dysfunction. The major molecules involved in redox regulation include GSH, which is a key antioxidant in cells, and nicotinamide adenine dinucleotide phosphate (NADPH), which serves as a cofactor for various antioxidant enzymes [20]. Multiple studies have demonstrated that dysregulated redox balance contributes to ferroptosis development. For example, a study by Yang et al. showed that GSH synthesis inhibition reduces cancer cells' sensitivity to ferroptosis, while NADPH oxidase overexpression enhances ROS accumulation, promoting ferroptosis [21]. P53 is a tumor suppressor protein that plays a critical role in the induction of ferroptosis. P53 induces ferroptosis by downregulating the expression of SLC7A11, which is a transporter system [22]. These findings suggest that redox balance regulation is crucial in ferroptosis induction. The overall view of ferroptosis is described in Fig. 1.

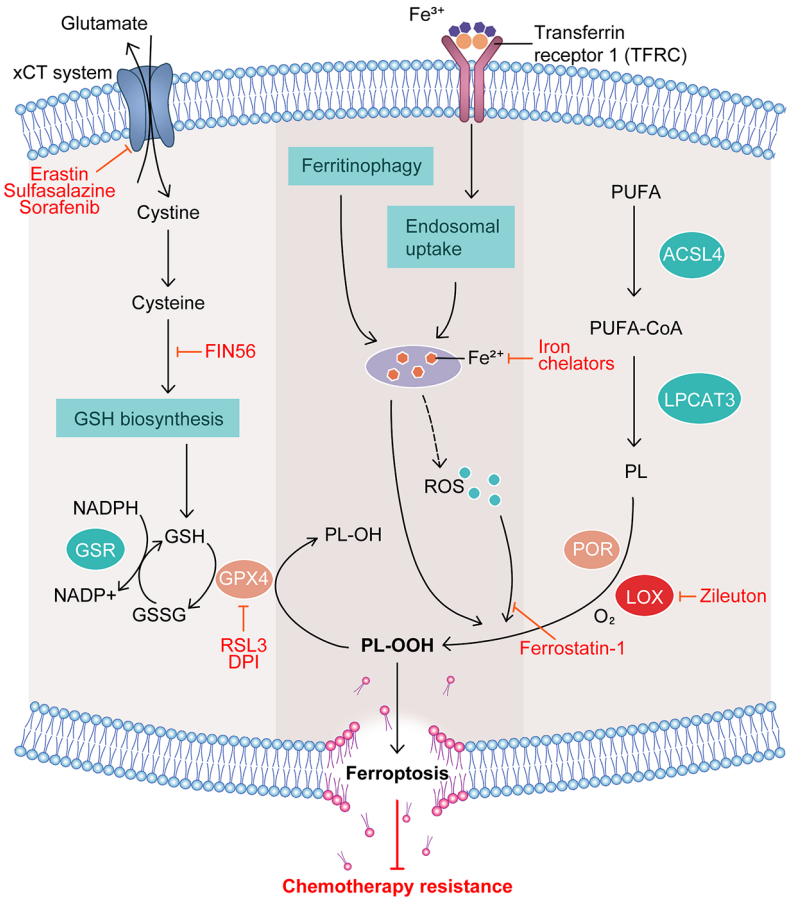

Fig. 1 Molecular mechanism to induce ferroptosis. One of the main mechanisms leading to ferroptosis is the lipid peroxidation process, which results in the accumulation of phospholipid hydroperoxides (PLOOH). The failure to eliminate PLOOH is a major cause of ferroptosis. To prevent PLOOH accumulation, two critical mechanisms involving glutathione peroxidase 4 (GPX4) and the system xc^- have been identified. The system xc^- mediates the uptake of cystine to generate cysteine and glutathione (GSH), while GPX4 converts GSH to glutathione disulfide (GSSG), leading to the reduction of PLOOH and inhibition of ferroptosis. Additionally, acyl-CoA synthetase long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenases (LOX) are other key proteins involved in the molecular mechanisms that induce ferroptosis. Abbreviations: PUFA: polyunsaturated fatty acids, ACSL4: acyl-CoA synthetase long-chain family member 4, LPCAT3: Lysophosphatidylcholine acyltransferase 3, PL: phospholipid, LOX: Lipoxygenases

Methods of Ferroptosis Detection

To study ferroptosis, it is important to have reliable and specific methods for measuring this process. Here, we review some of the current techniques that have been developed to measure ferroptosis specifically, including:

Lipid peroxidation assays

Ferroptosis is characterized by the accumulation of lipid peroxides, which can be measured using various assays that detect lipid peroxidation products, such as malondialdehyde (MDA) or 4-hydroxynonenal (4-HNE) [23]. These assays include the thiobarbituric acid reactive substances (TBARS) assay, the MDA assay, and the HNE assay. However, these assays are not specific to ferroptosis and can be affected by other forms of oxidative stress.

Iron-dependent cell death assays

Ferroptosis is an iron-dependent process, and therefore, assays that measure iron levels or the effect of iron chelators on cell death can be used to specifically measure ferroptosis [24]. One such assay is the iron sensor assay, which uses a fluorescent probe to detect intracellular iron levels. Another assay is the ferrostatin-1 (Fer-1) rescue assay, which measures the ability of the ferroptosis inhibitor Fer-1 to rescue cells from iron-induced cell death.

Glutathione depletion assays

Ferroptosis is associated with depletion of intracellular GSH, which can be measured using various assays that detect GSH or its oxidized form, glutathione disulfide (GSSG) [25]. These assays include the GSH/GSSG-Glo assay and the monochlorobimane assay. However, these assays can be affected by other forms of

oxidative stress or changes in cellular metabolism.

Genetic and pharmacological manipulations

Ferroptosis can be induced or inhibited using various genetic or pharmacological interventions, such as knockdown or overexpression of specific genes, or treatment with specific drugs or compounds. These interventions can be used to study the molecular mechanisms underlying ferroptosis, as well as to validate the specificity and sensitivity of other ferroptosis assays.

Overall, combining multiple assays can provide complementary and more robust information about the occurrence and characteristics of ferroptosis in different contexts. Future development of more specific and sensitive ferroptosis assays will be important for advancing our understanding of the role of ferroptosis in health and disease.

Role of Ferroptosis in Liver Diseases

Non-Alcoholic Fatty Liver Disease

NAFLD affects a significant proportion of the population in Western countries and is characterized by the accumulation of fat in the liver, which can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and cancer [26]. The pathogenesis of NAFLD is multifactorial and influenced by various genetic and environmental factors. Excessive dietary fat intake, obesity, insulin resistance, and dyslipidemia are all major risk factors for the development of NAFLD. Hepatic steatosis is the first stage of NAFLD, which can progress to inflammation, fibrosis, and cirrhosis. Oxidative stress and lipid peroxidation are critical factors in the progression of NAFLD to NASH and liver fibrosis. Although the pathogenesis of NAFLD is not fully understood, oxidative stress and lipid peroxidation are known to play important roles. Lipid peroxidation was found to be increased in NAFLD patients compared to controls, and iron accumulation and lipid peroxidation were observed in animal models of NAFLD and NASH, leading to ferroptosis and liver injury [27]. Inflammatory cells such as macrophages and neutrophils can also contribute to the progression of NAFLD by promoting oxidative stress and lipid peroxidation [28]. Ferroptosis induction has been suggested as a potential therapeutic strategy for NAFLD. Selective induction of ferroptosis may kill lipid-peroxidized hepatocytes, halting the progression of NAFLD to NASH and liver fibrosis [29]. Recent studies have shown that GPX4 can inhibit the progression of NASH by inhibiting ferroptosis [30]. Conversely, RSL-3, an inhibitor of GPX4, can aggravate NASH by facilitating ferroptosis. Sodium selenite, an activator of GPX4, has been found to improve the pathologic characteristics of NASH [31]. Additionally, ACSL4 inhibition has been shown to suppress ferroptosis and alleviate the progression of NASH. Nrf2, a transcription factor, regulates the synthesis of fatty acids and inhibits enzyme expression to suppress NASH progression via the p62-Keap1-Nrf2 axis [32]. Activation of the Nrf2 pathway decreases liver lipid deposition and improves the pathology of NAFLD *in vivo*. Dehydroabietic acid and Ginkgolide B have been found to improve NAFLD by inhibiting ferroptosis through upregulating Nrf2 and its downstream genes [33]. Regulating ferroptosis has also been reported as a mechanism for ECH1 and miR-33 to participate in the progression of NAFLD. [34]. Despite these findings, further exploration of ferroptosis in NAFLD is needed in relevant animal models and in patients, as no accurate treatment options are currently available for NAFLD.

Alcoholic Liver Disease

ALD results from excessive alcohol consumption. ALD ranges from fatty liver, which is reversible, to alcoholic hepatitis, which is characterized by inflammation and necrosis, and eventually to cirrhosis, which is irreversible and can lead to liver failure [35]. The development of ALD is a multifaceted process that involves both direct and indirect effects of alcohol on liver cells. Alcohol is metabolized in the liver by enzymes such as alcohol dehydrogenase, leading to the production of toxic byproducts such as acetaldehyde and ROS [36]. These harmful byproducts can cause liver cell damage, leading to inflammation, oxidative stress, and the accumulation of fat in the liver. Chronic alcohol consumption can also affect the gut microbiome and increase intestinal permeability, allowing harmful substances such as endotoxins to enter the bloodstream and further contribute to liver damage and inflammation. In addition, genetic predisposition, gender, and diet can all impact the development and progression of ALD. The pathogenesis of ALD is a complex interaction of various factors that lead to different liver pathologies such as steatosis, alcoholic hepatitis, and cirrhosis. Several studies have shown the involvement of ferroptosis in ALD. For example, Wang et al. demonstrated that the inhibition of ferroptosis by a GPX4 activator reduced lipid accumulation and liver injury in a mouse model of ALD [37]. The study also showed that the expression of ferroptosis-related genes, such as GPX4 and TFRC, was increased in human ALD samples with fatty liver. These findings suggest that ferroptosis plays a critical role in the development of fatty liver in ALD. Additionally, study showed that the inhibition of ferroptosis by a GPX4 activator reduced inflammation and fibrosis in a mouse model of alcoholic hepatitis. The study also showed that the expression of ferroptosis-related genes, such as GPX4 and acyl-CoA synthetase long-chain family member 4 (ACSL4), was increased in human ALD samples with alcoholic hepatitis. These findings suggest that the regulation of ferroptosis is critical for the pathogenesis of alcoholic hepatitis, and the inhibition of ferroptosis can be a good therapeutic target for the disease.

Viral Hepatitis

Viral hepatitis is a major cause of liver disease worldwide, and can lead to significant morbidity and mortality [38]. The pathogenesis of viral hepatitis is multifactorial, and involves a complex interplay between viral factors, host immune response, and environmental

factors. Oxidative stress and inflammation are key drivers of liver damage in viral hepatitis, and the development of new therapies that target these processes is an active area of research. Viral hepatitis is caused by infection with hepatitis viruses, including hepatitis A, B, C, D, and E viruses [39]. Hepatitis B and C viruses are major causes of chronic liver disease, and can lead to cirrhosis, liver failure, and hepatocellular carcinoma. The pathogenesis of viral hepatitis involves the interplay between viral factors, host immune response, and environmental factors. The immune response to viral infection can cause inflammation and oxidative stress, leading to liver damage. Ferroptosis has been implicated in the pathogenesis of viral hepatitis, and there is growing evidence that targeting ferroptosis may be a viable therapeutic strategy. Ferroportin-1 is upregulated and hepcidin is downregulated in chronic HCV infection, leading to iron accumulation, which is associated with worsening hepatic damage [40]. The role of ferroptosis in the development of HBV/HCV is still being investigated. A study showed that HCV replication was suppressed by ferroptosis mediated by FADS2, and inhibition of FADS2 enhanced HCV replication [41]. Conversely, the ferroptosis-inducing compound Erastin changed the construction of HCV replicases and sensitized it to anti-viral agents. Additionally, HBV-infected hepatocyte-secreted exosomes were found to aggravate hepatic fibrosis through the miR-222/TFRC axis. These studies suggest that ferroptosis may be a potential therapeutic strategy for viral hepatitis.

Liver Cancer

Liver cancer is one of the most common cancers worldwide and is a leading cause of cancer-related deaths. The major types of liver cancer include hepatocellular carcinoma (HCC) and cholangiocarcinoma [42]. The pathogenesis of liver cancer is complex and involves various genetic, environmental, and lifestyle factors. The dysregulation of these pathways can lead to the induction of ferroptosis and the development of liver cancer. Chronic liver inflammation and oxidative stress play critical roles in the development and progression of liver cancer. Several genes, such as retinoblastoma protein, Nrf2, metallothionein1G, CDGSH iron sulfur domain 1, and TP53 gene, have been identified as negative regulators of ferroptosis [43]. Reduced expression and function of Rb protein during liver carcinogenesis makes Rb-negative HCC cells more sensitive to death induced by Sorafenib compared to Rb-expressing HCC cells. Nrf2 protects HCC cells from ferroptosis induced by ferroptosis-inducing compounds by increasing the expression of several Nrf2-targeting genes [44]. MT-1G and CISD1 also negatively regulate Sorafenib-induced ferroptosis in HCC cells, and haloperidol has been reported to promote both Sorafenib and Erastin-induced ferroptosis, which may benefit HCC patients [45]. Lipoxygenase is the central inducer of ferroptosis by generating lipid hydroperoxides, and its effect depends on the excitation of ACSL4-dependent lipid biosynthesis. LDL-DHA can also induce ferroptosis and further kill HCC cells. Several genes, including IFN-γ, YAP/TAZ and ATF4, LIFR-NF-κB-LCN2 axis, lncRNA GABPB1-AS1 and GABPB1, and circular RNA cIARS, have been reported to play a functional role in the progression of HCC by targeting ferroptosis. Although inducing ferroptosis of HCC cells is a novel and promising approach for HCC treatment, further exploration is necessary to fully understand the pivotal regulator of lipid peroxidation in ferroptosis.

Conclusion

In summary, ferroptosis is a newly identified form of regulated cell death that plays a critical role in the pathogenesis of various liver diseases, including NAFLD, ALD, viral hepatitis, and liver cancer. The involvement of ferroptosis in the development of hepatic fibrosis has been proposed as a potential therapeutic target for the disease. The inhibition of ferroptosis by various strategies, such as GPX4 activators and inhibitors, has shown promising results in preclinical studies. However, further research is needed to better understand the mechanisms underlying ferroptosis in hepatic fibrosis and to develop safe and effective therapeutic strategies for the disease.

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