Kidney Diseases

Review Article

Kidney Dis
DOI: 10.1159/000530046

Received: December 31, 2022
Accepted: February 27, 2023
Published online: March 15, 2023

A Panoramic View of Ferroptosis in Cardiovascular Disease

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Keywords
Cardiovascular disease · Ferroptosis · Iron metabolism · Lipid peroxidation · Glutamine · Metabolism

Abstract
Background: Cardiovascular disease (CVD) remains the leading cause of disease burden worldwide. Ferroptosis, an iron-dependent form of programmed cell death, is characterized by the lethal accumulation of lipid peroxidation, which is morphologically, biochemically, and genetically distinct from apoptosis, necrosis, and pyroptosis. Emerging evidence provides exciting novel insights to allow for a deeper understanding of the physiology and pathology of ferroptosis in CVD. ***Summary:*** The rapidly evolving insights into ferroptosis have revealed its role in the pathogenesis of diverse forms of CVD, including cardiomyopathy, heart failure, atherosclerosis, pulmonary arterial hypertension, and cerebrovascular disease. Various types of metabolic pathways are involved in the regulation of ferroptosis, including iron metabolism, lipid metabolism, and redox metabolism. Modulators of ferroptosis, such as several clinical drugs, preclinical compounds, and other emerging materials, have been applied as promising approaches in the prevention and treatment of CVD. ***Key Message:*** In this review, we provide a 360 degree view of the latest progress in the field of ferroptosis in CVD, highlight the pathogenic role of ferroptosis in CVD, and also discuss the importance and future directions of targeting ferroptosis in CVD.

Introduction

Cardiovascular disease (CVD), which refers to a number of conditions, including atherosclerosis (AS), heart disease, heart attack, stroke, heart failure (HF), arrhythmia, and heart valve problems, remains the leading cause of disease burden in the world. Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019, and the number of CVD deaths has steadily increased from 12.1 million in 1990, reaching 18.6 million in 2019 [1]. Over 95% of all CVD-related deaths are attributable to 6 conditions: ischemic heart disease, stroke, hypertensive heart disease (which ultimately results in HF), cardiomyopathy, rheumatic heart disease, and atrial fibrillation [2]. CVD is also the main reason for both death and premature death in China; the annual number of deaths owing to CVD has increased from 2.42 million to

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4.58 million between 1990 and 2019 [1, 3]. Therefore, it is urgent to study the pathogenesis of CVDs and find effective therapeutic targets.

Ferroptosis is recognized as an iron-dependent lethal process based on lipid peroxidation. It has been defined as a new form of programmed cell death (PCD) that differs from other forms of PCD (e.g., apoptosis and necrosis) as it generally exhibits a differential morphology, including cellular swelling with ferroptotic-like nanopores in cytomembranes, an enhanced density of shrunken and fragmentated mitochondria with reduced or absent cristae and membrane crumpling, and a normal nucleus size with abnormalities in chromatin [4, 5]. The peroxidation of certain phospholipids, mainly from polyunsaturated fatty acids (PUFAs) through an intracellular Fenton reaction involving both enzymatic and non-enzymatic pathways, leads to an imbalanced antioxidant system and defects in membrane integrity due to an accumulation of hydroperoxyl (PLOOH) radicals in the membrane, which is currently considered as a determinant step in ferroptosis. The Xc^--glutathione-glutathione peroxidase 4 (GPX4) network, cooperating with coenzyme Q10-ferroptosis suppressor protein 1 (CoQ_{10}-FSP1), dihydroorotate dehydrogenase-ubiquinol, and GTP cyclohydrolase 1-tetrahydrobiopterin (GCH1-BH4) axis, is widely regarded as major antioxidant defensive system affected by ferroptosis-derived reactive oxygen species (ROS) [6–9]. Recently, mounting evidence shows that ferroptosis participates in the development of CVD, including cardiomyopathy, HF, vascular injury, AS, cardiorenal syndrome (CRS), and pulmonary arterial hypertension (PAH) (shown in Fig. 1). This review will mainly summarize the recent research progress between ferroptosis and CVD while pointing out the clinical relevance of ferroptosis, as well as providing new ideas for further studies regarding the biology and the therapeutic relevance of ferroptosis in CVD.

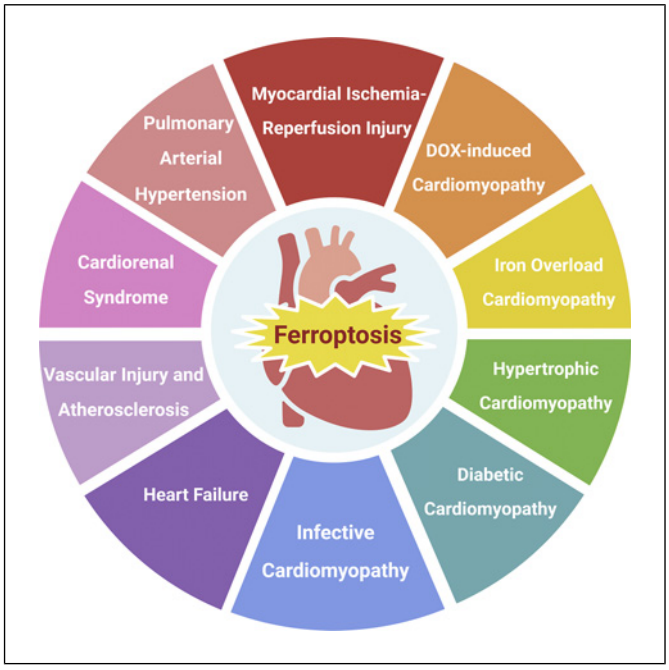

Fig. 1. Detrimental roles of ferroptosis in the pathological conditions of CVD. Ferroptosis has been suggested to participate in the development of CVD, including myocardial I/R injury, DIC, iron overload cardiomyopathy, HCM, DCM, infective cardiomyopathy, HF, vascular injury, AS, CRS, and PAH.

Features of Ferroptosis

Iron Metabolism in Ferroptosis

Under physiological conditions, there are two iron states: Fe^{2+} and Fe^{3+}. Heme carrier protein 1 (HCP1) transports Fe^{2+}-rich-protein heme into the cytoplasm, where heme oxygenase 1 (HMOX1) catalyzes the degradation of heme and the production of Fe^{2+} [10]. The plasma protein transferrin (TF) is the binding carrier of Fe^{3+}, which plays a protective role in liver ferroptosis in high-iron diet mouse models [11]. Fe^{3+} binding to TF is recognized by the transferrin receptor-1 (TFR1) in the cell membrane, and then the complexes are internalized into cells as endosomes, where Fe^{3+} is reduced to Fe^{2+} by the metalloreductase STEAP3 and this ionic form of iron is then released into the cytosol through the divalent metal transporter 1 (DMT1) [12]. DMT1 is required for iron uptake by the intestine and developing erythroid cells [13]. In addition, solute carrier family 39 member 14 (SLC39A14) is reported as an Fe^{2+} transporter [11]. Ferroportin (FPN), the only known mammalian iron exporter, mediates intracellular Fe^{2+} transport to the extracellular space [14]. Hepcidin acts by inducing endocytosis and subsequent degradation of FPN. The Tet1-RNF217-FPN axis, a newly recognized pathway, has been recently reported to regulate iron homeostasis [15]. Poly(RC) binding protein 1 (PCBP1) is a multifunctional protein that serves as a cytosolic iron chaperone, binding and transferring iron to recipient proteins in mammalian cells. PCBP1-deleted hepatocytes exhibit increased labile iron and production of ROS [16]. Nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy can increase the labile iron pool [17]. Under aerobic conditions, intracellular Fe^{2+} is catalyzed to Fe^{3+} via a Fenton reaction, which in turn produces hydroxyl radicals or peroxide radicals and further contributes to lipid peroxidation [18]. Moreover, prominin 2 (PROM2)

promotes the formation of ferritin-containing multivesicular bodies and exosomes, which transport iron out of cells and inhibit ferroptosis [19]. The content of labile Fe^{2+} increases during iron overload or in the presence of mutations in iron transport-related genes, which then drives overwhelming lipid peroxidation (shown in Fig. 2).

Lipid Metabolism in Ferroptosis

The peroxidation of PUFA-containing phospholipids in cell membranes is an important step in ferroptosis [12]. Lipid peroxidation preferentially oxidizes PUFAs. Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) are important enzymes responsible for the biosynthesis and remodeling of PUFA-phosphatidylethanolamines [20]. PKCβII senses the initial lipid peroxides and amplifies lipid peroxidation linked to ferroptosis through phosphorylation and activation of ACSL4 [21]. Moreover, other ACSL enzymes, such as ACSL1 and ACSL3, also participate in the regulation of ferroptosis [22, 23]. It is worth noting that free oxidized PUFAs are not toxic to the cell itself, and PUFAs are required to be transported into the membrane phospholipid to drive ferroptosis and cause cell death [4]. The action of arachidonate ALOXs, including ALOX5, ALOX12, and ALOX15, contributes to the accumulation of doubly and triply oxygenated arachidonic acid-containing PE species, which have been identified by lipidomic analyses of cells undergoing ferroptosis [12]. LOX inhibitors have been shown to be effective antioxidants for the capture of free radicals, and they protect lipids from self-oxidation through the autocatalytic free radical chain reaction of lipid hydroperoxide [24]. A picture has emerged wherein LOX activity may contribute to the cellular pool of lipid hydroperoxides that initiates ferroptosis, but lipid autoxidation drives the cell death process. The small molecules RSL3 and ML162 induce ferroptosis by inhibiting GPX4 function, which is blocked by the cooperation of GPX4 and vitamin E [25, 26]. Similarly, the LIFR-targeting molecules EC330/EC359 inhibit the activity of GPX4 in cells, but unlike RSL3, they reduce the level of GSH in cells [27]. iPLA2β acts as a major ferroptosis repressor to mediate detoxification of peroxidized lipids in a GPX4-independent manner [28]. Ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1) inhibit ferroptosis by acting as radical-trapping antioxidants (RTAs) to block lipid peroxidation, similarly to the lipophilic antioxidants BHT, BHA, and vitamin E [26] (shown in Fig. 2).

The Antioxidant System in Ferroptosis

There exist at least four protective systems against ferroptosis: GPX4 in the cytosol and mitochondria, FSP1 on the plasma membrane, DHODH in mitochondria, and the GCH1-BH4-phospholipid axis (shown in Fig. 2). Reduced GSH and GPX4 enzymes are important components of the intracellular antioxidant system that neutralize lipid peroxides and are also the main antioxidant system of ferroptosis [26]. GPX4 converts lipid hydrogen peroxide into nontoxic lipid alcohol with GSH as a cofactor, thus protecting cells from lipid peroxides [9]. There are two steps for GSH biosynthesis: cystine and glutamate are exchanged in and out of the cell by system Xc^- (composed of SLC7A11 and SLC3A2, at a ratio of 1:1), and then intracellular cystine are catalyzed into GSH by glutamate-cysteine ligase (GCL) [29, 30]. Erastin blocks extracellular cystine import and causes GSH depletion to induce ferroptosis [26].

FSP1 possesses NADH-dependent CoQ oxidoreductase which can generate the reduced form of CoQ_{10} and acts as a lipophilic RTA that halts the propagation of lipid peroxides [7]. The FSP1-CoQ_{10}-NAD(P)H pathway influences lipid peroxidation and ferroptosis which is independent of GPX4 pathway. Moreover, the FSP1-dependent non-canonical vitamin K cycle acts to protect cells against detrimental lipid peroxidation and ferroptosis [31]. One recent study has reported that $NADP^+$-dependent malic enzyme l inhibits ferroptosis via mediating the production of NADPH, cysteine and GSH [32]. DHODH, catalyzing a rate-limiting step in de novo pyrimidine nucleotide synthesis, operates in parallel to mitochondrial GPX4 (but independent of cytosolic GPX4 or FSP1) to inhibit ferroptosis in the mitochondrial inner membrane through reducing mitochondria CoQ_{10}, an RTA with anti-ferroptosis activity [6, 33]. The GCH1-BH4-phospholipid axis acts as a master regulator of ferroptosis resistance, controlling endogenous production of the antioxidant BH4 and then blocking lipid peroxidation [8]. Nuclear factor erythroid 2-related factor 2 (NRF2) is another master antioxidant regulator, and many of its downstream target genes are involved in ferroptosis [34]. For example, trigonelline and brusatol induce ferroptosis through suppressing the exrepssion of NRF2 [26].

Administration of exogenous compounds alters ferroptosis sensitivity. For example, the iron chelator deferoxamine directly inhibits ferroptosis by reducing intracellular iron levels [35]. Fer-1, one of the "functional" tests for ferroptosis versus other types of PCD, can rescue the injury induced by erastin and RSL3 [5, 26, 36]. Due to the weakness of Fer-1, which suffers from low water solubility and a poor biodistribution profile and is

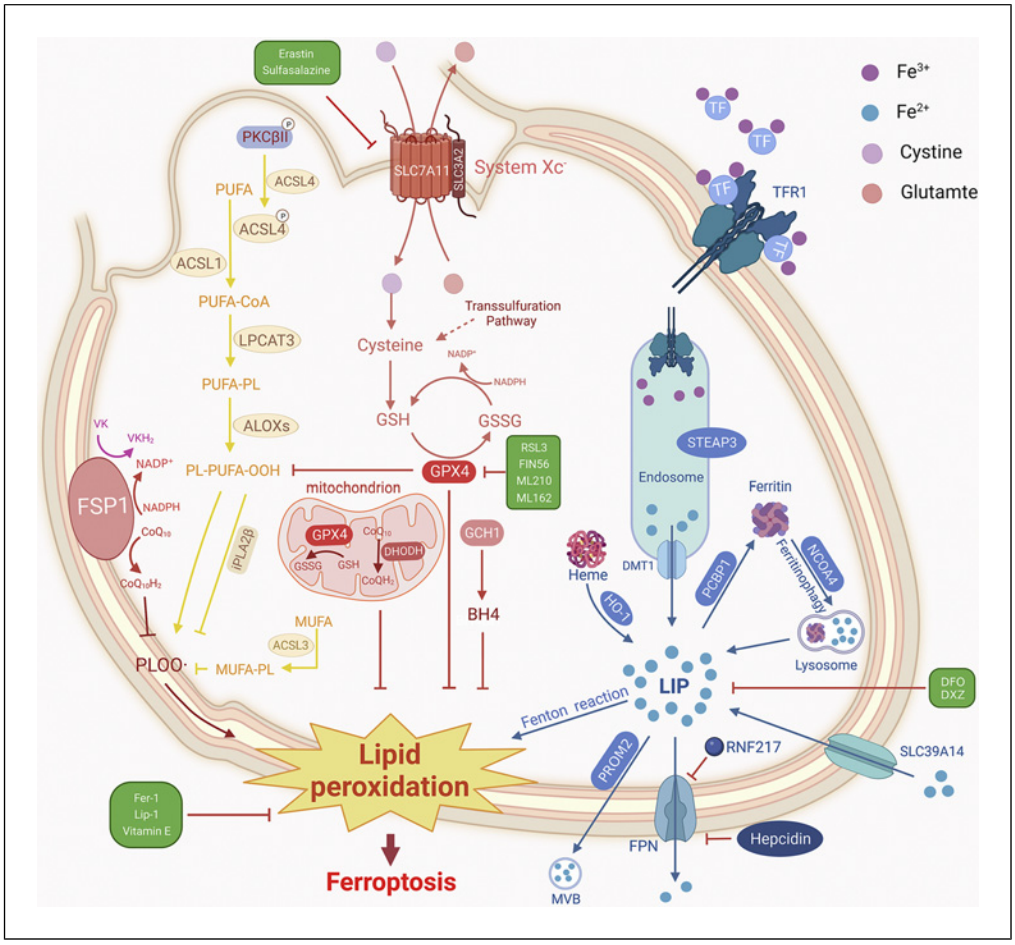

Fig. 2. Molecular mechanisms of ferroptosis. Ferroptosis mainly includes iron metabolism, lipid metabolism, and the antioxidant system. Antioxidant system: GPX4 in the cytosol and mitochondria, ferroptosis suppressor protein 1 (FSP1) on the plasma membrane, dihydroorotate dehydrogenase (DHODH) in mitochondria, and GCH1-BH4-phospholipid axis. Erastin and sulfasalazine are inhibitors of system Xc^-. RSL3, FIN56, ML210, and ML162 are inhibitors of GPX4. Deferoxamine (DFO) and dexrazoxane (DXZ) are iron chelators. Ferrostatin-1 (Fer-1), liproxstatin-1 (Lip-1), and vitamin E are ferroptosis inhibitors. MVB, multivesicular bodies; LIP, labile iron pool; SLC3A2, solute transporter family 3 members 2; SLC7A11, solute transporter family 7 member 11; System Xc^-, the cystine/glutamate antiporter system; TF, transferrin; TFR1, transferrin receptor 1; STEAP3, six-transmembrane epithelial antigen of the prostate 3; DMT1, divalent metal transporter 1; HO-1, heme oxygenase 1; PCBP1, Poly(RC) binding protein 1; NCOA4, nuclear receptor coactivator 4; FPN, ferroportin; RNF217, ring finger protein 217; SLC39A14, solute carrier family 39 member 14; PROM2: prominin 2; ALOXs, arachidonic acid lipoxygenases; PKCβ II, protein kinase C beta-type isoform 2; PUFA, polyunsaturated fatty acid; PUFA-CoA, polyunsaturated fatty-acid-acyl-coenzyme A; PUFA-PL, polyunsaturated fatty acid-containing phospholipid; PL-PUFA-OOH, phospholipid with peroxidized polyunsaturated fatty acyl tail; iPLA2β, phospholipase A2 group VI; MUFA: mono-unsaturated fatty acids; ACSL1/3/4, acyl-CoA synthetase long-chain family member 1/3/4; LPCAT3, lysophosphatidylcholine acyltransferase 3; GCH1: GTP cyclohydrolase 1; BH4: tetrahydrobiopterin; DHODH, dihydroorotate dehydrogenase; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; VK: vitamin K; VKH_2, vitamin K hydroquinone; GSH, glutathione; GSSG, oxidized glutathione; NADPH, nicotinamide adenine dinucleotide phosphate; CoQ_{10}, coenzyme Q10; $CoQ_{10}H_2$, ubiquinol.

thus unsuitable for clinical application, the irreversibly conjugated Fer-1 polymer-drug conjugates show greatly increased anti-ferroptosis activity compared to reversibly (Schiff base) linked Fer-1 [37]. Modifying ferroptosis and its regulatory genes, such as GPX4 and NRF2, has effects on the progression of ferroptosis to some extent.

Ferroptosis and CVD

Ferroptosis and Cardiomyopathy

Cardiomyopathy is a group of CVDs with poor prognosis and high mortality. The American Heart Association (AHA) classifies cardiomyopathy into primary and secondary: the etiology of primary cardiomyopathy is still unclear and the leading causes of secondary cardiomyopathy include metabolism, endocrine, ischemia, infection, allergy, and poisoning [38]. Ferroptosis plays a role in cardiomyopathy, including in myocardial ischemia-reperfusion (I/R) injury (MIRI), doxorubicin (DOX)-induced cardiomyopathy (DIC), iron overload cardiomyopathy, hypertrophic cardiomyopathy (HCM), diabetic cardiomyopathy (DCM), and infective cardiomyopathy.

Myocardial Ischemia-Reperfusion Injury

I/R includes two parts: tissue ischemia and blood reperfusion. The recovery of blood flow and reoxygenation is often accompanied by reperfusion injury, leading to aggravation of tissue injury and a strong inflammatory reaction, resulting in severe cellular damage and cardiomyocyte death [39]. In the reperfusion injury model, ferroptosis aggravates inflammation-induced injury by the TLR4/Trif signaling pathway, while inhibition of ferroptosis reduces the infarction areas and provides a better condition after heart transplantation [40]. Our team has found that MI/R leads to increased transcription of cardiac non-heme iron regulators, FTH and FTL, while Fer-1 and the iron chelator dexrazoxane (DXZ) significantly reduce myocardial injury and hypertrophy caused by I/R [41]. Increased expression of TFR1 in cardiac I/R is responsible for lipid peroxidation and oxidative damage through increasing cardiac iron uptake [42, 43]. Rapamycin (an mTOR inhibitor) inhibits myocardial injury through modulating TFR1 stability and restoring cardiac iron homeostasis [44]. Further, ferroptosis is involved in the process of cardiac I/R and aggravates cardiomyocyte injury by increasing endoplasmic reticulum stress in the setting of diabetes mellitus [45].

Studies have shown that ferroptosis is involved in the development of myocardial infarction (MI) [46, 47], and there has been much focus on exploiting ferroptosis pathways to improve the pathological process of MI. Exosomes of human umbilical cord blood-derived mesenchymal stem cells exert cardioprotective effects in murine models of hypoxia-induced injury, mainly through inhibiting ferroptosis [48]. Downregulation of GPX4 during MI contributes to ferroptotic cell death in cardiomyocytes upon metabolic stress such as cysteine deprivation [47]. Disturbed GSH metabolism in cardiomyocytes is also detected in post-MI hearts [49]. Certain clinical drugs, including dexmedetomidine, Shenmai injection, and Naringenin, have been approved for attenuating cardiac I/R by targeting ferroptotic mechanisms, indicating ferroptosis may be a promising strategy for treating CVD [50–52].

DOX-Induced Cardiomyopathy

Though DOX is an anti-cancer drug used for the treatment of many cancers, it has fatal cardiotoxicity [53]. Fang et al. [41] find that ferroptosis inhibitors (Fer-1 and DXZ) significantly reduce DIC and prolong the survival time of mice compared with PCD inhibitors (e.g., apoptosis and necrosis). Low iron feeding improves heart injury and the survival rate of DOX-treated mice, which confirms major role of iron in DIC. Mechanistically, DOX increases HMOX1 in cardiomyocytes through upregulating the expression of NRF2, causing the degradation of a large amount of heme and the accumulation of excessive free iron in mitochondria and resulting in lipid peroxidation and ferroptosis of cardiomyocytes. In addition, downregulation of GPX4 in mitochondria promotes DIC and overexpression of GPX4 in cardiomyocytes can prevent such injury [54]. Meanwhile, DXZ inhibits cardiomyopathy-related ferroptosis in rats by regulating HMGB1 [55]. Acyl CoA thioesterase 1 (Acot1), which is responsible for the biosynthesis of PUFAs, is downregulated in DIC, and overexpression of Acot1 effectively rescues ferroptosis-induced myocardial injury [56]. Therefore, the mechanism of ferroptosis is of great clinical significance in preventing and reducing the pathological process of DIC, but the specific signal transduction pathway of ferroptosis and its clinical translation still need to be further studied.

Iron Overload Cardiomyopathy

Iron metabolism is particularly critical for maintaining cardiomyocyte homeostasis. Previous studies have shown that treatment with an iron-chelating agents and depletion therapy reduce the risk of cardiovascular events [35, 57]. FTH-rich ferritin, abundant in the heart, protects the organ from excessive accumulation of iron [58]. A high-iron diet aggravates myocardial injury and left ventricular hypertrophy in cardiac Fth-deficient mice, and Fer-1 rescues the

cardiac phenotypes, indicating the potential role of ferroptosis in this setting. Further, defects in the cardiac SLC7A11-GSH system are responsible for the cardiac dysfunction and adverse progression overexpression of SLC7A11 in cardiomyocytes, highlighting the key role of ferroptosis in iron overload cardiomyopathy [59]. In another model of HF, down-regulation of FTH leads to cardiomyocyte death by toxic iron-mediated oxidative stress [60]. These studies demonstrate the importance of iron overload and ferroptosis in cardiomyopathy and HF.

Hypertrophic Cardiomyopathy

HCM is the most common primary cardiomyopathy with thickened heart muscle which makes it harder for the heart to pump blood, contributing to HF and sudden death [61]. The ferroptosis suppressor gene SLC7A11 inhibits angiotensin II-induced myocardial hypertrophy [62], suggesting targeting ferroptosis could be a potential strategy for the treatment of HCM. In addition, in aortic banding- or isoproterenol-induced models of HF, the expression of cardiac NADPH oxidase 4 (NOX4) is increased and cardiac GPX4 is decreased, and knock-down of TLR4 and NOX4 protect myocardial cells from ferroptosis-mediated cardiomyocyte death [29]. Frataxin mediates the biogenesis of Fe-S clusters, and its deficiency leads to an increase in mitochondrial iron accumulation and lipid peroxidation, resulting in Friedreich's ataxia [63]. The leading cause of Friedreich's ataxia-related death is HCM, which is attenuated by the combined therapy of idebenone and oral low-dose deferiprone [64, 65]. Microarray data analysis showed that some ferroptosis genes are associated with HCM, such as ATF3, LPCAT3, and solute carrier family 1 member 5 (SLC1A5) [66].

Diabetic Cardiomyopathy

DCM is a pathophysiological condition caused by diabetes that contributes to HF where the decline of myocardial cell function is an important mediating mechanism [67]. Activation of GPX4 or NRF2/SLC7A11 axis alleviates diabetic heart damage suggesting a role of ferroptosis in DCM and providing important clues for the treatment of ferroptosis-related dilated cardiomyopathy [68, 69]. In addition, compared with normal people, patients with type 2 diabetes have lower GSH and higher iron [70, 71]. Obesity and hyperglycemia result in iron overload, mitochondrial lipid peroxidation, and myocardial hypertrophy in mice, indicating ferroptosis may be a significant cause of DCM [72, 73].

Infective Cardiomyopathy

Infection caused by various agents leads to serious complications, including myocarditis [74]. Lipopolysaccharide increases the expression of NCOA4 and the level of intracellular iron ions, and it mediates mitochondrial ROS production and ferroptosis, whereas Fer-1 and DXZ treatment improve the cardiac function and survival rate of mice challenged with lipopolysaccharide [75]. In addition, ACSL4 is involved in the formation of viral replication organelles. Inhibiting ACSL4-mediated ferroptosis reduces the viral production of enteroviruses and coronaviruses, fundamentally rescuing cardiomyopathy caused by viral infection [74].

Ferroptosis and HF

HF is not an independent disease, but the final stage of the development of heart disease. It refers to the failure of the systolic function and/or diastolic function of the heart to fully discharge the blood from the veins to the heart. Myocardial hypertrophy is the main sign of HF, which is marked by an increase in brain natriuretic peptide and myosin heavy chain 7 (Myh7) [60]. Estimates from the Institute of Health Metrics Global Burden of Disease (GBD) project suggest that HF as a consequence of ischemic heart disease, hypertensive heart disease, or cardiomyopathy/myocarditis contributes significantly to disease burden [76]. Treatment with intravenous ferric carboxymaltose in patients with chronic HF and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life [77, 78]. However, a 1-year period clinical study also showed this treatment might be associated with risk reduction of hospitalization for worsening HF [79]. Neurohormonal activation impairs mitochondrial function, which is manifested by the accumulation of ROS in myocardial cells, impaired mitochondrial membrane potential, and reduced ATP levels [80]. When H9c2 cells are treated with angiotensin II and amygdalin, oxidative stress proteins (NRF2, catalase, SOD-2, and GPX4) are markedly increased, resulting in oxidative stress effects [81]. All of these findings suggest that ferroptosis may influence the development of HF. Indeed, Fang et al. [41] showed that suppression of ferroptosis by Fer-1 and iron chelation ameliorated HF induced by iron overload and heart injury in mice [59]. Similarly, treatment with Fer-1 attenuates the development of cardiac remodeling in a transverse aortic constriction-induced HF mouse model [17]. In a rat model of chronic HF, HMOX1 activation by prolonged administration of hemin improves survival and exerts protective effects [82]. TLR4-NOX4 and circRNA may

be potential therapeutic targets for HF [83, 84]. Ferroptosis plays an emerging role in the mechanism of HF. GPX4, PTGS2, and HMOX1 are potential biomarkers of ferroptosis in HF, and targeting these ferroptosis genes represents a strong potential strategy for the treatment of HF. In fact, there are some indirect hints demonstrating the potential role of ferroptosis in HF with preserved ejection fraction which is one of the heaviest burdens of CVD on public health systems due to its high prevalence and the absence of effective therapies [18]. Thus, additional studies in the future are needed to define the key role of ferroptosis in HF with preserved ejection fraction to lay the foundation for the discovery of novel therapeutic strategies.

Ferroptosis in Vascular Injury and in AS

Vascular injury, a complex type of CVD, results from endothelial dysfunction and vascular smooth muscle cell damage. It is reported that ferroptosis is a novel mechanism for ZnONP-induced endothelial cytotoxicity and that NCOA4-mediated ferritinophagy is required for ZnONP-induced ferroptotic cell death [85]. By metabolomics analysis, it is found that sepsis induces significant ferroptosis in vascular endothelial cells, which includes increased lipid peroxidation and decreased mitochondrial cristae [86]. Inhibiting ferroptosis through activation of SLC7A11/GPX4 reduces cerebral I/R injury [87]. Metformin attenuates hyperlipidemia-associated vascular calcification through anti-ferroptotic effects [88]. β-Caryophyllene has significant neuroprotective effects in attenuating ischemic stroke injury, which is correlated with ferroptosis via the activation of the NRF2/HMXO1 axis [89]. Furthermore, baicalein and Xingnaojing injection reverse the injury of transient middle cerebral artery occlusion treatment via anti-ferroptosis, indicating ferroptosis is important in the development of cerebral I/R-induced injury [90, 91]. These findings suggest that ferroptosis casts new light on the treatment of vascular injury and CVD and has therapeutic potential.

AS is a condition that develops when there is a plaque building up in the walls of the arteries, characterized by endothelial dysfunction. The severity of AS, shown in 40 human coronary artery AS specimens, is positively associated with the expression of PTGS2 and ACSL4 and negatively associated with the expression of GPX4 [92]. MiR-17-92 protects human umbilical vein endothelial cells from erastin-induced ferroptosis by targeting the A20-ACSL4 axis [93]. Endothelial progenitor cell-secreted extracellular vesicles suppress ferroptosis of endothelial cells and alleviate the occurrence of AS via a miR-199a-3p/SP1 axis [94]. Moreover, Fer-1 alleviates AS lesion in HFD-fed $ApoE^{-/-}$ mice, including partially inhibiting iron accumulation, lipid peroxidation, and reversing the expression of the ferroptosis protectors SLC7A11 and GPX4 in aortic endothelial cells [95]. These findings indicate that ferroptosis might occur during the initiation and development of AS. Furthermore, upregulation of HMOX1 is responsible for the development of diabetic AS, suggesting that HMOX1 may serve as a potential therapeutic or drug development target for diabetic AS [96]. The overexpression of LOXs enhances ferroptosis and AS progression [24]. Activation of SIRT1 and NRF2 inhibits ferroptosis in AS, providing novel therapeutic targets (SIRT1 and PDDSS2) for AS [97, 98]. These studies show that ferroptosis plays an important role in AS.

Ferroptosis and CRS

CRS is defined as the interactions between the cardiovascular system and the kidney, in which an insult of the heart or kidney results in damage to other organs [99]. The renin-angiotensin-aldosterone system, the sympathetic nervous system, inflammation, and oxidative stress play pivotal roles in the pathogenesis of this syndrome [100]. Accumulating evidence for the emergence and importance of ferroptosis has been reported in different pathological models of kidney diseases, including acute kidney injury and chronic kidney disease. For example, *Acsl4* knockout significantly reduces ferroptosis and inhibits the functional and pathological injury of I/R-induced acute kidney injury in mice [101]. Furthermore, loss of FSP1 or the targeted manipulation of the selenoprotein Gpx4 sensitize kidneys to tubular ferroptosis, resulting in a unique morphological pattern of tubular necrosis [102]. Repression of the SLC7A11/GSH/GPX4 axis triggers ferroptosis to promote vascular calcification during chronic kidney disease [103]. Inhibition of ferroptosis may be a better choice for improving pathological remodeling and promoting regression of renal fibrosis. In addition, blocking lipid peroxidation protects mice from injury and ferroptosis in experimental nonseptic multiorgan dysfunction, suggesting that targeting ferroptosis serves as a possible treatment option for a stratifiable subset of multiorgan dysfunction syndrome [104]. It is reported that ROS increases in patients with CRS type 1 [105], and oxidant activity is elevated in the heart and kidney of renal I/R-induced CRS type 3 [106]. MitoQ, the mitochondria-targeted antioxidant, effectively reduces oxidative stress, both in the heart and the kidney [107, 108]. However, no direct evidence supports the association of ferroptotic progression and CRS,

indicating the in-depth exploration of ferroptosis in CRS may provide new insights into its pathological progression to further delineate the interaction between the kidney and the heart, which is a solid basis for future novel clinical therapeutic strategies in this field.

Ferroptosis and PAH

PAH, an abnormal blood flow state, is a rare disease with rapid progression and thus is easy to be undiagnosed. In the rat PAH model treated with monocrotaline, Fer-1 alleviates the pulmonary artery endothelial cell injury and pulmonary vascular remodeling, which opens a new door to the treatment of PAH [109]. Iron supplementation is beneficial for patients with PAH [110]. Rats fed a low-iron diet display pulmonary vascular remodeling and iron supplements ameliorate the symptoms [111]. In a recent study, it is found that 7 genes of ferroptosis (including *BCL2*, *GCLM*, *MSMO1*, *SLC7A11*, *SRXN1*, *TSPAN5*, and *TXNRD1*) expressed differently in lung samples from patients with IPAH (a type of PAH with a poor prognosis) and the controls [112]. Similarly, in the mRNA expression profiles of lung samples downloaded from a public database (from 15 patients with PAH and 11 normal controls), 8 ferroptosis-related genes (*IDH1*, *DPP4*, *HIF-1α*, *ACSL4*, *SLC7A11*, *PLIN2*, *EIF2S1*, and *TXNRD1*) are upregulated in PAH group [113]. Recently, the key hallmarks of ferroptosis, such as dysregulated iron homeostasis, glutathione metabolism, and lipid peroxidation, can be observed in decompensation of right ventricular failure induced by PAH, suggesting that effective suppression of ferroptosis may be a potential therapeutic target for ameliorating the function of right ventricular in PAH [114]. Therefore, ferroptosis plays a special role in the pathological process of PAH. However, the exact role and target need further experimental support. Addressing these questions may broaden our horizons and provide more options for the treatment of PAH.

Conclusion and Future Perspective

As one type of PCD, ferroptosis has unique mechanisms. To summarize the scientific significance and clinical implication in the field of CVD, there are still some fundamental questions to be answered. In fact, in the absence of understanding the execution mechanism of ferroptosis, lipid peroxidation of specific lipids rather than general ROS has been considered the most important step to trigger ferroptotic stress. Lipids coupled with a disorder of iron and glutamine metabolism occurs within ferroptotic cells; however, the primordial mechanisms remain to be further deciphered. Recently, ACSL4 has been shown to be more essential for ferroptosis induced by direct inhibition of GPX4 rather than by inhibition of the Xc^- system or cystine deprivation, highlighting the existence and complexity of context-dependent mechanisms of ferroptosis [115]. Meanwhile, an additional intriguing question regarding the initiation of ferroptosis induced by SLC7A11 inhibition or cystine starvation without the function of ACSL4 has been investigated in depth. Emerging work has focused on the treatment of CVD targeting ferroptosis as the main mechanism. Nevertheless, due to its complexity and heterogeneity under practical clinical conditions, the occurrence and progression of ferroptosis in CVD remain markedly unclear. For example, iron availability is a key factor in driving ferroptosis, and TF-bound iron is transported into cardiomyocytes from TFR1, which plays a crucial role in maintaining cardiac function and resisting cardiac I/R-induced injury [116]. FPN is the only channel for myocardial cells to excrete iron, which is critical to maintain iron homeostasis in cardiomyocytes [14, 117]. FPN is regulated by hepcidin, and hepcidin loss in myocardial cells leads to iron deficiency in the heart and eventually to fatal cardiomyopathy [118]. In addition, iron regulatory proteins recognize and bind to iron-responsive elements in various ferroptosis-related genes, such as *TFR1*, *DMT1*, *FPN*, *HIF-2α*, and *ALAS2*, exerting negative feedback regulation [119, 120]. Iron entering cardiac myocytes is stored in the cytoplasm by binding with ferritin to reduce ROS-induced injury [59]. Iron-saturated ferritin releases its iron through lysosomal degradation mediated by NCOA4, and free-iron overload and increased lipid peroxidation are inhibited in NCOA4-deficient hearts, which improves cardiac function through inhibiting ferritinophagy-mediated ferroptosis [17]. Notably, L-type and T-type calcium channels and SLC39A14 mediate the uptake of NTBI (non-TF-bound iron) in cardiomyocytes when iron overload occurs. Blocking these channels will be a promising strategy to protect cardiomyocytes [121]. This also highlights the complexity and uniqueness of iron cooperating with other metal ions in the development of ferroptosis in heart diseases. Indeed, iron chelation corrects SARS-CoV-2-induced cardiac arrhythmias through blocking of infection-associated ferroptosis in cardiac cells [122]. Furthermore, dissecting the role of ferroptosis-related immune disorders may represent new therapeutic targets to alleviate the burdens of CVD [123].

Given the obvious association between ferroptosis and CVD, targeting ferroptosis appears to be a promising

Table 1. Clinical drugs have been proved to treat CVD through targeting ferroptosis-related mechanisms

Disease	Drug name	Clinical status	Target	Reference
IR/MI	Dexmedetomidine	Clinical	AMPK/GSK-3β/NRF2	Wang et al., 2022 [50]
	Baicalin	Clinical	ACSL4	Fan et al., 2021 [131]
	Naringenin	Clinical	NRF2/Xc^-/GPX4	Xu et al., 2021 [52]
	Etomidate	Clinical	NRF2/HMOX1	Lv et al., 2021 [132]
	Propofol	Clinical	AKT/p53	Li et al., 2022 [133]
	Metformin	Clinical	AMPK/ERK	Zhao et al., 2022 [134]
	Shenmai injection	Clinical	NRF2/GPX4	Mei et al., 2022 [51]
	Resveratrol	Phase 1	GPX4/KAT5	Liu et al., 2022 [135]
	Salvianolic acid B	Phase 1	NRF2	Shen et al., 2022 [136]
DIC	Empagliflozin	Clinical	NLRP3 and MyD88-related pathways	Quagliariello et al., 2021 [137]
	LCZ696	Clinical	AKT/SIRT3/SOD2	Liu et al., 2022 [138]
	Melatonin	Clinical	Modulating YAP expression	Sun et al., 2022 [139]
	Salidroside	Discontinued	AMPK	Chen et al., 2022 [140]
DCM	Canagliflozin	Clinical	Xc^-/GSH/GPX4	Du et al., 2022 [141]
	Sulforaphane	Phase 3	AMPK/NRF2	Wang et al., 2022 [68]
	Curcumin	Phase 3	NRF2/GPX4/HMOX1	Wei et al., 2022 [142]
HF	Puerarin	Clinical	FTH1	Liu et al., 2018 [125]
	Imeglimin	Clinical	GPX4	Kitakata et al., 2021 [143]
	Atorvastatin	Clinical	Ferritinophagy	Ning et al., 2021 [144]
Vascular injury	Puerarin	Clinical	AMPK/PGC1α/NRF2	Hung et al., 2022 [124]
	Xingnaojing injection	Clinical	TFR/HMOX1/GPX4/FPN/DMT1	Liu et al., 2022 [91]
	Edaravone	Clinical	NRF2/FPN	Liu et al., 2022 [145]
	Metformin	Clinical	p53	Ma et al., 2021 [88]
	Dexpramipexole	Phase 3	GPX4/FSP1	Wang et al., 2022 [146]
	Baicalein	Phase 3	GPX4/ACSL4/ACSL3	Li et al., 2022 [90]
	Dihydromyricetin	Phase 2	SPHK1/mTOR/GPX4	Xie et al., 2022 [147]
	β-Caryophyllene	Phase 2	NRF2/HMOX1	Hu et al., 2022 [89]
AS	Qing-Xin-Jie-Yu Granule	Clinical	GPX4/Xc^-	Zhang et al., 2022 [148]
	Tongxinluo	Clinical	GPX4/ACSL4/FSP1	Wang et al., 2022 [149]

I/R, ischemia-reperfusion; MI, myocardial infarction; DIC, DOX-induced cardiomyopathy; DCM, diabetic cardiomyopathy; HF, heart failure; AS, atherosclerosis.

avenue for the therapy of CVD. Although specific ferroptosis inhibitors (e.g., Fer-1 and Lip-1) are still in the preclinical stage, some clinical drugs have been shown to regulate ferroptosis and exhibit preventive and therapeutic actions against CVD, such as metformin and dexmedetomidine (shown in Table 1). It has also been shown that traditional Chinese medicine with different components exerts multiple beneficial effects on the risk, progression, and severity of CVD by modulating ferroptosis-related targets. Puerarin, a clinical drug, improves neurobehavioral impairments and attenuates oxidative stress-induced brain ferroptosis after subarachnoid hemorrhage in rats, activating the AMPK/PGC1α/NRF2-signaling pathway [124]. Meanwhile, puerarin protects against HF induced by pressure overload through mitigation of ferroptosis [125]. Sulforaphane prevents ferroptosis and associated pathogenesis via AMPK-mediated NRF2 activation in DCM [68]. Notably, advances and innovations thrive in materials sciences, biochemistry, and biotechnology, such as a TF-based radiolabeled probe or an anti-TFR1 antibody, predicting the sensitivity of cell ferroptosis [126, 127]. Polydopamine nanoparticles effectively reduce Fe^{2+} deposition and lipid peroxidation in a MIRI mouse model via preventing ferroptosis, considered to be a new strategy for managing MIRI [128]. Natural melanin/alginate hydrogels achieve cardiac repair [129]. In addition, the diversity and balance of micronutrients are important to promote and maintain cardiovascular health in diverse populations [130]. Such findings provide more motivation to promote the development of ferroptosis-related medicines, aiming to further contribute to the diagnosis, surveillance, prevention, and treatment of CVD. A network connecting tissue repair with functional rebuilding

and modulation of ferroptosis in CVD is being choreographed piece by piece. However, limited information has been established regarding the precise relationship between ferroptosis and certain contexts, including HF, PAH, and CRS, which is indeed worthy of further exploration. Given the rising interest in ferroptosis, translating this process into applicable clinical treatments shows much promise.

Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding Sources

This work was supported by the National Natural Science Foundation of China (31970689 to J.M., 31930057 to F.W.) and the National Key R&D Program (2018YFA0507801 to J.M., 2018YFA0507802 to F.W.)

Author Contributions

Fudi Wang and Junxia Min conceptualized the review. Xihao Cheng, Chao Yu, and Xinquan Yang provided valuable input in the collection of data and drafting the article. All authors read, drafted, reviewed, and equally contributed to this paper. All authors read and approved the manuscript and met the criteria for authorship.

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