Advances in the Regulation of Ferroptosis by Heme Oxygenase-1 in Non-alcoholic Fatty Liver Disease: A Postprint

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Abstract

Ferroptosis is a novel form of programmed cell death that plays a significant role in the progression of non-alcoholic fatty liver disease (NAFLD). Studies have demonstrated that heme oxygenase-1 (HO-1), functioning as an inducible oxidase, can counteract oxidative stress responses, inhibit hepatocyte necrosis, and thereby prevent or delay NAFLD progression. However, the mechanisms through which HO-1 influences NAFLD pathogenesis and progression by regulating ferroptosis remain poorly understood. This review systematically and comprehensively summarizes the effects of HO-1 on NAFLD via ferroptosis regulation by synthesizing recent literature, and elucidates the mechanisms by which HO-1 prevents NAFLD onset and progression. The present work reveals that in NAFLD, HO-1 modulates ferroptosis through multiple mechanisms, including the synthesis of antioxidant molecules (such as bilirubin and CO), activation of the System Xc^- system, and promotion of ferrous ion accumulation, thereby providing a theoretical foundation for targeted HO-1 gene therapy in NAFLD through pharmacological interventions and offering valuable insights for future NAFLD research.

Full Text

Non-alcoholic fatty liver disease (NAFLD) is a genetic-environmental-metabolic stress-related disorder whose incidence is rising annually in China, posing a significant public health challenge. Epidemiological surveys indicate that NAFLD affects up to 2 billion people globally, with a prevalence of approximately 29.38% and an associated mortality rate of about 2.39% per year. By 2030, the prevalence of NAFLD is projected to increase by 18% [1]. Consequently, NAFLD has become a major focus of disease prevention and treatment both in China and worldwide.

The pathogenesis of NAFLD is complex, involving hepatic lipid peroxidation, inflammatory responses, and ferroptosis. Heme oxygenase-1 (HO-1) is a key enzyme in heme metabolism, and both HO-1 and its metabolites play important roles in chronic liver disease by exerting anti-lipid metabolism, anti-oxidative stress, anti-inflammatory, and anti-apoptotic functions [2], suggesting that HO-1 may play a crucial biological role in protecting hepatic tissue cells. Ferroptosis is an iron- and lipid toxicity-dependent form of regulated cell death that is distinct from apoptosis, necrosis, and autophagy [3]. Studies have shown that ferroptosis is closely associated with the occurrence and development of NAFLD, with ferroptotic events in NAFLD leading to exacerbated hepatocellular inflammation, fibrosis, and liver injury [4]. Current research suggests that HO-1 may influence the development and progression of NAFLD by regulating ferroptosis; however, the specific mechanisms through which HO-1 modulates ferroptosis remain unclear. Elucidating these regulatory mechanisms will help further clarify the pathological processes of NAFLD and provide novel strategies for its prevention, treatment, and progression delay.

This review systematically and comprehensively summarizes the mechanisms of action of HO-1 and ferroptosis in the development of NAFLD, and explores the specific molecular mechanisms by which HO-1 regulates ferroptosis, inhibits oxidative stress, and prevents lipid peroxidation during NAFLD progression. This review is expected to provide new molecular markers for NAFLD diagnosis and offer a novel theoretical framework and strategy for disease prevention and treatment, holding significant translational medical importance.

1 Literature Search Strategy

A computerized search was conducted in PubMed, CNKI, and other databases from inception to February 2023. Chinese search terms included "non-alcoholic fatty liver disease," "heme oxygenase-1," "ferroptosis," "anti-oxidative stress response,"and "lipid peroxidation."English search terms included "Non-alcoholic fatty liver disease," "Heme oxygenase-1," "Ferroptosis," "antioxidative stress response," and "lipid peroxidation." Inclusion criteria: literature addressing the effects of HO-1 on NAFLD development and progression, the mechanisms of ferroptosis, and the role of ferroptosis in NAFLD. Exclusion criteria: literature unrelated to the topic, poor quality, or with unavailable full text. A total of 56 articles were ultimately included.

2 Biological Characteristics of HO

HO is a key enzyme involved in heme metabolism, widely distributed in mammalian tissues and organs. Its most important function is regulating heme metabolism, while also participating in iron metabolism, oxidative stress, and pathogen responses [5]. Recent studies have found that HO exists in three forms in animals: HO-1, HO-2, and HO-3 [6].

HO-1, also known as heat shock protein 32 (HSP32), is an inducible enzyme

with a molecular weight of 30-32 kD. It is primarily distributed in the microsomes of the mononuclear-macrophage system, with high expression levels in parenchymal organs, bone marrow, and reticuloendothelial cells. Research has shown that HO-1 is an important stress protein, and its appropriate increased expression under stress conditions can protect against stress responses by reducing cellular damage, protein oxidation, and lipid peroxidation. HO-2 is a constitutive isoenzyme and the main form of HO under physiological conditions, primarily distributed in the mitochondria of endothelial and neuronal cells in most tissues, including the brain, retina, vascular endothelium, and testes. HO-3 is also a constitutive isoenzyme expressed in the brain, liver, kidneys, and testes, but it lacks catalytic activity for heme degradation.

3 HO-1 Slows NAFLD Progression

The pathophysiological mechanisms of NAFLD are complex, involving hepatic lipid peroxidation, ion transport imbalance, hepatocyte injury, and inflammatory infiltration. Studies have found that HO-1 plays important biological roles in the development of NAFLD by inhibiting reactive oxygen species (ROS)-dependent endoplasmic reticulum stress and necrosis, exerting anti-oxidative stress, anti-lipid metabolism, anti-fibrotic, and anti-apoptotic effects [7-10].

3.1 Anti-lipid Metabolism

HO-1 can increase adiponectin levels, enhance insulin sensitivity, promote fatty acid oxidation [11], improve glucose uptake capacity, and effectively reduce triglyceride levels [12]. Low expression of reduced glutathione (GSH) in NAFLD patients suggests that the compensatory increase in HO-1 expression is an adaptive response against lipid peroxidation, which can delay oxidative stress damage to tissue cells caused by sustained ROS increase to a certain extent, playing a key role in the progression of nonalcoholic steatohepatitis (NASH).

3.2 Anti-oxidative Stress

The Nrf2/HO-1 signaling pathway plays an important role in NAFLD progression by regulating the oxidative-antioxidative axis balance and inhibiting endoplasmic reticulum stress and lipid accumulation in NAFLD [13]. Nuclear factor-erythroid 2-related factor 2 (Nrf2) promotes the generation of CO, Fe2+, and biliverdin by activating the responsive expression of downstream HO-1, thereby reversing the progression of NAFLD. This pathway can also inhibit activated protein kinase C (PKC) and nicotinamide adenine dinucleotide phosphate (NADPH) activity, clear accumulated oxidative products, reverse hepatocellular oxidative stress injury, and delay or prevent NASH progression [2]. Ren et al. [14] established a NASH mouse model using a high-fat purified diet and confirmed that Zhiming Hongshan granules could activate the Nrf2/HO-1 pathway to ameliorate NASH liver injury.

3.3 Anti-inflammatory Response

In many inflammatory animal models, high expression of HO-1 has been shown to significantly downregulate adhesion molecule expression and leukocyte adhesion, inhibit lipopolysaccharide-induced production of inflammatory cytokines [15], and exert anti-inflammatory effects. During NAFLD progression, massive lipid accumulation in hepatocytes causes increased intracellular ROS, which activates nuclear transcription factor NF- B and initiates inflammatory responses. Xu et al. [16] constructed an NAFLD mouse model and found that the Nrf2/HO-1 pathway could inhibit the production of pro-inflammatory cytokines and NO in macrophages and downregulate IL-6 and TNF-α levels to combat hepatic inflammation.

3.4 Anti-apoptotic Effects

HO-1 can upregulate the expression of the cyclin-dependent kinase inhibitor (p21), arrest the cell cycle, reduce the expression of Caspase-8 and Caspase-10, and inhibit apoptosis. Nan et al. [17] found that intervention with the HO-1 agonist hemin or Ad-HO-1 could upregulate HO-1 expression, reduce liver thiobarbituric acid-reactive substances (TBARS) levels, and alleviate methionine- and choline-deficient diet (MCD)-induced hepatocellular apoptosis injury. Additionally, the HO-1 metabolite CO can increase Bcl-2 expression or decrease Bax expression in hepatocytes and hepatic sinusoidal cells, inhibiting liver ischemia-reperfusion-mediated apoptosis [18].

3.5 Autophagy Response

Studies have shown that HO-1 can induce autophagy to alleviate liver inflammation and improve acute liver failure and hepatic ischemia-reperfusion injury [19]. Endogenous HO-1 promotes autophagy signal transduction by mediating p38 MAPK phosphorylation and upregulating LC3 and PI3K pathways, thereby inhibiting Caspase-3-mediated apoptosis and protecting hepatocytes. Conversely, using HO-1 inhibitors to reduce HO-1 activity accelerates lipopolysaccharide (LPS)-induced hepatocyte death [20].

4 The Role of Ferroptosis in NAFLD

Ferroptosis is a complex form of cell death regulated by multiple cellular metabolic pathways [21], characterized by iron-dependent extensive lipid peroxidation and ROS accumulation [22], accompanied by glutathione depletion, which affects normal cellular function. Excessive lipid peroxidation damages cell membrane fluidity, permeability, and cell integrity, ultimately leading to cell death [23].

Research has shown that hepatocyte ferroptosis is closely related to the development of NAFLD. When serum iron levels exceed 1.5×ULN, hepatocytes undergo inflammatory responses with stellate cell activation, indicating that

elevated serum iron is an independent risk factor for NASH progression. Moreover, significantly increased serum ferritin levels and hepatic iron accumulation can be observed in NAFLD patients, and oxidative stress damage caused by iron overload plays an important role in the pathogenesis of liver injury [24]. Tsurusaki et al. [25] found that ferroptosis triggers inflammatory responses in simple hepatic steatosis (nonalcoholic fatty liver, NAFL) and accelerates NASH progression. Through establishing an NAFLD animal model, they discovered that ferroptosis occurred significantly earlier than apoptosis in the early stage of NAFLD, causing severe liver damage; ferroptosis inhibitors (including iron chelators and antioxidants) could effectively combat hepatocyte death.

Increasing evidence indicates that ferroptosis induced by iron homeostasis imbalance, lipid peroxidation, System Xc-GSH-GPX4 axis imbalance, insulin resistance, and other pathways participates in the development of NAFLD [26-28].

4.1 Iron Homeostasis Imbalance

Various causes of hepatic iron metabolism disorders lead to increased generation of free iron (Fe3+), significantly enhancing the sensitivity of hepatic cells to ferroptosis. After Fe3+ enters the cytoplasm and mitochondrial matrix, it is reduced to active divalent iron (Fe2+). Excessive ferrous ions (Fe2+) cause iron homeostasis imbalance, forming a labile iron pool that catalyzes oxygen free radical production. During electron transfer, O2 accepts electrons to form hydrogen peroxide (H2O2), and Fe2+ reacts with H2O2 through the Fenton reaction to generate highly reactive hydroxyl radicals that are strongly toxic to cells. These radicals synergize with polyunsaturated fatty acids (PUFA) on phospholipid cell membranes to initiate lipid peroxidation reactions, inducing ferroptosis [23]. Abnormal iron accumulation in the liver may result from downregulation of the hepatic iron exporter FPN1 and upregulation of iron importers DMT1 and Trf1, thereby initiating the Fenton reaction, accelerating lipid ROS accumulation, and inducing ferroptosis and NAFLD progression [29].

4.2 Lipid Peroxidation

Lipid peroxidation is the main driver of ferroptosis. In NAFLD, lipid accumulation in hepatocytes causes lipid peroxidation, leading to massive ROS generation. Lipid peroxidation is a chain reaction catalyzed by iron and oxygen. When intracellular ROS accumulation exceeds the clearance capacity of antioxidants, macromolecules such as phospholipids, enzymes, and PUFA on biological membranes react under lipoxygenase (LOX) catalysis to form toxic lipid peroxides (L-OOH), altering cell membrane fluidity and permeability, mitochondrial structure and function, and ultimately damaging cell membrane stability, leading to ferroptosis [30]. Li et al. [31] found in animal studies that the ferroptosis inducer RSL3 (GPX4 inhibitor) exacerbated hepatic lipid accumulation in an MCD-induced NASH mouse model, while increased levels of Fe2+ and arachidonic acid (AA) metabolism synergistically promoted lipid peroxidation, accelerating NASH steatosis, oxidative stress, inflammation, and hepatocyte injury.

The iron chelator deferoxamine (DFO) significantly reduced lipid accumulation and hepatic triglyceride levels, delaying NASH progression.

4.3 System Xc-GSH-GPX4 Axis Imbalance

The cystine/glutamate antiporter System Xc- is a heterodimeric transmembrane protein that mediates transport between intracellular and extracellular cystine and glutamate, representing an important component of the cellular antioxidant system. Cystine entering the cell is converted to cysteine (cys), which participates in GSH synthesis. As a reducing agent for glutathione peroxidase 4 (GPX4), GSH is a necessary cofactor for GPX4 to reduce ROS and reactive nitrogen species and inhibit lipid peroxide formation. In the early stage of NAFLD, massive lipid droplet deposition undergoes β-oxidation in hepatocytes. When generated ROS exceeds the clearance capacity of GPX4, it induces massive consumption of long-chain PUFA in the liver, reducing cell membrane stability and altering mitochondrial structure and function, thereby triggering liver injury and inflammation. Zhu et al. [32] found that GPX4-deficient hepatocytes had higher lipid droplet accumulation and ROS levels, highlighting the importance of GPX4 in cellular defense against lipid peroxidation, as it can reduce hepatic oxidative stress and clear lipid peroxides, thereby further reducing recruitment of inflammatory factors and activation of apoptotic signaling pathways.

4.4 Insulin Resistance

The main triggers of NAFLD/NASH are often diabetes, obesity, and other metabolic conditions, with insulin resistance being a critical step in NAFLD progression [33]. Evidence shows a close relationship between systemic iron levels and insulin signaling, with iron metabolism markers helping to induce adipocyte insulin resistance in the early pathogenesis of type 2 diabetes mellitus (T2DM). Both ferritin and transferrin, two markers of iron metabolism, are negatively correlated with adiponectin levels. Insulin resistance and the resulting early hyperinsulinemia can accelerate NAFLD progression and represent one of the risk factors for NAFLD fibrosis [34].

5 The Role of HO-1-Mediated Ferroptosis in NAFLD

Lipid peroxidation-induced oxidative stress damage is an important factor in NAFLD development. It remains unclear whether HO-1, as a potent antioxidant, can delay the occurrence of hepatocyte ferroptosis in NAFLD. Current evidence suggests two perspectives on HO-1-mediated ferroptosis pathways. On one hand, heme metabolism can convert heme proteins and heme oxidants into bilirubin, biliverdin, and CO, exhibiting antioxidant cytoprotective effects. On the other hand, excessive activation of HO-1 releases large amounts of ferrous ions, leading to accumulation of the labile iron pool and exacerbating oxidative stress [37]. This dual effect makes HO-1 a double-edged sword.

Furthermore, during NAFLD progression, activation of hepatic stellate cells

(HSCs) is a key step in hepatic fibrosis development, and targeted inhibition of HSC activation is crucial for slowing NAFLD progression. Zhang et al. [39] found that sorafenib and erastin can target and induce HSC ferroptosis. Magnesium isoglycyrrhizinate can enhance HO-1 expression, leading to intracellular iron accumulation and lipid peroxide aggregation, triggering HSC ferroptosis and inhibiting hepatic fibrosis formation. Therefore, targeted activation of HO-1 to promote HSC ferroptosis may represent a novel therapeutic approach for treating hepatic fibrosis and delaying NAFLD progression.

5.1 Nrf2/HO-1 Signaling Pathway Inhibits Ferroptosis Through Anti-oxidative Stress

Current evidence indicates that Nrf2, as an important transcription factor, regulates glutathione, iron, and lipid metabolism and mitochondrial function, participating in the expression of various target genes that regulate ferroptosis [40]. Increased intracellular free radicals can induce dissociation of the Nrf2-Keap1 complex, and activated Nrf2 protein translocates to the nucleus to bind to antioxidant response elements (ARE) in the HO-1 gene promoter, initiating transcription of downstream antioxidant stress genes, including HO-1 and ferritin heavy chain (FTH1), thereby reducing ROS-induced cell damage and maintaining redox homeostasis. Li et al. [41] found that Panaxydol (PX) could inhibit LPS-induced ferroptosis and inflammatory responses by activating Keap1-Nrf2/HO-1 signaling, indirectly indicating that Nrf2/HO-1 is an important negative regulator of ferroptosis. Additionally, Nrf2 can affect genes encoding GSH synthesis proteins, such as solute carrier family 7 member 11 (SLC7A11), GCLC/GLCM, and GSS [42], inhibiting peroxide generation. Lin et al. [43] found that downregulating SLC7A11 expression leads to decreased cysteine-dependent glutathione peroxidase activity and increased lipid peroxidation, ultimately resulting in ferroptosis. Therefore, activating the Nrf2/HO-1 pathway can reduce oxidative stress, resist inflammatory responses, and play a role in inhibiting ferroptosis.

5.1.1 Anti-oxidant Effects of HO-1 and Its Metabolites Inhibit Ferroptosis As an important antioxidant factor, HO-1 can clear accumulated oxidative products and plays a significant role in oxidative stress-related liver injury. Additionally, HO-1 activation promotes expression of the System Xc- system, accelerating cystine/glutamate transport to clear accumulated LPO and reduce cellular sensitivity to ferroptosis. Enhanced HO-1 activity promotes heme degradation, and its product bilirubin acts as a natural antioxidant that can be oxidized to biliverdin, which can then be reduced back to bilirubin by biliverdin reductase. This oxidation-reduction cycle can amplify the antioxidant effect of bilirubin, clearing excess superoxide and hydrogen peroxide radicals, helping cells evade partial oxidative stress, and to some extent altering intracellular iron distribution to reduce cellular iron uptake. Furthermore, CO generated from HO-1 catabolism can block electron transfer in cytochrome C oxidase (COX), affecting electron transport chain redox balance, increasing ROS generation, and disrupting antioxidant defense systems. Yao et al. [44] found that CO can

significantly reduce cystathionine β-synthase (CBS) protein expression, thereby decreasing GPX4 activity, increasing intracellular ROS concentration, and inducing ferroptosis. Recent studies have shown that physiological doses of CO can act as an intracellular second messenger to target and promote mitochondrial regeneration and restore mitochondrial membrane potential, thereby reducing mitochondrial ROS production [45], but its relationship with ferroptosis remains unclear.

5.1.2 HO-1 Promotes Ferroptosis Through Intracellular Ferrous Ion Accumulation Some studies suggest that the Nrf2/HO-1 pathway can promote Nrf2 nuclear translocation, upregulate HO-1 expression, catalyze heme degradation, promote free iron release, and induce ferroptosis. HO-1 has also been shown to cause intracellular Fe2+ accumulation by stimulating increased transferrin receptor (TFR) and decreased SLC40A1. Unstable iron accumulation also increases HO-1 expression, creating a vicious cycle between HO-1 upregulation and iron accumulation that exacerbates ferroptosis. SLC7A11 gene encodes the cystine/glutamate antiporter (xCT) and participates in regulating iron overload-ferroptosis processes. Dong et al. [46] found that SLC7A11 can negatively regulate Nrf2/HO-1 signal transduction, and HO-1 is activated due to intracellular ROS accumulation, exacerbating the vicious cycle effect between HO-1 and Fe2+. Tang et al. [47] found that knocking out the HO-1 gene or using the HO-1 inhibitor zinc protoporphyrin (ZnPP) could inhibit HO-1 overexpression, promote specific Fe2+ binding, thereby escaping the harmful cyclic effect between HO-1 and ferrous ion accumulation, further reducing oxidative product generation to prevent ROS overload and block ferroptosis caused by lipid peroxidation.

5.2 HO-1 Inhibits Ferroptosis by Upregulating Ferritin Expression

As early as 1992, Balla et al. [48] demonstrated that in endothelial cells exposed to H2O2-induced oxidative stress, increased HO-1 expression was accompanied by elevated ferritin, likely due to increased Fe2+ release from enhanced heme degradation. Ferritin is a protective protein that chelates iron ions, and its antioxidant properties depend on its high iron chelation capacity and the ferroxidase activity of its H chain. Soares et al. [49] found that HO-1 not only has antioxidant effects but also increases ferritin levels, enhances endoplasmic reticulum ATP-dependent iron transport pump activity, promotes iron efflux, and reduces cellular iron content, thereby playing a role in protecting cells from ferroptosis.

Ferritinophagy is the process by which intracellular ferritin is specifically recognized by nuclear receptor coactivator 4 (NCOA4) and degraded in lysosomes with iron release. After ferritinophagy initiation, ferritin degradation releases free Fe2+, increasing cellular labile iron content. Excessive Fe2+ generates large amounts of ROS in a short period through the Fenton reaction, sensitizing cells to ferroptosis. The accumulation of labile iron pools driven by ferritinophagy

has become a widely recognized pathway of ferroptosis, but its relationship with HO-1 remains unclear.

Lipid metabolism disorders and oxidative stress are key factors in the development of chronic liver diseases, and current research has confirmed that HO-1 plays important roles in anti-inflammation, anti-apoptosis, anti-oxidative stress, and anti-lipid metabolism. Numerous animal and human studies have provided strong evidence supporting the critical role of ferroptosis in NAFLD pathogenesis, making it a potential therapeutic target for preventing NAFLD progression [31,50-51]. As discussed above, we believe that HO-1 may have a positive effect in regulating oxidative stress responses triggered by ferroptosis in NAFLD progression, delaying and reducing liver damage from oxidative stress. However, the mechanisms by which HO-1 participates in regulating ferroptosis remain unclear, and whether upregulating HO-1 leads to ferroptosis acceleration through ferrous ion accumulation has not been confirmed. The specific biological functions of ferroptosis in promoting NAFLD development have not been fully validated, and the clinical feasibility of treating NAFLD by inhibiting ferroptosis requires further investigation. Currently, multi-center, double-blind, prospective, large-sample clinical studies on NAFLD are urgently needed to demonstrate the correlation between HO-1 and ferroptosis. Accurately understanding the role of HO-1 in NAFLD and the relationship between ferroptosis, HO-1, and NAFLD will facilitate the development of more effective and precise therapeutic strategies for NAFLD and promote the development of anti-NAFLD drugs.

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