

Ferroptosis: A new perspective in the diagnosis and treatment of coronary atherosclerotic heart disease

Abstract

Ferroptosis is an iron dependent lipid Reactive Oxygen Species (ROS) induced form of non-apoptotic cell death. It is governed by three antioxidant axes, such as the cyst(e)ine/GSH/GPX4 axis, the GCH1/BH4/DHFR axis, and the FSP1/CoQ10 axis. Emerging evidence has revealed that disorders of iron metabolism are the common denominator in the occurrence and development of diverse cardiovascular disease, including atherosclerosis, myocardial Ischemia Reperfusion and (I/R), and myocardial infarction. Some genes/proteins that are involved in lipid metabolism have been used as biomarkers of Ferroptosis. Those biomarkers have facilitated the development of potential methods for disease diagnosis. Iron chelators, antioxidants, Ferroptosis inhibitors, and genetic manipulations may alleviate Coronary Atherosclerotic Heart Disease (CHD) by blocking Ferroptosis pathways. Our found also suggest that Angiotensin Type1/2 Receptors (AT1/2R) blocker may inhibit Ferroptosis of vascular endothelial cells. Thus, suppression of Ferroptosis is a potential therapeutic option for CHD. Here, we aimed to highlight the effects of Ferroptosis in CHD and summarize new diagnoses and treatments based on Ferroptosis of CHD.

Keywords: Ferroptosis • Atherosclerosis • Coronary atherosclerotic heart disease • Potential therapeutic option

Introduction

Although cell death is an often necessary process in multicellular organisms during development, it can also play a crucial role in causing disease in many organs including the heart [1]. In the past 10 years, many studies support the notion that Ferroptosis has a pathophysiological role in the development of cardiovascular diseases [2]. CHD is one of the most common types of heart diseases and causes the highest mortality rate worldwide. Mounting evidence indicates that dysregulation of iron metabolism is associated with CHD [3,4]. Disordered iron metabolism runs through the whole pathological progression of CHD [5]. Ferroptosis is involved in vascular injury and cardiomyocytes death, promoting the development of Atherosclerosis (AS), myocardial I/R, and myocardial infarction. Some studies have directly or indirectly proved that Ferroptosis exists in ischemic heart disease and plays an essential role in the process of cardiomyocytes death [5]. Therefore, Ferroptosis, the form of regulated cell death characterized by iron-dependent lipid peroxidation, Glutathione (GSH) depletion, and Glutathione Peroxidase-4 (GPX4) inactivation, has received great attention in CHD [2,6]. However, the regulatory mechanisms of Ferroptosis death in CHD remain largely uncharacterized. Acquiring a fundamental understanding of the relevant molecular and pathological mechanisms may contribute to future therapeutic targets for CHD [7]. By gaining a deeper understanding of Ferroptosis and its role in CHD, we may uncover new therapeutic targets and strategies to combat this prevalent disease.

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For this reason, this research aimed to highlight the effects of Ferroptosis in CHD, summarize new pathogenesis and treatments based on Ferroptosis of CHD, and identify research trends and hotspots in this field.

Materials and Methods

Characteristics and regulation of Ferroptosis

Basic properties: The morphological, biochemical, genetic, and metabolic features in Ferroptosis are unique in comparison with other known forms of cell death. The morphological transformation of cells that undergo Ferroptosis generally includes a loss of plasma membrane integrity, cytoplasmic swelling, cell membrane rupture, the release of intracellular content, and moderate chromatin condensation. The mitochondria in Ferroptosis cells usually present shrinkage, an increase in membrane density, reduced or absent cristae, and rupturing of the outer membrane [2,8-15].

The two main biochemical properties of Ferroptosis are iron accumulation and lipid peroxidation. Intracellular free ferrous iron accumulation generates excessive ROS through the Fenton reaction, thereby triggering lipid peroxidation and Ferroptosis [10,16-19]. Some genes related to Ferroptosis were overexpressed including Prostaglandin End Peroxide Synthase-2 (PTGS2), Acyl-CoA synthetase Long-chain family member-4 (ACSL4), Transferrin Receptor-1 (TFR1), Nuclear Receptor Coactivator-4 (NCOA4). Correspondingly, many other genes are downregulated in Ferroptosis, such as Glutathione Peroxidase-4 (GPX4), Solute Carrier Family-7 Member-11 (SLC7A11), Nuclear factor erythroid 2-Related Factor-2 (NRF2), Ferroptosis Suppressor Protein-1 (FSP1) and Ferritin Heavy Chain-1 (FTH1). In addition, many noncoding RNAs are associated with Ferroptosis [10,20,21].

Regulation of Ferroptosis

Ferroptosis regulatory pathways: At present, a large number of studies have shown that the regulation mechanism of Ferroptosis involves multiple signaling and metabolic pathways. Those regulatory pathways can be roughly classified into three types: The first involve iron metabolism, including NCOA4 regulation of ferritin degradation, and the Nrf2-HO-1 pathway, which affects iron. The pathway is the key to Ferroptosis. Unstable iron pools, especially ferrous iron-induced Fenton reaction, produce many lipid-free radicals triggering Ferroptosis. The second is glutathione metabolism, the GSH/GPX4 pathway, including system Xc-(a cystine/glutamate antiporter system) inhibition, the transsulfuration pathway, the Mevalonate pathway (MVA pathway), the glutamine pathway, and p53. Amino acid metabolism is also closely related to Ferroptosis regulation. Cysteine availability restricts GSH biosynthesis, while cysteine starvation induces Ferroptosis. The third type is that of lipid metabolism, including ACSL4, P53/spermidine/Spermine N1-Acetyltransferase-1

(SAT1)/Arachidonate Lipoxygenase (ALOX15), and lipophagy, which are related to lipid regulation and Ferroptosis, as well as the FSP1-CoQ10-NAD(P)H pathway synergies with GPX4 and GSH, which reduce phospholipid peroxidation and Ferroptosis. In addition, Endoplasmic Reticulum (ER) stress facilitates Ferroptosis via ATF4-induced Glutathione Specific Gamma-Glutamyl Cyclo transferase-1 (CHAC1) expression. Mitochondria are the major source of ROS production. It hosts many important metabolism processes such as glutaminolysis and play pivotal roles in governing multiple forms of Regulated Cell Death (RCD). However, the role of mitochondria in Ferroptosis is still not fully clarified [8,10,14,22-39].

Potential roles of noncoding RNA in Ferroptosis regulation:

Noncoding RNA is widely expressed in the cardiovascular system and plays an important role in the occurrence and development of cardiovascular diseases. It can regulate the expression of genes associated with different Ferroptosis-related events, including iron homeostasis, cell protection, iron importation, and oxidative stress attenuation [40]. Numerous studies have confirmed that miRNAs and lncRNA participate in the process of cardiovascular disease by regulating Ferroptosis. Currently, many related miRNAs are reported, including miRNA-17-92, miR-15a-5p, miR-29b-3p, miR-190a-5p, miR-30d, miR-199a-5p and so on. Sun, et al., found that miR-135b-3p can promote Ferroptosis by targeting GPX4, then aggravating myocardial I/R injury. Similarly, miR-29b-3p can also aggravate cardiomyocyte I/R injury by down regulating the expression of PTX3 to exacerbate the inflammatory response. Known recently that the lncRNAs are involved in CHD include: lncRNA-KCNQ1OT1, lncRNA-XXYLT1-AS2, lncRNA-UCA1, lncRNA-p21, lncAABR07025387.1, lncRNA Mir9-3hg, etc. Some researchers have indicated that lncRNA PVT1 silencing significantly reduces infarct size and inhibits Ferroptosis [40,41-57].

Significantly, emerging studies have supported the vital role of circRNAs in CHDs, such as AS, and Myocardial Infarction (MI) [40,58]. Team Hou found that hsa_circ_0001558, hsa_circ_0021570, hsa_circ_0005941, hsa_circ_0002995, hsa_circ_0002665 and hsa_circ_0000530 may be closely related to the development of Ferroptosis in human coronary artery endothelial cells. The violated 6 circRNAs may function as circRNA-protein interactions to regulate the progression of Ferroptosis [59]. However, due to the lack of relevant research in this field, noncoding RNA regulates Ferroptosis and thus affects the pathophysiology of CHD remains to be further investigated.

Inducers and inhibitors of Ferroptosis: The known mechanisms of Ferroptosis inducers are as follows: Firstly, the inhibition of system Xc; and depletion of intracellular GSH; Secondly, the inhibition of GPX4; Thirdly, the degradation of GPX4 and exhaustion of

antioxidant CoQ10; and Fourth, the direct oxidation of ferrous iron and lipidome, or indirect inactivation of GPX4. In contrast, there are mechanisms of Ferroptosis inhibitors: Inhibiting the accumulation of iron and lipid peroxidation [1,10,60].

Results

Implications of Ferroptosis in CHD

Current research indicates that Ferroptosis has a significant impact on many diseases. Numerous researchers report that Ferroptosis regulates the occurrence and progress of CHD [1-7]. A more precise understanding of the causes and mechanisms of CHD progression may be beneficial for the treatment of patients.

Ferroptosis and atherosclerosis

The primary pathological mechanism of CHD lies in the formation, growth, and even rupture of atherosclerotic plaques. AS is the pathological basis of CHD, which involves abnormal lipid metabolism, oxidative stress, and inflammation, as well as other processes. Some researchers have confirmed the relationship between iron levels and AS [61]. Ferroptosis has been found to participate in atherogenesis and atherosclerotic progression through multiple physiological mechanisms, such as iron metabolism, lipid metabolism, and amino acid metabolism. The imbalance of iron metabolism may mediate Ferroptosis and promote the formation and development of AS. The relevant molecular mechanism is shown in Figure 1 [62-68].

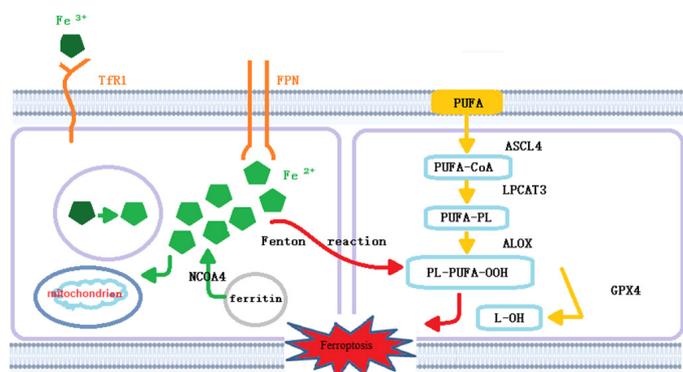


Figure 1: Iron metabolism and Ferroptosis.

Extracellular Fe³⁺ is transported into cells through TfR1 and reduced to Fe²⁺, which plays an effect in mitochondria or is stored in the form of ferritin. The remainder is transported out of cells through ferritin to maintain iron homeostasis. The reaction of PUFAs with excess reactive oxygen species occurs on the cell membrane, which is catalyzed *via* ACSL4 and LPCAT3, and mediated by ALOX, resulting in lipid peroxidation. GPX4 can reduce Ferroptosis *via* inhibiting lipid peroxidation. PUFAs: n-3 Polyunsaturated Fatty Acids; ACSL4: Acyl-CoA Synthetase Long chain family member-4; LPCAT3: Lysophosphatidylcholine Acyltransferase-3; ALOX: Arachidonate Lipoyxygenase; PL: Phospholipid; GPX4: Glutathione Peroxidase-4; NCOA4: Nuclear

Receptor Coactivator-4; TfR1: Transferrin Receptor 1 [61,69].

Lipid peroxidation is the core process of Ferroptosis. At the same time, iron is involved in various stages of lipid peroxide generation, including iron-catalyzed lipid oxidation and esterification, Polyunsaturated fatty acid oxidation, and lipid ROS generation through the fenton reaction. The Fenton reaction (Figure 2), and other peroxidation processes that incorporate iron can convert the mitochondrial oxidation respiration product, hydrogen peroxide, into hydroxyl radicals *via* the catalysis of ferrous ions [61,70-73]. During the oxidative phosphorylation of the electron transport chain, which occurs on the inner mitochondrial membrane, electrons leak from the complex and oxygen forms ROS through a series of redox processes [71]. Excessive generation of ROS can lead to DNA damage, protein degeneration, and lipid peroxidation and can induce Ferroptosis. Nevertheless, ROS derived from mitochondria may also activate the Nucleotide-binding Oligomerization Domain (NOD)-Like Receptor NLR family pyrin domain containing-3 (NLRP3) inflammatory bodies and cause the activation of the iron death signaling pathway degeneration, and lipid peroxidation and can induce Ferroptosis. Under normal physiological conditions [74], extracellular cystine is imported into cells in exchange for intracellular glutamate *via* the cystine/glutamate antiporter system xc-, maintaining glutamate balance inside and outside the cell (Figure 2). Cysteine reductase promotes the conversion of intracellular Cystine to cysteine, and GSH is generated *via* glutamate-cysteine ligase and GSH synthetase. The depletion of GSH also leads to glutamate-mediated iron and ROS generation and triggers oxidative cell death; specifically, Ferroptosis through the amino acid metabolic pathway [61,75].

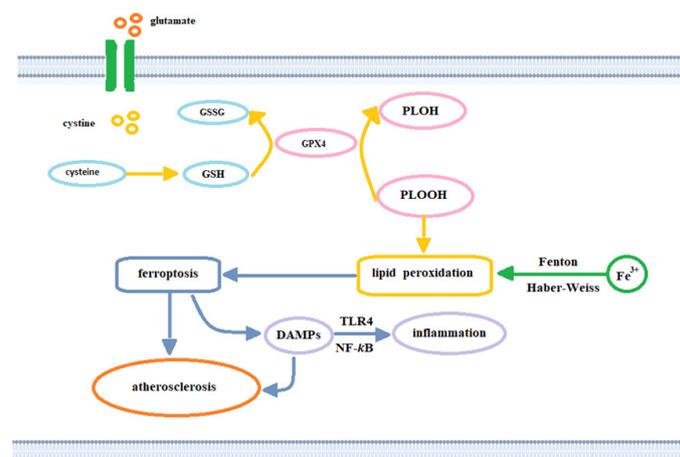


Figure 2: Ferroptosis and Atherosclerosis (AS).

Intracellular free iron generates hydroxyl radicals through the Fenton reaction and participates in the synthesis of lipoxygenase to generate lipid peroxides. Cystine and intracellular glutamate may exchange with system xc as a transporter. After a series of reactions, Cystine is converted into GSH. GPX4 inhibits Ferroptosis by

reducing lipid peroxide to its lipid alcohol with GSH. Inhibition of this process will lead to Ferroptosis, trigger the release of DAMP, and Atherosclerosis will be formed and aggravated. GSH: Glutathione; GPX4: GSH peroxidase-4; DAMPs: Danger-Associated Molecular Patterns; GSSG: Oxidized Glutathione [61].

Ferroptosis and cardiac I/R injury

I/R is a pathological condition characterized by the initial restriction of the blood supply to the heart, followed by the restoration of blood flow and reoxygenation. Insufficient blood supply leads to tissue hypoxia and cellular metabolic imbalance, and subsequent reperfusion and reoxygenation cause excessive inflammatory responses and exacerbate ischemic tissue damage, which is known as I/R injury [76]. Stable angina pectoris and acute coronary syndrome are mostly caused by myocardial cell ischemia. Timely reperfusion is now an effective treatment method

[77-79]. However, myocardial I/R injury caused by reperfusion therapy can affect the prognosis of patients. Mounting evidence indicates that Ferroptosis is one of the key drivers of the onset and progression of ischemic heart injury. Ferroptosis primarily occurs during the period of myocardial reperfusion rather than ischemia [80]. After cardiac IR, the cardiomyocytes around the scar tissue appear iron deposition. An increase in intracellular iron concentration leads to lipid oxidation and then induces Ferroptosis [40]. Team Cai, suggests that 15-Lipoxygenase (Alox15)/15-Hydroperoxyeicosatetraenoic acid (15-HpETE)-mediated cardiomyocyte Ferroptosis plays an important role in prolonged I/R injury [81]. Team Cao reported that Lysine-specific Methyltransferase 2B (KMT2B)-dependent Riboflavin Kinase (RFK) transcription activates the Tumor Necrosis Factor (TNF)- α /NADPH Oxidase- 2 (NOX2) pathway and enhances Ferroptosis caused by myocardial I/R as shown in the Figure 3 [82].

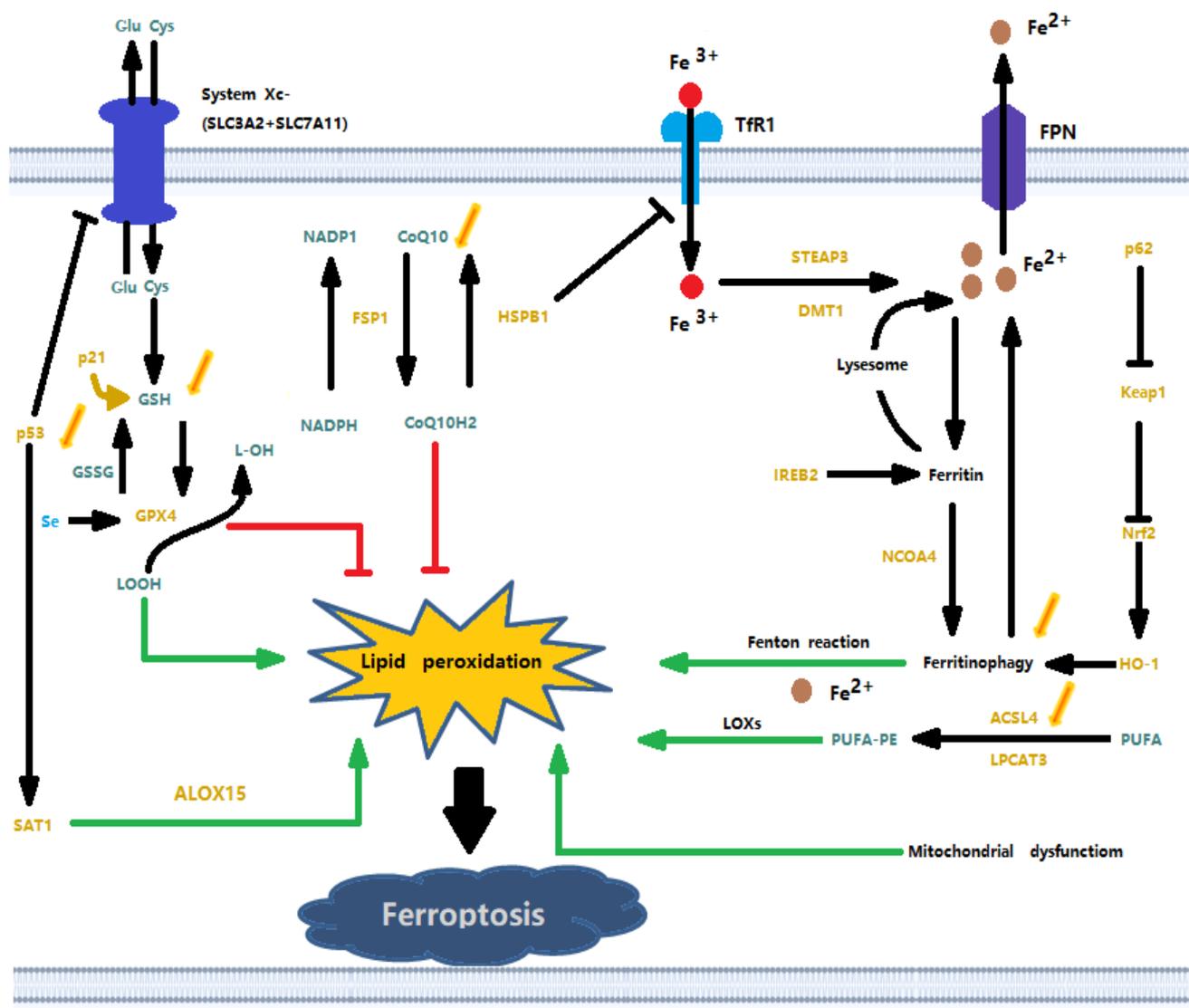


Figure 3: The regulatory mechanism of Ferroptosis in ischemia-reperfusion. Note: (T-bar) Inhibition effect; (arrow) Promotion effect; (green arrow) Enhanced promotion effect; (red arrow) Weakened inhibition effect; (lightning bolt) I/R

Genetic interventions and single pharmacological therapies of Ferroptosis investigated in I/R injury are summarized in the Figure 4. Green capsules represent well-recognized Ferroptosis inhibitors and purple for myocardial. I/R: Ischemia-Reperfusion; GPX4: Glutathione Peroxidase-4; ACSL4: Acyl-CoA Synthetase Long-Chain family member-4; NCOA4: Nuclear Receptor Coactivator-4; SLC7A11: Solute Carrier Family-7 Member-11; Nrf2: Nuclear factor erythroid-2-related factor-2; HO-1: Heme Oxygenase-1; MAO-B: Monoamine Oxidase-B; IREB2: Iron Response Element-Binding protein-2; TfR1: Transferrin Receptor-1; AMPK α 2: Adenosine 5'-Monophosphate-Activated Protein Kinase α 2; p53: protein 53; FPN: Ferroprotein; USP7: Ubiquitin-Specific Peptidase-7; USP14, Ubiquitin-Specific Peptidase-14; USP19: Ubiquitin-Specific Peptidase-19; USP22: Ubiquitin-Specific Peptidase-22; TRF: Transferrin; Gln: Glutamine; MiR: MicroRNA; OxPCs: Oxidized Phosphatidylcholines; LncRNA: Long non-coding RNA; ELAVL1: Embryonic Lethal-Abnormal Vision Like protein-1; DNMT-1: DNA (cytosine-5)-Methyltransferase-1; Nrf2: Nuclear factor erythroid-2-related factor-2; TERT: Telomerase Reverse Transcriptase; STAT3: Signal Transducer and Activator of Transcription-3; Sp1: Special protei-1; TRPV1: Transient Receptor Potential cation channel subfamily V member-1; LSD1: Lysine-Specific Demethylase-1; Panx1: Pannexin-1; CIRBP: Cold-Inducible RNA-Binding Protein;IDO: Indoleamine 2,3-Dioxygenase-1; ALR: Augmenter of Liver Regeneration; HUWE1: HECT domain-containing Ubiquitin E3 ligase; SAT1: Spermidine/Spermine N1-Acetyltransferase-1; PVT1: Plasmacytoma Variant-1; UBIAD1: UbiA prenyltransferase Domain Containing-1; PGE2: Prostaglandin E2; Fer-1: Ferrostatin-1; Lip-1: Lipoxstatin-1; DFO: Deferoxamine; DXZ: Dexrazoxane; α -Toc: α -Tocopherol; GAA: Gossypol Acetic Acid; C3G: Cyanidin-3-Glucoside; XN: Xanthohumol; HC: Histochole; PDA NPs: Polydopamine Nanoparticles; APG: Apigenin-7-O- β -D-(6''-p-coumaroyl)-Glucopyranoside; CAR: Carvacrol; Se: Selenium; Res: Resveratrol; CAT: Capsiate; CY: Carthamin Yellow; ROSI: Rosiglitazone; KF: Kaempferol; DEX.

Discussion

Pharmacological interventions

Iron chelators and lipid peroxidation inhibitors: Iron chelation may provide a novel disease-modifying treatment approach in alleviating AS [6]. They can bind to iron in the body to effectively increase iron excretion, thus blocking the redox reaction caused by iron overload [5]. Myocardial I/R injury can be alleviated when iron chelators block Ferroptosis. Further *in vivo* data provided additional evidence indicating that chelating iron during both acute and chronic myocardial I/R injury can provide cardio protective benefits, highlighting the potential of targeting Ferroptosis as a promising novel therapeutic strategy for I/R injury. Lipid

peroxidation inhibitors (Such as Ferrostatin-1 and lipoxstatin-1) may also pharmacologically inhibit Ferroptosis. Growing evidence shows that Ferrostatin-1 rescues lipid peroxidation and Lipoxstatin-1 reverses Ferroptosis by scavenging free radicals to prevent PUFA oxidation, whose therapeutic effects were like Fer-1 [6,7,102,103].

Clinical drugs: Some clinical drugs have shown the potential to inhibit Ferroptosis [6]. The commonly prescribed heart medications might have previously unidentified anti-ferroptotic activity. A variety of agents with different biological activities have been shown to inhibit Ferroptosis in myocardial I/R injury [89]. For instance, carvedilol for the treatment of hypertension and heart failure has been shown to suppress Ferroptosis independent of its effect on β -adrenergic receptors, and the underlying mechanism might contribute to its capacity to scavenge lipid peroxides and chelate iron [104-106]. Propofol, a frequently used anesthetic agent, has been shown to protect against myocardial injury by suppressing I/R-induced Ferroptosis through the AKT/p53 signaling pathway [89,107]. Ferulic Acid (FA), the main active component of *Angelica sinensis*, was reported to alleviate myocardial I/R injury by enhancing AMPK α 2 expression-mediated Ferroptosis inhibition [89,108]. Rapamycin also plays a crucial role in reducing excess iron and Ferroptosis in cardiomyocytes [89].

Natural products: With the rapid development of studies on Ferroptosis, increasing evidence has revealed that natural products can regulate Ferroptosis, and are related to cardiovascular disease. For example, the ethylacetate-extracted fraction of the total Ginkgo biloba flower extract showed an anti-Ferroptosis effect in vascular endothelial cells. Compared with classical Ferroptosis inhibitors, natural products have the advantages of stable structure, high safety, low cost, and easy access, so it is a valuable and promising effort to explore natural products as Ferroptosis inhibitors [6].

Genetic manipulation

Noncoding RNA: The roles of several miRNAs and lncRNAs in regulating Ferroptosis have been found in myocardial I/R [40]. Zhang, et al., suggest that miR-199a-5p plays a central role in stimulating Ferroptosis-induced cardiomyocyte death during ischemic/hypoxic injury *via* inhibiting Akt/eNOS signaling pathway [48]. Wu, et al., confirmed the protective effect of lncRNA SEMA5A-IT1 carried by sEVs after CPB on cardiomyocytes after I/R [109,110]. Recently, miR-135b-3p was shown to exert an inhibitory effect on GPX4 expression, thereby exacerbating Ferroptosis during myocardial I/R injury [44]. Accumulating evidence suggests that lncRNAs can act as competing endogenous RNAs (ceRNAs) and sponge miRNAs to upregulate downstream gene expression [110]. LncAABR07025387.1 was shown to function as a ceRNA to sponge miR-205 (downregulating miR-205 expression) and consequently enhanced ACSL4 expression

to exacerbate Ferroptosis during myocardial I/R [5]. In contrast, several lncRNAs are cardio protective against I/R injury. The Bone Marrow Mesenchymal Stem Cell (BMSC)-derived lncRNA Mir9-3hg has been reported to suppress I/R-induced cardiomyocyte Ferroptosis through regulating the Pumilio RNA binding family member-2 (Pum2)/Peroxisome Proliferator-activated Receptor-γ (PPAR-γ) axis [55]. These findings highlight the therapeutic potential of using functional noncoding RNAs to treat myocardial I/R injury by suppressing Ferroptosis.

Although the role of Ferroptosis and circRNAs in the development of CHD pathology and the molecular mechanisms remains unclear, a few studies still provide some insights. Hou reveals that certain circRNAs may regulate Ferroptosis, which further affects the acceleration process of CHD. [59] These results provide new sight into the character of circRNAs in the progress of Human Coronary Artery Endothelial Cells (HCAECs) Ferroptosis and contribute significant data for further investigating the potential mechanisms of CHD. Protecting cells from Ferroptosis through circRNAs treatment may be an effective therapeutic strategy to prevent or treat CHD. The key circRNAs involved in Ferroptosis were identified and the mechanisms of Ferroptosis in CHD were explored in this study. The results suggested that circRNAs may be a new target for the future treatment of Ferroptosis-involved CHD. Homson, et al., indicated that the circular antisense noncoding RNA in circANRIL slows down the development of atherosclerosis by regulating the maturation of rRNA and affects the formation of atherosclerosis, thus attenuating the development of atherosclerosis [40,111]. With the continuous deepening of circRNA and Ferroptosis research, whether circRNA can impact CHD by regulating Ferroptosis has become a focus of attention. Low-density Lipoprotein Receptor-related Protein-6 (LRP6) has a significant effect on the process of Ferroptosis. circRNA1615 regulated the expression of LRP6 through sponge adsorption of miR-152-3p. Then, it prevents Ferroptosis mediated by autophagy in cardiomyocytes [40,112]. Zheng, et al., showed that low expression of circSnx12 and high expression of miR-224-5p may downregulate the expression of FTH1 to make myocardial cells iron overloaded, then leading to Ferroptosis. The specific mechanism is that circSnx12 promotes the expression of FTH1 *via* inhibiting the expression of miR-224-5p, thus maintaining an iron steady state in the cell [40,113,114].

Related gene: Ferroptosis has multiple regulatory genes, such as GPX4, ACSL4, Solute Carrier Family-7 Member-11 (SLC7A11), Nuclear factor erythroid-2-related factor-2 (Nrf2), Nuclear Receptor Coactivator-4 (NCOA4), and Heme Oxygenase-1 (HO-1). These genes are involved in multiple mechanisms related to Ferroptosis, such as iron metabolism, oxidative stress, and lipid peroxidation, and targeted therapeutic strategies associated with these genes have also been investigated in I/R injury [114].

Studying the influence of genes on Ferroptosis can find a new therapeutic approach. Meng suggests that Ferroptosis-related genes GPX4 and TFRC were closely correlated with the identified overlapping genes CCNA2 and CDK1, which may serve as targeted therapies for the treatment of CHD [115]. The research results of Zhang, et al., show that Ferroptosis promotes neointima formation after arterial injury in mice and Vascular Smooth Muscle Cell (VMSC) phenotypic transition from a differentiated contractile to a dedifferentiated synthetic phenotype. Ferroptosis-induced VMSC phenotypic switching is associated with ROS accumulation. Thus, their findings support that inhibition of Ferroptosis or limiting ROS generation is a promising strategy to treat occlusive vascular diseases caused by restenosis of arteries following surgical interventions and injury [116,117]. Aybike Sena Ozuynuk reported that the genes related to oxidative stress and Ferroptosis were involved in biochemical parameters associated with CHD risk. P53 plays a dual role in Ferroptosis [117]. It reduces intracellular GSH by suppressing SLC7A11 expression to induce Ferroptosis [118]. Also, P53 enhances Ferroptosis *via* the transcriptional induction of SAT1 or GSL2 [36]. On the other hand, p53 inhibits Ferroptosis by inducing CDKN1A/p21 (cyclin-dependent kinase inhibitor 1 A) expression [119]. P53 may also block Dipeptidyl Peptidase-4 (DPP4) activity through a transcriptional independent mechanism to limit erastin-induced Ferroptosis [120]. We also found that the renin-angiotensin-aldosterone system participates in Ferroptosis regulation through P53 [121]. These results may provide a new perspective to further exploration of the therapeutic method [122].

Conclusion

In conclusion, Ferroptosis represents a novel and promising therapeutic approach for the management of CHD, potentially revolutionizing current treatment paradigms. The unique features of Ferroptosis could provide valuable insights for the development of diagnostic and prognostic tools, enhancing our ability to detect and monitor CHD at both tissue and systemic levels. However, the application of Ferroptosis in CHD treatment is not without challenges. Further research is needed to fully understand the underlying mechanisms, optimize therapeutic strategies, and mitigate potential side effects. Nonetheless, the potential of Ferroptosis-based therapies to improve patient outcomes and quality of life makes it a compelling avenue for future research in CHD management.

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