PREFACE
Gastroenterology & Hepatology Research 2024;6(2):7. https://doi.org/10.53388/ghr2024007

The relationship between ferroptosis and non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a kind of metabolic disorder characterized by excessive fat deposition in the liver and ranging from simple steatosis (simple NAFLD) to nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma [1]. It has recently been increasing annually; for example, it was recently estimated to have a global prevalence of 32.4%, which seriously threatens human health [2]. Thus, the discovery of new therapeutic targets is of great importance because there is no specified drug for the treatment of NAFLD. On the other hand, the pathogenesis of NAFLD is complicated and still unclear. Recent studies have proposed ferroptosis as related to the disease progressions of NAFLD. Preliminary evidence indicated that ferroptosis in hepatocytes and hepatic macrophages could induce NASH and that complex regulatory mechanisms were involved. In the future, inhibition of ferroptosis may hopefully become an emerging target in treating NAFLD.

Mechanisms of ferroptosis

Ferroptosis is a form of cell death that is non-apoptotic, iron-dependent, and primarily characterized by the accumulation of reactive oxygen species within cells [3]. Cells are known to both produce substrates and oxidants for lipid peroxidation and inhibitors of the process themselves to establish a balance during normal processes. In the case of ferroptosis, however, the imbalance induced due to lipid peroxidation and defense against the buildup of peroxidized lipids is established in the affected system, eventually leading to cell death [4]. Morphological alterations in ferroptosis are characterized by destabilization of the cell membrane, cytoskeletal rearrangement, decreased cell volume, loss or diminution of mitochondrial cristae, increased density of the mitochondrial membrane, and rupturing of the outer mitochondrial membrane. Biochemically, this process is marked by enhanced lipid peroxidation and elevated reactive oxygen species (ROS) levels; concurrently, there is a decline in the expression of glutathione peroxidase 4 (GPX4), the key enzyme in the antioxidant system [5].

The process of ferroptosis is very complex and multifactorial in its mechanisms. It is now understood to be tightly connected to the imbalance of iron homeostasis and lipid peroxidation, along with the dysregulation of the System Xc-/GSH/GPX4 axis [6]. This mechanism houses several components: (Figure 1).

Imbalance of the System Xc-/GSH/GPX4 axis

System Xc- is a transmembrane protein complex that includes SLC7A11 and SLC3A2 subunits. It mainly plays the role of transferring extracellular cystine into a cell and, on the other hand, releasing glutamate out of the cell. After being reduced to cysteine following entry through the dimeric System Xc- located on the surface of the cell membrane, cysteine is further metabolized into glutathione (GSH) after being catalyzed by glutamate-cysteine ligase (GCLC) and glutathione synthetase (GSS) [7]. It is a selenoprotein, GPX4, which converts the cellular phospholipid hydroperoxides (PUFA-PL-OOHs) into non-toxic phospholipid alcohols, thus providing resistance to cell

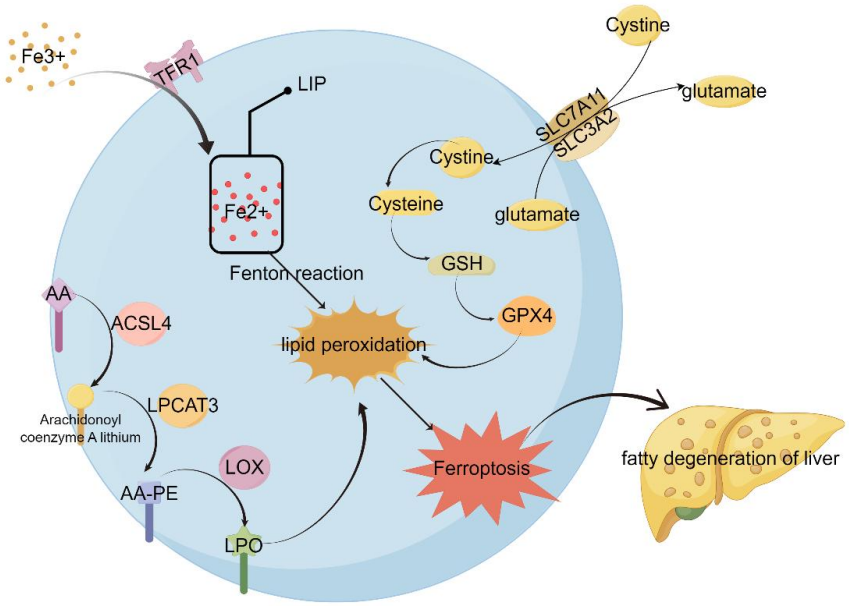

Figure 1 The relationship between ferroptosis and NAFLD. Source of figure: author using Figdraw. ID: ISITW22887. ACSL4, Acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; GSH, glutathione; GPX4, glutathione peroxidase 4.

ferroptosis [4]. As a result, either directly or indirectly, GPX4 is inactivated, leading to ferroptosis. For instance, elastin was found to induce ferroptosis by inhibiting System Xc-, which then reduced GSH synthesis and is followed by GPX4 inactivation [8]. In contrast, RAS-selective lethal 3 (RSL3) exerts ferroptosis via GPX4 inactivation with the subsequent accumulation of phospholipid hydroperoxides and cell death by ferroptosis – accordingly, there is an imbalance in the System Xc-/GSH/GPX4 [9].

Iron metabolism disorder

Iron, an essential trace element, circulates in the bloodstream as ferric iron (Fe^{3+}). Within the blood circulation, Fe^{3+} binds to transferrin for transport, enters cells via transferrin receptor 1, is reduced to ferrous iron (Fe^{2+}), and joins the labile iron pool in the cytoplasm, where excess iron is sequestered in ferritin. Due to its instability and high reactivity, Fe^{2+} participates in the Fenton reaction with H_2O_2, producing hydroxyl radicals. These radicals attack polyunsaturated fatty acids in cellular and plasma membranes, leading to extensive lipid ROS formation and cell death. Studies indicate that elevated Fe^{2+} levels intensify lipid peroxidation, exacerbating ferroptosis and contributing to various diseases [10].

Accumulation of lipid peroxides

The accumulation of lipid peroxides constitutes the core mechanism of ferroptosis [11]. Lipidomic studies have demonstrated that relative to the other PUFAs, arachidonic acid (AA) and its metabolites are the most sensitive substrates to oxidation during ferroptosis. Three enzymatic steps are involved in the catalysis of this process [12]. Acyl-CoA synthetase long-chain family member 4 (ACSL4) esterifies. Subsequently, it gets incorporated into phosphatidylethanolamines (PEs) by lysophosphatidylcholine acyltransferase 3 (LPCAT3) to form AA-PE; finally, it is oxidized by lipoxygenases into lipid peroxides [13]. These oxidative products compromise membrane structural integrity and result in cell death.

The relationship between ferroptosis and NAFLD

Ferroptosis is closely related to the pathology of several human diseases, including metabolic and neural diseases, cancer, and mainly NAFLD. Tsurusaki et al. proposed that ferroptosis might induce inflammatory phenomena in simple steatosis and further lead to the development of NASH, thus, inhibition of ferroptosis might control the occurrence of NAFLD [14]. Moreover, ferroptosis has been shown to propagate the progression of NASH by Qi et al., where its potentiality has further putative implications with the onset of the disease, such as inflammation, oxidative stress, and cellular damage [15]. Furthermore, the most recent research by Li et al. has shown that elevation in lipid peroxides leads to an accumulation of lipid droplets in the liver and that GPX4 plays an essential role in the maintenance of homeostasis of lipid droplets in the progression of NASH [16]. Ma and others opine that NAFLD seems to have an association with hepatic iron deposition, which can exacerbate inflammation, oxidative stress, and cellular damage in the body, thus further worsening hepatocyte swelling, inflammation, and fibrosis, which deteriorates the condition [14]. They hypothesize that increased hepatic iron concentration may be a triggering factor for the development of NAFLD. It might augment the disease processes by promoting hepatocyte swelling, inflammation, and fibrosis and may even lead to the progression of NAFLD to NASH [15]. Ferroptosis, driven by lipid peroxidation, is involved in NAFLD. In this context, lipid peroxidation products target the liver's predominant hepatocytes, triggering programmed cell death in the presence of Fe^{2+} and inflicting cellular damage through oxidative stress [16]. Disrupted hepatic iron metabolism results in excessive free iron, which, via the Fenton reaction, produces hydroxyl radicals and generates significant ROS, leading to steatosis and inflammation [17]. Studies show a connection between body iron stores and insulin signaling; iron excess may worsen insulin resistance, a key feature of NAFLD/NASH [18]. Thus, excessive iron and lipid peroxidation play a role in the pathogenesis of metabolic dysfunction-associated fatty liver disease, making the inhibition of ferroptosis a potential therapeutic target for metabolic dysfunction-associated fatty liver disease.

Regulation of NAFLD through ferroptosis by traditional Chinese medicine

Recent studies have demonstrated that traditional Chinese medicine can manage NAFLD by modulating ferroptosis. Yang and colleagues found that ginkgolide B enhances the antioxidant signaling pathway, boosts GPX4 expression, speeds up ROS clearance, minimizes lipid peroxide accumulation, suppresses ferroptosis, alleviates oxidative stress, and reduces fat deposition, thus improving NAFLD symptoms [19]. Chen et al. observed that dihydroartemisinin elevates ROS and reduces GPX4 availability, triggering ferroptosis in glioma cells due to iron toxicity [20]. Song et al. reported that saponins from *Ophiopogon japonicus* lead to ferroptosis in pancreatic cancer cells by increasing intracellular iron levels and ROS [21]. Additionally, in vitro and in vivo studies indicate that tanshinone IIA, derived from *Salvia miltiorrhiza* extracts, initiates ferroptosis in breast cancer cells by decreasing GPX4 levels, thereby inhibiting tumor growth [22]. Jiang et al. showed that gastrodin counteracts ferroptosis in mouse hippocampal neurons induced by glutamate [23].

At present, numerous compounds are recognized for their roles in either inducing or inhibiting ferroptosis. The potential of traditional Chinese medicine to curb ferroptosis and decelerate the progression of NAFLD warrants further research. Overall, ferroptosis significantly influences the pathogenesis and progression of fatty liver disease and may emerge as a new therapeutic target.

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Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This research received no specific grant from any funding agency inthepublic, commercial, or not-for-profit sectors.

Abbreviations

NAFLD, non-alcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; GSH, glutathione; ROS, reactive oxygen species; GPX4, glutathione peroxidase 4; AA, arachidonic acid; PE, phosphatidylethanolamines.

Citation

Li MN, Liao JB, Wang N, et al. The relationship between ferroptosis and non-alcoholic fatty liver disease. *Gastroenterol Hepatol Res.* 2024;6(2):7. doi: 10.53388/ghr2024007.

Executive editor: Jing-Yi Wang.

Received: 29 June 2024; **Accepted:** 01 July 2024; **Available online:** 02 July 2024.