



Ferroptosis: A Promising Therapeutic Target for Cardiovascular Diseases

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Abstract

Cardiovascular diseases (CVDs) refer to a group of conditions that affect the heart and blood vessels and are a leading cause of death worldwide. Ferroptosis is an iron-dependent regulated cell death process that occurs due to unlimited lipid peroxidation and subsequent plasma membrane rupture. Impaired ferroptosis has been linked to the pathophysiology of various CVDs, including

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cardiomyopathies, myocardial infarction and ischemia, coronary atherosclerosis, and heart failure. Excessive iron accumulation can trigger phospholipid hydroperoxide accumulation in the cell membrane and ferroptosis, ultimately causing CVD. Conversely, iron deficiency, which often develops under conditions of malnutrition, negatively affects cardiac metabolism and function in humans. This chapter delves into the role of ferroptosis in the pathophysiology of CVD and explores therapeutic targets and compounds for preventing ferroptosis-related CVD.

13.1 Introduction

Proper function of the cardiovascular system requires a fine-tuned homeostasis of many trace elements including iron. Ferroptosis refers to highly regulated iron-dependent cell death, which is implicated in the pathophysiology of a broad range of cardiovascular diseases (CVD) such as in cardiomyopathies, myocardial infarction and ischemia, coronary atherosclerosis, and heart failure (Del Re et al. 2019; Ajoolabady et al. 2021). Iron deficiency frequently develops under malnutrition and negatively impacts cardiac metabolism and function in humans (Bi et al. 2021). Conversely, iron overload is associated with intracellular oxidative stress, contributing to cardiovascular pathologies (Bi et al. 2021; Berdoukas et al. 2015). In cardiomyocytes, excessive iron triggers ferroptosis via phospholipid hydroperoxide accumulation in the cell membrane, ultimately causing CVD (Fang et al. 2019). In this chapter, we discuss the role of ferroptosis and its underpinning mechanisms in the pathophysiology of CVD, as well as highlighting potential pre-clinical targets and therapeutic compounds for the prevention of ferroptosis in CVD.

13.2 Role and Signaling Pathways of Ferroptosis in CVD and Potential Therapeutic Targets

13.2.1 Myocardial Infarction and Heart Ischemia

Multiple pieces of evidence have identified ferroptosis in the pathogenesis of myocardial infarction (MI) and ischemia (Zhao et al. 2021). During acute and subacute stages of MI, *GPX4* downregulation leads to lipid peroxidation and induction of ferroptosis in H9c2 cardiomyocytes under conditions of hypoxia-reperfusion (H/R) (Park et al. 2019). Meanwhile, cysteine deprivation aggravates ferroptosis due in part to effects on glutathione (GSH) synthesis (Park et al. 2019). Moreover, upregulation of the long noncoding RNA (lncRNA) *Erd1y/Gm47283* in a murine model of MI blocks microRNA *Mir706*, leading to upregulation of *Ptgs2* mRNA, induction of ferroptosis, and ultimately, exacerbation of MI (Gao et al. 2022). Conversely, inhibition of *Erd1y* lncRNA and/or overexpression of *Mir706* alleviate myocardial injury in this model (Gao et al. 2022). Hence, modulation of the *Erd1y*

lncRNA-*Mir706*-PTGS2 axis may alleviate ferroptosis and cardiac injury. In most cell types, SLC11A2/DMT1 takes up non-heme iron and its upregulation in cardiomyocytes triggers ferroptosis (Song et al. 2021). In line with this, mesenchymal stem cells (MSCs) of human umbilical cord release exosomes containing *MIR23A-3p* that target/block *SLC11A2*, resulting in the inhibition of ferroptosis and alleviation of myocardial injury (Song et al. 2021). Therefore, MSCs-exosomes through activation of the *MIR23A-3p*-*SLC11A2* pathway may confer protection against ferroptosis upon MI.

A large body of evidence highlights the importance of ferroptosis in the onset and development of myocardial ischemia-reperfusion (I/R) injury. In vitro, cardiac myocyte ischemia induces ALOX15-mediated peroxidation of polyunsaturated fatty acids/PUFAs, resulting in ferroptosis induction and cell damage. These findings suggest that targeted inhibition of ALOX15 might be a promising strategy to combat ferroptosis during I/R injury (Ma et al. 2022b). In H9c2 cells exposed to H/R, *Mir190a-5p* reduces reactive oxygen species (ROS), malondialdehyde, and Fe²⁺ accumulation by sponging *Gls2* mRNA, thus antagonizing ferroptosis (Zhou et al. 2021). These findings indicate that the *Mir190a-5p*-GLS2 axis could serve as a potential target for the prevention of ferroptosis and myocardial damage. Besides, inducing *Fndc5* overexpression or administration of its cleaved form (namely irisin) attenuates ferroptosis and mitochondrial impairment through activation of the NFE2L2/NRF2-HMOX1 signaling cascade in hypoxic cardiomyocytes (Cao et al. 2022a). Therefore, inducible activation of the FNDC5-NFE2L2-HMOX1 signaling axis may represent a promising strategy to block ferroptosis under H/R settings in cardiomyocytes. Moreover, myocardial I/R injury is accompanied by generation of oxidized phosphatidylcholines (OxPCs) which elicit ferroptosis and cardiac dysfunction in rats (Stamenkovic et al. 2021). Mechanistically, OxPCs-induced ferroptosis involves a dramatic reduction of GPX4 activity in rat cardiomyocytes. Additionally, OxPCs contribute to ferroptosis by dampening calcium transients and mitochondrial bioenergetics (Stamenkovic et al. 2021). Neutralizing antibodies against OxPCs blocks ferroptosis during the perfusion stage. Both in vivo and in vitro, myocardial I/R upregulates *Elavl1* via FOXC1. ELAVL1 then binds and stabilizes *Becn1* mRNA, inciting autophagy-dependent ferroptosis and myocardial injury (Chen et al. 2021), which can be rescued by *Elavl1* knockout. These observations indicate that the FOXC1-ELAVL1-BECN1 signaling cascade plays an essential role in autophagy-mediated ferroptosis in the context of myocardial I/R injury. Furthermore, upon myocardial I/R injury, bone marrow MSCs-exosomes containing *Mir9-3hg* lncRNA reduces ferroptosis by promoting cell proliferation, GSH content, and by reducing ROS and iron overload in mice and HL-1 cardiomyocytes (Zhang et al. 2022a). From the mechanistic point of view, *Mir9-3hg* lncRNA binds and inhibits PUM2, thereby activating *Prdx6* transcription, mitigating ferroptosis (Zhang et al. 2022a). Thus, the *Mir9-3hg* lncRNA-PUM2-PRDX6 pathway renders protection against ferroptosis and myocardial I/R injury. Similar to *Mir9-3hg* lncRNA, MTOR protects against ferroptosis and iron overload by suppressing mitochondrial ROS in mice subject to myocardial I/R (Baba et al. 2018). In early reperfusion, upregulation of *ATF3* leads to regression of ferroptosis

and myocardial I/R injury (Liu et al. 2022a). The underlying mechanism appears to be linked to binding of ATF3 to the *FANCD2* promoter, leading to its transactivation and thus inhibition of ferroptosis in AC16 human cardiomyocytes (Liu et al. 2022a). Conversely, *ATF3* ablation retrieves ferroptosis and aggravates I/R injury. These findings imply that the ATF3-FANCD2 axis could serve as a potential target for prevention of ferroptosis in ischemic hearts.

KMT2B induces histone H3 methylation and upregulation of *Rfk* to activate TNF/TNF- α -CYBB/NOX2 signaling, resulting in ferroptosis and cardiac injury in a rat myocardial I/R model and H9c2 cardiomyocytes (Cao et al. 2022b). Hence, *Kmt2b* ablation significantly curbs ferroptosis and infarct size (Cao et al. 2022b). In this sense, targeted inhibition of KMT2B-RFK-TNF-CYBB/NOX2 signaling or genetic ablations of its key components might suppress ferroptosis upon myocardial I/R. Furthermore, NFE2L2 upregulates SLC40A1, thereby limiting iron overload and ferroptosis, ultimately alleviating myocardial I/R injury in diabetic rats and H9c2 cardiomyocytes (Tian et al. 2022). These observations indicate that the NFE2L2-SLC40A1 axis endows protection against ferroptosis under conditions of diabetic myocardial I/R injury. Finally, it is worth mentioning that ferroptosis genes including *CAT*, *HMOX1*, *RTN3*, *GPX4*, and *SLC25A1* are correlated with other biochemical risk factors in patients with coronary artery disease/CAD expression of oxidative stress, suggesting a cardinal role for ferroptosis in the progression of this disease (Ozuyunuk et al. 2022) (Figs. 13.1 and 13.2).

13.2.2 Cardiomyopathy

Ferroptosis is thought to be critical in the pathogenesis of cardiomyopathy (Li et al. 2022a). In the *cox10*^{-/-} mouse model of mitochondrial cardiomyopathy, the mitochondrial peptidase OMA1 induces mitochondrial fragmentation and integrated stress response/ISR via activation of OMA1-DELE1-ATF4 signaling, resulting in improved GSH metabolism and inhibition of lipid peroxidation and ferroptosis (Ahola et al. 2022). Therefore, the OMA1-DELE1-ATF4 axis plays a protective role against ferroptosis. In contrast, palmitic acid (PA) downregulates *Hsf1* and *Gpx4* in a dose- and time-dependent manner, leading to lipid peroxidation and ferroptosis in mice and H9c2 cardiomyoblasts in vitro (Wang et al. 2021). However, inducing *Hsf1* expression alleviates these effects, renormalizes iron metabolism, and upregulates *Gpx4* (Wang et al. 2021). These findings indicate an anti-ferroptotic role of HSF1 in PA-induced cardiomyopathy. In an in vitro model of doxorubicin (DOX)-induced cardiomyopathy, *Carm1/Prmt4* overexpression triggers ferroptosis and aggravates cardiomyocyte injury (Wang et al. 2022b). Mechanistically, PRMT4 methylates NFE2L2 thus dampening its nuclear translocation and reducing *Gpx4* transcription, ultimately, resulting in ferroptosis (Wang et al. 2022b). Therefore, NFE2L2 activation, administration of Fer-1, and genetic ablation or pharmacological inhibition of CARM1/*Carm1* have all been shown to alleviate ferroptosis and cardiomyopathy in vitro (Wang et al. 2022b). These data suggest that forcible

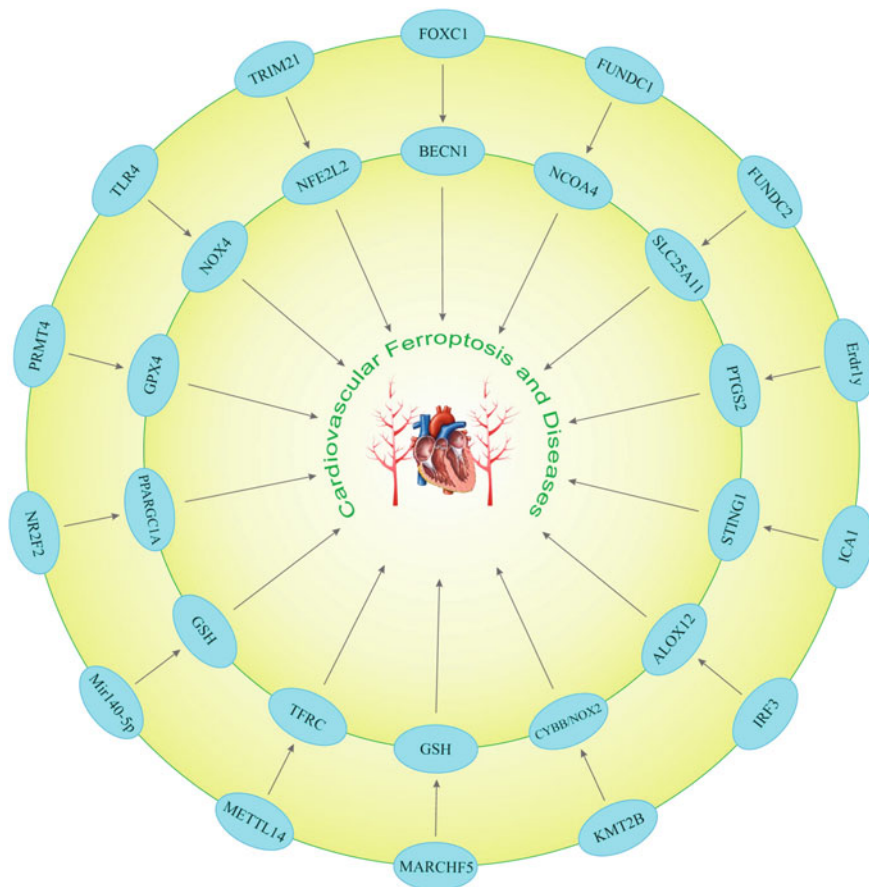


Fig. 13.1 Signaling cascades inducing ferroptosis in CVD. The underpinning mechanisms of ferroptosis in various CVDs constitute complex signaling pathways demanding immense work by scientists in the field to develop proper therapeutic strategies

inhibition of CARM1-NFE2L2-GPX4 signaling could be a potent approach for suppression of ferroptosis and alleviation of DOX-induced cardiomyopathy.

Similarly, the presence of ferroptosis in the pathophysiology of diabetic cardiomyopathy has also been reported. Also, in db/db mice and glucose-challenged cardiomyocytes, the lncRNA *Zfas1* binds and inhibits *Mir150-5p*, leading to downregulation of *Cnd2*, ferroptosis, and progression of diabetic cardiomyopathy, all of which can be alleviated by inhibition of *Zfas1* (Ni et al. 2021). Furthermore, ferroptosis contributes to obesity-associated cardiomyopathy. In obese mice, exosomes derived from adipose tissue macrophages impair mitochondria, provoking upregulation of malondialdehyde and 4-hydroxynonenal (lipid peroxides) in cardiomyocytes (Zhao et al. 2022). *Mir140-5p* in these exosomes targets and sponges *Slc7a11*, causing loss of GSH and induction of ferroptosis (Zhao et al.

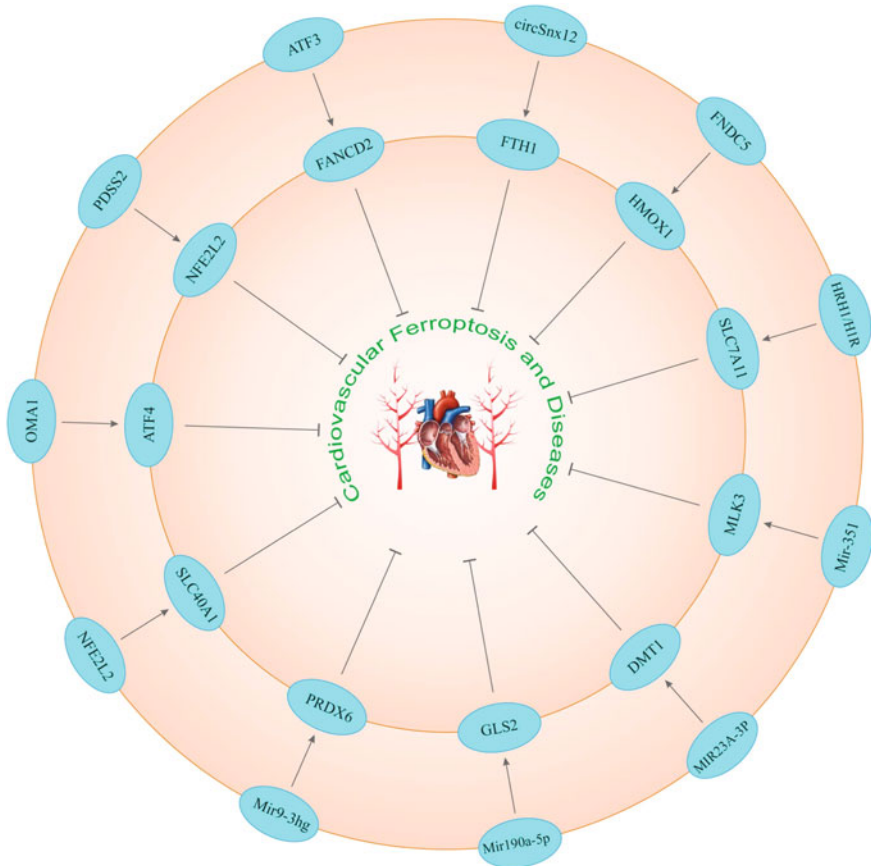


Fig. 13.2 Signaling cascades resisting ferroptosis in CVD. Despite the complexity of ferroptosis in CVD, a glimpse of hope exists due to the promising potential of anti-ferroptosis mechanisms in cardiomyocytes capable of alleviating CVD

2022). Inhibition of exosomal *Mir140-5p* can retard ferroptosis and cardiac injury in obesity-associated cardiomyopathy (Zhao et al. 2022). These findings indicate the possible role of the *Mir140-5p*-*SLC7A11*-*GSH* signaling cascade as a promising target for neutralization of ferroptosis and mitigation of obesity-induced cardiomyopathy.

Likewise, in septic cardiomyopathy, *ical* knockout overtly augments cardiac function through suppression of inflammatory cytokines, oxidative stress, and ferroptosis in lipopolysaccharide (LPS)-challenged mice (Kong et al. 2022). The underlying mechanism appears to involve *Ical* upregulation to turn on *STING1* signaling, resulting in lipid peroxidation, ferroptosis, and cardiotoxicity (Kong et al. 2022). Moreover, septic patients exhibit increased *ICA1* levels in plasma and mononuclear cells (Kong et al. 2022). Therefore, the *ICA1*-*STING1* pathway may serve as a key target for inhibition of ferroptosis and septic cardiomyopathy. In mice

with sepsis/LPS-induced cardiac injury and H9c2 cardiomyocytes, *tmem43* ablation aggravates ferroptosis and iron overload (Chen et al. 2022b). Conversely, inducing *Tmem43* overexpression blocks lipid peroxidation and ferroptosis, thereby ameliorating cardiac dysfunction and injury (Chen et al. 2022b). Mechanistically, LPS elicits ferroptosis through upregulation of *Trp53/p53* and ferritin as well as downregulation of *Slc7a11* and *Gpx4* (Chen et al. 2022b). TMEM43 overexpression reverses these effects and protects against sepsis-induced cardiac injury (Chen et al. 2022b), indicating a possible role of TMEM43 as a novel target for ferroptosis in cardiomyocytes (Figs. 13.1 and 13.2).

13.2.3 Cardiotoxicity

Proper use of anti-cancer drugs is frequently limited by their cardiotoxic side effects (Yarmohammadi et al. 2021). Substantial evidence implicates ferroptosis in drug-induced cardiotoxicity. For instance, histamine deficiency or inhibition of its receptor, HRH1/H1R, ignites ferroptosis in cardiomyocytes, to exacerbate DOX-induced cardiotoxicity in mice and cultured hiPSC-CMs and HL-1 models (Zhu et al. 2022). Mechanistically, disruption of histamine-HRH1/H1R signaling inactivates STAT3, leading to *Slc7a11* downregulation and ferroptosis, which can be rescued by histamine administration (Zhu et al. 2022). Thus, forcible activation of HRH1/H1R-STAT3-SLC7A11 signaling (e.g., using histamine) alleviates DOX-induced cardiotoxicity.

Binding of APELA peptide hormone to its receptor, APLNR, provokes pronounced activation of KLF15-GPX4 signaling and upregulation of GSH, SLC7A11, and NFE2L2, to alleviate ROS production, ferroptosis, and DOX-induced cardiotoxicity in rat aortic fibroblasts (Zhang et al. 2022b). These findings favor the idea that APELA could be a promising target for abrogation of cardiotoxic ferroptosis. The outer mitochondrial membrane-located protein FUNDC2 interacts with and destabilizes SLC25A11 in the inner membrane, resulting in the reduction of mitochondrial GSH, which fosters ferroptosis (Ta et al. 2022). Additionally, FUNDC2 is capable of modulating GPX4 stability (Ta et al. 2022). Hence, the FUNDC2-SLC25A11-GPX4 signaling pathway is a major contributor to mitochondria-initiated ferroptosis. In mice and H9c2 cells, the E3 ubiquitin ligase TRIM21 ubiquitinates SQSTM1/p62 and interferes with the SQSTM1-KEAP1-NFE2L2 signaling cascade, causing lipid peroxidation and ferroptosis (Hou et al. 2021). Genetic ablation of *Trim21* rescues DOX-induced cardiotoxicity (Hou et al. 2021). These data imply that targeted inhibition of the TRIM21-SQSTM1-KEAP1-NFE2L2 axis may rescue ferroptosis and cardiotoxicity under DOX challenge. In rat neonatal and AC16 cardiomyocytes, DOX exposure initiates *Mettl14* upregulation, which in turn, methylates and activates lncRNA *Kcnq1ot1*, leading to the inhibition of *Mir7-5p* and subsequent upregulation

of TFRC/TFR1, iron overload, lipid peroxidation, and ultimately, induction of ferroptosis (Zhuang et al. 2021). Importantly, IGF2BP1 enhances the stability of the lncRNA *Kcnq1ot1* thus inducing its activation and subsequent blockade of *Mir7-5p* (Zhuang et al. 2021). Therefore, the METTL14-*Kcnq1ot1* lncRNA-*Mir7-5p*-TFRC cascade plays an indispensable role in DOX-induced ferroptosis. Hence, targeted inhibition of METTL14-*Kcnq1ot1* lncRNA-*Mir7-5p*-TFRC may abate cardiotoxicity.

Under DOX exposure, *Marchf5* downregulation leads to upregulation of *Chac1* that overtly degrades GSH and downregulates *Gpx4*, thereby favoring lipid peroxidation and ferroptosis in rat neonatal cardiomyocytes (Kitakata et al. 2021). This finding suggests that the MARCHF5-CHAC1-GSH axis incites ferroptosis in cardiomyocytes, which may be a novel target for maneuvering ferroptosis and DOX cardiotoxicity. Triptolide is another anti-cancer medication with its clinical application limited by its cardiotoxicity (Liu et al. 2022c). Cardiotoxic effects of triptolide are partially attributed to induction of ferroptosis through accumulation of lipid peroxides (e.g., malondialdehyde and 4-hydroxynonenal), Fe^{2+} overload, GSH reduction, ferritin degradation, and ROS generation, as well as blockade of the NFE2L2-HMOX1 axis in human AC16 cardiomyocytes (Liu et al. 2022c). Importantly, activation of the TF-TRFC-SLC11A2 pathway accounts for triptolide-induced Fe^{2+} overload (Liu et al. 2022c). Furthermore, triptolide interrupts the SLC7A11-GPX4 axis through a direct binding with SLC7A11 (Liu et al. 2022c). Likewise, herceptin (trastuzumab) renders cardiotoxicity and heart failure (HF) through elevation of mitochondrial/intracellular ROS and downregulation of *Gpx* and *Slc7a11*, resulting in ferroptosis in H9c2 cardiomyocytes (Sun et al. 2022a). Administration of the iron chelator deferoxamine, or Fer-1, reverses these effects (Sun et al. 2022a). Conceivably, safe treatment of ERBB2/HER2⁺ breast cancer with herceptin could be improved by blocking ferroptosis. Imatinib mesylate-associated cardiotoxicity is linked to ROS production, iron overload, NFE2L2 downregulation, and ultimately, induction of ferroptosis in mice and H9c2 cardiomyocytes (Song et al. 2022). Conversely, findings from our group indicated that paraquat triggers cardiotoxicity and contractile dysfunction through downregulation of SLC7A11, GPX4, and ferritin, and activation of a FUNDC1-MAPK/JNK-NCOA4 axis, ultimately, leading to lipid peroxidation and ferroptosis in mice (Peng et al. 2022). Not surprisingly, *fundc1* ablation confers resistance against ferroptosis and alleviates myocardial toxicity and dysfunction (Peng et al. 2022). This study illustrates that inhibition of FUNDC1-MAPK/sJNK-NCOA4 signaling could avert ferroptosis and cardiotoxicity upon paraquat exposure (Figs. 13.1 and 13.2).

13.2.4 Cardiac Remodeling and Hypertrophy

Strong evidence support the role of ferroptosis in cardiac remodeling and hypertrophy (Wu et al. 2021). In mice, when a high-fat diet (HFD) is fed, *Fundc1* deficiency elicits ACSL4-induced ferroptosis and cardiac remodeling (Pei et al. 2021). Therefore, targeted inhibition of the FUNDC1-ACSL4 axis might reverse cardiac remodeling owing to the handicap of ferroptosis. In the early stage of angiotensin II-mediated cardiac hypertrophy, *Slc7a11* downregulation triggers ferroptosis, thereby promoting interstitial fibrosis, cardiac hypertrophy, and cardiac contractile dysfunction (Zhang et al. 2022c). Thus, suppression of ferroptosis using Fer-1 or upregulation of *Slc7a11* reverts these effects (Zhang et al. 2022c). Given the anti-ferroptotic role of SLC7A11, it could be a promising target for retardation of cardiac hypertrophy. Pressure overload leads to downregulation of *Irf3*, resulting in endothelial ferroptosis and cardiac injury in rats (Shi et al. 2022). Mechanistically, *Irf3* downregulation culminates in SLC7A11 downregulation and enhanced ALOX12 activity, leading to lipid peroxidation and ferroptosis in rat microvascular endothelial cells (Shi et al. 2022). However, docosahexaenoic acid treatment interrupts ferroptosis through upregulation of IRF3, thereby protecting against endothelial damage and cardiac hypertrophy (Shi et al. 2022). Based on these findings, the IRF3-SLC7A11-ALOX12 axis should play a cardinal role in cardiac hypertrophy and ferroptosis, and thus its targeting merits attention. Moreover, in a mouse model of angiotensin II-mediated hypertension, reduction of APELA elicits ferroptosis, myocardial fibrosis, and hypertrophy due to induction of ferroptosis in microvascular endothelial cells (Zhang et al. 2022d). APELA addition or ferroptosis inhibition using Fer-1 retards myocardial dysfunction and remodeling owing to the attenuation of iron overload and lipid peroxidation, and activation of GPX4 (Zhang et al. 2022d). These data indicate that APELA antagonizes ferroptosis upon hypertension, therefore, resulting in alleviated cardiac hypertrophy and remodeling (Figs. 13.1 and 13.2).

13.2.5 Atherosclerosis

Increasing clinical and experimental evidence has delineated a critical role of ferroptosis in atherosclerosis (Ouyang et al. 2021). During atherosclerosis, *PDSS2* overexpression prevents ROS generation and ferroptosis through activation of NFE2L2 signaling, thereby alleviating atherosclerosis in vivo and reducing ferroptosis in human coronary artery endothelial cells/HCAECs (Yang et al. 2021). Consistent with, atherosclerotic patients exhibit reduced levels of *PDSS2* and *NFE2L2* in plasma as compared to healthy controls (Yang et al. 2021). Hence, the *PDSS2*-*NFE2L2* pathway appears to play an anti-ferroptotic role and inducing its activation might alleviate atherosclerosis. Moreover, *Nod1* deficiency reduces iron level in murine spleen, liver, and heart. In line with this, splenic deficiency of *Nod1*

induces ferroptosis and CXCR2 signaling in ADGRE1/F4/80⁺ macrophages, leading to their recruitment to atherosclerotic plaques (Fernández-García et al. 2022). Tangibly, *Nod1* upregulation inhibits ferroptosis by restraining macrophage migration and raising GPX4 and anti-ferroptosis proteins in macrophages, ultimately, resulting in alleviation of atherosclerotic plaques (Fernández-García et al. 2022). These data indicate that NOD1 is a favorable target for retardation of plaque growth through inhibition of ferroptosis in macrophages/splenic cells.

In addition, endothelial progenitor cells (EPCs)-released extracellular vesicles induce attenuation of ROS, iron content, GSH consumption, and lipid peroxidation, thereby favoring ferroptosis in aortic endothelial cells and atherosclerotic mice (Li et al. 2021). Mechanistically, EPCs-exosomes contain *Mir199a-3p* that is transferred into endothelial cells and then targets/inhibits *Sp1* mRNA, leading to mitigation of ferroptosis and atherosclerosis (Li et al. 2021). Hence, inducing activation of *Mir199a-3p*-SP1 signaling via administration of EPCs-exosomes might regress atherosclerosis. Conversely, ferroptosis contributes to the development of diabetic atherosclerosis. In this regard, HMOX1 upregulation promotes ferroptosis by inducing ROS generation, Fe²⁺ overload, and lipid peroxidation, thus promoting diabetic atherosclerosis in human endothelial cells (Meng et al. 2021). Hence, inhibition of ferroptosis using ferrostatin-1 (Fer-1) or genetic ablation of *HMOX1* ameliorates diabetic atherosclerosis, indicating that HMOX1 could be a potential target for suppression of ferroptosis in diabetic atherosclerosis (Meng et al. 2021). Importantly, in hyperlipidemic *Jak2*^{V617F} mice, increased hematocrit induces ferroptosis in plaque macrophages through excessive phagocytosis of red blood cells, thereby leading to macrophage ferroptosis and aggravation of atherosclerosis (Liu et al. 2022b) (Figs. 13.1 and 13.2).

13.2.6 Heart Failure

HF entails ferroptosis in the frontline of its pathogenesis (Yang et al. 2022b). In mouse cardiomyocytes, *Fth1* deficiency induces *Slc7a11* downregulation, leading to ferroptosis and development of HF (Fang et al. 2020). However, specific overexpression of *Slc7a11* in cardiomyocytes increases GSH levels and retards ferroptosis (Fang et al. 2020). In rat HF, activation of TLR4-NOX4 signaling contributes to ferroptosis. However, ablation of *Tlr4* or *Nox4* averts ventricular remodeling and ferroptosis (Chen et al. 2019). Hence, the TLR4-NOX4 axis favors ferroptosis and thus could be a potential target for its suppression upon HF. In diabetic mice, cardiomyocyte upregulation of *Nr2f2* aggravates HF by inducing ferroptosis, mitochondrial dysfunction, and oxidative stress through activation of PPARC1A/PGC-1 α signaling (Miao et al. 2022). Unsurprisingly, in vitro ablation of *Nr2f2* blocks ferroptosis and rescues HF (Miao et al. 2022). These findings

delineate the NR2F2-PPARGC1A signaling cascade as a potential target to foil ferroptosis upon diabetic HF. Under pressure overload stress, a circular RNA, *circSnx12*, binds and sponges *Mir224-5p* thus activating *Fth1* mRNA, leading to hinderance of iron overload and ferroptosis in cardiomyocytes (Zheng et al. 2021). In this sense, induction of *Mir224-5p* upregulation and downregulation of *circSnx12* ignites ferroptosis due to intracellular overload of Fe^{2+} (Zheng et al. 2021). Therefore, augmentation of the *circSnx12-Mir224-5p-FTH1* pathway might be a potent strategy to curtail elevated ferroptosis upon HF.

Furthermore, in the early stage of chronic HF, *Map3k11/Mlk3* initiates NFKB-NLRP3 signaling, culminating in inflammation, pyroptosis, and cardiac fibrosis in mice (Wang et al. 2020). Surprisingly, in the advanced stages, MAP3K11 activates the MAPK/JNK-TRP/p53 axis, leading to oxidative stress, ferroptosis, and myocardial fibrosis. Interestingly, inducing *Mir351* upregulation blocks ferroptosis and pyroptosis by suppressing *Map3k11* expression, thereby improving cardiac function (Wang et al. 2020). In compliance with these findings, inducing activation of the *Mir351*-MAP3K11 cascade might be a potential approach for regression of ferroptosis upon HF (Figs. 13.1 and 13.2).

13.3 Concluding Remarks and Therapeutic Directions

To date, multiple lines of evidence have substantiated a vital role for ferroptosis in the pathophysiology of CVD. Ferroptosis functions either as an underscoring mechanism or as a contributing factor for the pathogenesis of CVD. Either way would involve commencement of complicated signaling pathways and gene expression modulations, altering antioxidant capacity, lipid peroxidation status, and iron metabolism in cardiomyocytes, ultimately culminating in massive ROS generation, iron overload, and the induction of ferroptosis. Owing to the complexity of ferroptosis mechanisms and gene expression patterns, the intervention of ferroptosis in various types of CVD requires targeted inhibition or activation of several signaling cascades along with robust modulation of multiple genes. Hence, despite the advances in targeted therapy of ferroptosis in pre-clinical studies using natural or pharmaceutical compounds (Table 13.1), clinical inertia still runs deeper than achieving desirable therapeutics for targeting ferroptosis in CVD. Nonetheless, future discoveries may reveal master key mechanisms encompassing the large portion of ferroptosis incidence and origination in CVD and, thereby, facilitating and simplifying pharmacological or genetic intervention of ferroptosis. Moreover, advances in drug development and targeted therapy approaches are pending to match the clinical demands. However, parallel advances in biotechnology and nanotechnology techniques might be game changers in our combat against ferroptosis in the context of CVD.

Table 13.1 Pre-clinical therapeutics for suppression of ferroptosis in CVD

Compound	Description	Mechanism of action	Ref
Atorvastatin	A type of statins medication	Inhibits oxidative stress, Fe ²⁺ overload, lipid peroxidation, and ferroptosis through upregulation of <i>Gsh</i> , <i>Slc7a11</i> , and <i>Gpx4</i> , thereby augmenting cardiac function and alleviating its remodeling in mice and H9c2 cells	Ning et al. (2021)
Berberine	A protoberberine alkaloids	Suppresses lipid peroxidation, ROS generation, and ferroptosis in murine neonatal cardiomyocytes and H9c2 cardiomyoblast cells under RSL3 and erastin treatment	Yang et al. (2022a)
Britanin	Sesquiterpene compound	Inhibits ferroptosis due to activation of AMPK-GSK3B-NFE2L2 axis and upregulation of <i>Gpx4</i> , resulting in alleviation of myocardial I/R injury and reduction of infarct size in rat and H9c2 cells	Lu et al. (2022)
Canagliflozin	Anti-diabetic C-glycosyl compound	Blocks ferroptosis by reducing iron overload and lipid peroxidation, thereby ameliorating HF with preserved ejection fraction (HFpEF) in rats	Ma et al. (2022a)
Curcumin	A natural phenolic compound	Neutralizes ferroptosis by promoting NFE2L2 nuclear transfer and upregulation of <i>GPX4</i> and <i>HMOX1</i> , leading to alleviation of glucose-induced cardiomyopathy in diabetic rabbit	Wei et al. (2022)
Dexrazoxane	Bisdioxopiperazine	Prevents ferroptosis through downregulation of HMGB1, resulting in DOX detoxification in rats and H9c2 cells	Zhang et al. (2021)
Etomidate	Anesthetic agent	Alleviates myocardial I/R injury, cardiac dysfunction, and fibrosis via upregulation of the NFE2L2-HMOX1 axis and inhibition of ferroptosis in rats	Lv et al. (2021)
Ferulic acid	Synthesized in plants	Blunts ferroptosis by plummeting ROS and malondialdehyde levels, elevation of GPX4, CAT, and SOD1, as well as activation of PRKAA2/AMPK α 2 signaling upon myocardial I/R injury	Liu et al. (2022e)
Icariin	A type of chemical flavonoid	Protects against H/R-induced ferroptosis and oxidative stress through upregulation and activation of NFE2L2-HMOX1 signaling in H9c2 cells	Liu et al. (2021)

(continued)

Table 13.1 (continued)

Compound	Description	Mechanism of action	Ref
LCZ696	A type of neprilysin inhibitors medication	Reduces ROS and lipid peroxides, increases GPX4, and ceases ferroptosis through activation of AKT1-SIRT3-SOD2 signaling, alleviation of DOX cardiotoxicity, and augmentation of ventricular function in Wistar rats and H9c2 cells	Liu et al. (2022d)
Melatonin	A natural hormone found in animals and plants	Averts DOX-induced ferroptosis and myocardial injury via downregulation of <i>Yap1</i> in SD rats and H9c2 cardiomyocytes	Sun et al. (2022b)
Puerarin	Natural isoflavone glycoside	Hinders lipid peroxidation, ROS generation, and ferroptosis, thereby alleviating HF in rats and H9c2 myocytes	Liu et al. (2018)
Resveratrol	Natural nonflavonoid polyphenol	Suppresses oxidative stress, Fe ²⁺ overload, and inhibits ferroptosis due to downregulation of <i>Tfrc</i> and upregulation of <i>Gpx4</i> and <i>Fth1</i> in myocardial I/R rats and in vitro H9c2 cells	Li et al. (2022b)
Ruscogenin	Natural anti-inflammatory steroid	Significantly mitigates myocardial ischemia and infarct size by suppressing oxidative stress and ferroptosis through upregulation of <i>Gpx4</i> , downregulation of <i>Ftl/Flc</i> and <i>Acs14</i> , and upregulation of BCAT1 and BCAT2, leading to activation of KEAP1-NFE2L2-HMOX1 signaling in mice	Fu et al. (2022a)
		Alleviates MI and infarct size, and inhibits oxidative stress and ferroptosis through downregulation of <i>Acs14</i> and upregulation of <i>Gpx4</i> , <i>Bcat1</i> and <i>Bcat2</i> , resulting in activation of the KEAP1-NFE2L2-HMOX1 axis in mice and in vitro	Fu et al. (2022b)
Salidroside	Phenylpropanoid glycoside derived from <i>Rhodiola rosea</i>	Ameliorates cardiac dysfunction and fibrosis via inhibition of ferroptosis through reduction of Fe ²⁺ and ROS levels, GPX4 upregulation, and retardation of lipid peroxidation, as well as activation of AMPK signaling in mice under DOX treatment	Chen et al. (2022a)
Salvianolic acid B	Natural anti-oxidant derived from <i>Salvia miltiorrhiza Bunge</i>	In a dose-dependent pattern mitigates iron overload, ferroptosis, lipid peroxidation, and mitochondrial injury, mainly through upregulation of NFE2L2 signaling in MI rats	Shen et al. (2022)

(continued)

Table 13.1 (continued)

Compound	Description	Mechanism of action	Ref
Tanshinone IIA	A natural compound in <i>Salvia miltiorrhiza</i> plant	Markedly reduces ROS production and lipid peroxidation, restores GSH level, and upregulates NFE2L2, thereby regressing atherosclerotic ferroptosis in human coronary artery endothelial cells	He et al. (2021)
Tongxinluo	Traditional Chinese medicine used for the treatment of atherosclerosis	Shuts off oxidative stress and ferroptosis, hence, improving microvascular barrier, leading to retardation of chronic pulmonary dysfunction and its impact on atherosclerosis development in mice and in vitro	Wang et al. (2022a)
Xanthohumol	A flavonoid derived from <i>Humulus lupulus</i>	Rescues from ferroptosis through reduction of lipid peroxidation, ROS generation, Fe ²⁺ overload, and modulation of GPX4 and NFE2L2 levels in cardiomyocytes	Lin et al. (2022)

Conflict of Interest Statement None of the authors declare any conflict of interest.

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