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REVIEW

Ferroptosis: The Pivotal Link in Cardiovascular Diseases Pathogenesis and Therapy

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Abstract: In the pathogenesis of cardiovascular diseases (CVDs), ferroptosis is increasingly implicated as a key mechanism. This iron-driven, regulated cell death is characterized by the accumulation of lipid peroxides and a deficiency in glutathione. This comprehensive review delineates the molecular underpinnings of ferroptosis—encompassing dysregulated iron metabolism, GPX4 inactivation, and lipid peroxidation—and elucidates its pivotal role in a spectrum of cardiac pathologies. Notably, ferroptosis contributes to oxidative stress, mitochondrial dysfunction, and inflammatory responses, accelerating myocardial damage and functional decline. Emerging evidence indicates that several drugs targeting the ferroptosis pathway including iron chelators, antioxidants, and small-molecule inhibitors such as ferrostatin-1 and liproxstatin-1, demonstrate cardioprotective effects in preclinical models. However, translational challenges remain, including context-dependent roles of regulators like p53 and AMPK, and the need for organelle-specific interventions. This review synthesizes current knowledge and proposes ferroptosis as a promising target for precision medicine in CVDs, urging further research into biomarkers and combination therapies to mitigate the global burden of cardiovascular morbidity and mortality.

Keywords: ferroptosis, cardiovascular diseases, reactive oxygen species, lipid peroxidation, pathogenesis, therapy

Introduction

Cardiovascular diseases (CVDs) represent the leading cause of death and disability worldwide, with an increasingly heavy disease burden that is rising particularly among younger populations, posing a significant public health challenge.[1–3] CVDs encompass a range of pathological processes, including myocardial infarction (MI), heart failure, atherosclerosis, and ischemia-reperfusion injury, with irreversible myocardial cell damage and death often serving as common endpoints.[4,5] In recent years, the role of regulated cell death in cardiovascular pathophysiology has garnered increasing attention. Beyond classical apoptosis, ferroptosis—a novel iron-dependent form of cell death formally named in 2012—has emerged as a frontier in CVD research due to its unique metabolic context and molecular characteristics.[6,7]

The core mechanism of ferroptosis involves elevated intracellular unstable iron pools, collapse of antioxidant defense systems (particularly GPX4-mediated lipid peroxide repair), and uncontrolled accumulation of lipid peroxides, ultimately leading to damage of cell membrane structures and cell death.[8–10] Research indicates ferroptosis extensively participates in the pathological processes of multiple CVDs, including myocardial cell death induced by ischemia-reperfusion, inflammation and lipid core formation within atherosclerotic plaques, myocardial remodeling in heart failure, and drug-induced cardiotoxicity from agents like doxorubicin.[11–15]

Despite significant advances in understanding the fundamental mechanisms of ferroptosis, critical gaps remain in the current knowledge framework: First, the interactive network between ferroptosis and other cell death pathways (apoptosis, necrotic apoptosis, pyroptosis) within the cardiovascular context remains unclear; Second, whether ferroptosis possesses specific regulatory mechanisms in different cardiovascular cell types—such as cardiomyocytes, endothelial cells, and macrophages—remains to be elucidated. Furthermore, although multiple ferroptosis inhibitors demonstrate cardioprotective effects in preclinical models, their feasibility, safety, and specific strategies for clinical translation require further exploration.

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This review aims to systematically integrate current research advances on the molecular mechanisms of ferroptosis and its role in cardiovascular diseases, focusing on elucidating its pathological contributions in major CVDs and evaluating the therapeutic potential of targeting ferroptosis. By synthesizing and analyzing existing evidence, we seek to provide a robust theoretical foundation and new research directions for future precision intervention strategies targeting cardiovascular ferroptosis.

Discovery of Ferroptosis

As early as 2001, research indicated that oxygen toxicity, a novel, oxidative stress-induced form of programmed cell death, may contribute to neuronal cell death in neurological trauma and disease.[16] In 2003, the compound Erastin was demonstrated to selectively kill tumor cells via an unknown mechanism, providing crucial clues for subsequent studies.[17] In 2012,Dixon and colleagues formally coined the term "ferroptosis", defining it as an iron-dependent, lipid peroxidation (LPO)-driven form of regulated cell death. Its occurrence can be specifically inhibited by iron chelators like DFO or lipophilic antioxidants like Fer-1.[7] This discovery marked a new phase in ferroptosis research, transitioning from phenomenological description to mechanistic elucidation. Morphologically, ferroptotic cells exhibit mitochondrial atrophy, outer membrane rupture, and reduced cristae architecture, observable via electron microscopy.[18] Biochemical hallmarks, as shown in Figure 1, include GSH depletion, GPX4 inactivation, and ROS accumulation resulting from polyunsaturated fatty acids (PUFAs) oxidation.

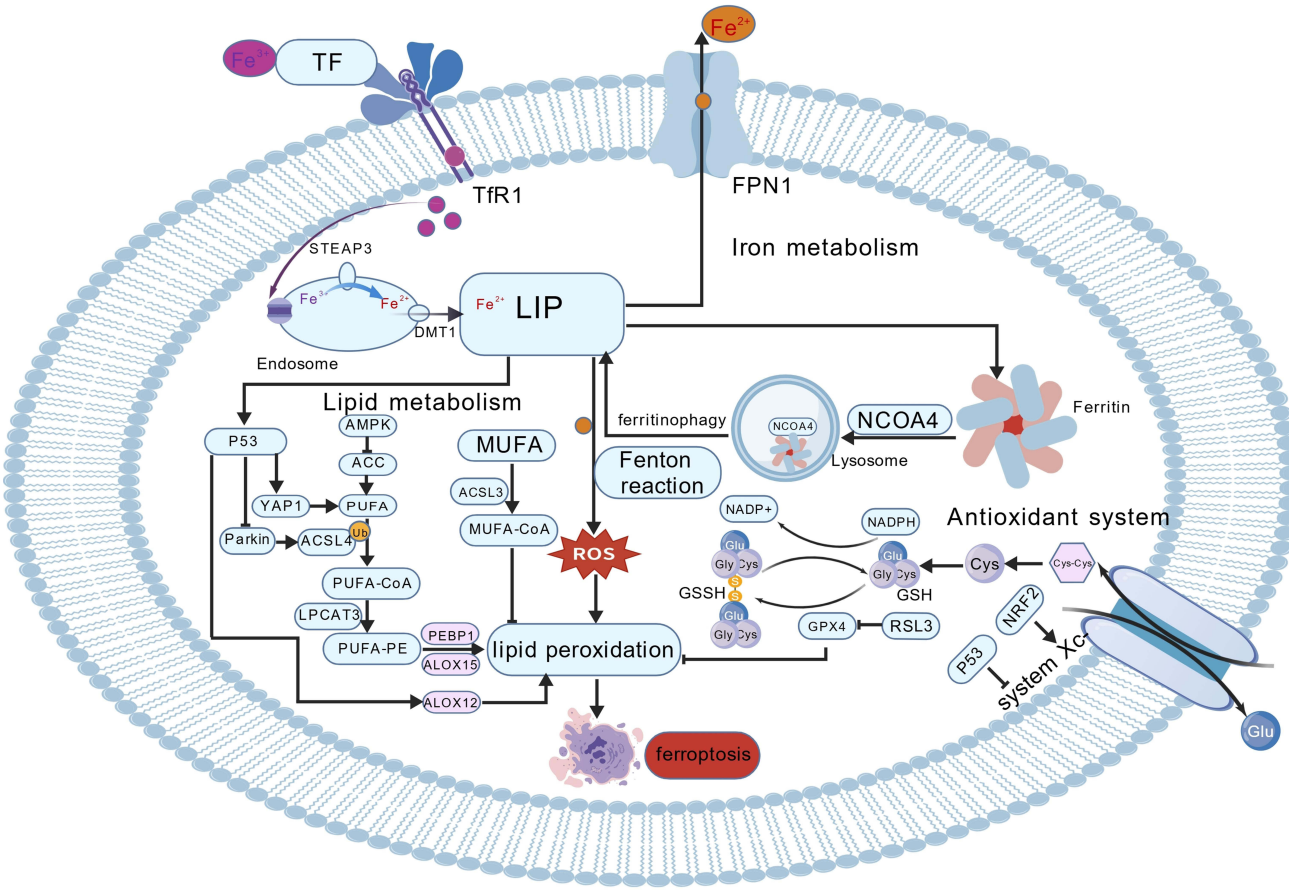

Figure 1 Core Molecular Pathways Driving Ferroptosis in CVDs. The three primary molecular pathways driving ferroptosis: Iron Metabolism; Glutathione Metabolism and GPX4 and Lipid Metabolism and Enzymatic Drivers. The pattern was created with BioGDP.com.[19]

Abbreviations: ACC, acetyl-CoA carboxylase; ACSL3, acyl-CoA synthetase long-chain family member 3; ACSL4, acyl-CoA synthetase long-chain family member 4; AMPK, AMP-activated protein kinase; DMT1, doublesex and mab-3 related transcription factor 1; FPN1, ferroportin; GPX4, glutathione peroxidase 4; GSH, glutathione; LPCAT3, lysophosphatidylcholine acyltransferase 3; LIP, labile iron pool; LOX, lipoxygenase; MUFA, monounsaturated fatty acid; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor2; PEBP1, phosphatidylethanolamine-binding protein 1; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; RSL3: SLC3A2, solute carrier family 3 member 2; SLC7A11, solute carrier family 7 member 11; STEAP3, six-transmembrane epithelial antigen of prostate 3; TF, transferrin; TFR1, transferrin receptor 1; YAP1, Yes-associated protein 1.

Molecular Drivers of Ferroptosis

Iron Metabolism

Iron homeostasis imbalance, as one of the core drivers of ferroptosis, can directly trigger cell death by promoting LPO. Under physiological conditions, iron is primarily taken up by cells in the form of Fe^{3+} bound to transferrin. During endosomal transport, Fe^{3+} is reduced to Fe^{2+} by six-transmembrane epithelial antigen of prostate 3 and is then exported into the cytoplasm by the transporter doublesex and mab-3 related transcription factor.[20,21] Free Fe^{2+} in the cytoplasm can be metabolized via two pathways: first, it binds to ferritin, consists of two subunits—ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL)—for storage; second, it is exported from the cell via the membrane transporter ferroportin (FPN1).[22] Regulation of iron homeostasis relies on iron-regulatory proteins(IRPs): under low-iron conditions, IRPs bind to the UTR regions of target mRNAs, enhancing iron uptake and inhibiting storage;[23] conversely, under high-iron conditions, IRP activity is suppressed, thereby promoting iron storage and efflux.[24]

Iron Overload and Fenton Reaction

The core pathological feature of ferroptosis lies in the abnormal accumulation of labile iron pool (LIP). Within this process, Fe^{2+} catalyzes the generation of ROS through Fenton reaction and Haber–Weiss reactions.[7,25] ROS are byproducts of aerobic metabolism, including superoxide anion ($O_2^{\bullet -}$), hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$).[26] Among these, the highly reactive hydroxyl radical (•OH) attacks polyunsaturated fatty acids abundant in cell membranes, initiating a chain reaction of LPO. LPO products like malondialdehyde(MDA) disrupt membrane structural integrity, leading to organelle dysfunction,[27] taking cardiomyocytes as an example, mitochondrial membrane LPO not only triggers abnormalities in the electron transport chain but also further exacerbates explosive ROS production, ultimately forming a vicious cycle of oxidative stress.[28]

Iron Metabolism Disorders in Cardiovascular Diseases

Hereditary hemochromatosis and thalassemia, among other iron overload disorders, are frequently accompanied by myocardial iron deposition, leading to arrhythmias, cardiomyopathy, and heart failure. The common pathway in iron overload cardiomyopathy involves free iron entering cardiomyocytes through L-type calcium channels,[29] triggering the Fenton reaction to generate free radicals, which result in LPO and cell death.[30] But differences exist between the two conditions: hereditary hemochromatosis results from primary mutations in iron metabolism genes (primarily HFE), whereas thalassemia involves secondary iron overload due to blood transfusions. Clinical studies indicate that iron chelators can improve cardiac function by reducing LIP levels and decreasing LPO.[31] Furthermore, a meta-analysis revealed a positive correlation between excessive dietary heme iron intake and cardiovascular event risk,[32] suggesting the potential value of iron metabolism interventions in cardiovascular disease prevention and management.

Glutathione Metabolism

Beyond iron metabolism abnormalities, ferroptosis can be triggered by accumulation of glutamate/iron/PUFAs phospholipids, deficiencies in cysteine or cystine, and the depletion of critical protective components such as GSH, NADPH, GPX4, and vitamin E.[33] GSH is the most important intracellular antioxidant molecule, primarily existing as reduced glutathione and oxidized glutathione (GSSG). The production of GSH is limited by the availability of cysteine, as this amino acid is the rate-limiting precursor in the synthesis process that also requires glutamate and glycine.[34] Although cells possess pathways for cysteine synthesis and recycling, most depend primarily on the system Xc^- for uptake. This system transports cysteine into the cytoplasm, where it is reduced to cystine via an NADPH-dependent reaction. The resulting cystine subsequencely used for glutathione synthesis.[35] Glutathione is a pivotal substance in amino acid metabolism during ferroptosis. As a crucial antioxidant, it protects cells from oxidative damage while also serving as a substrate for GPX4-mediated lipid repair. During ferroptosis, the core regulator GPX4 is a crucial enzyme that scavenges lipid peroxyl radicals,[36] its primary function is to detoxify LOOHs by converting them into harmless lipid alcohols (L-OH).[37]

Regulation of the System Xc^- and Sensitivity to Ferroptosis

By exchanging intracellular glutamate for extracellular cystine, the solute carrier family 7 member 11 (SLC7A11) /solute carrier family 3 member 2 (SLC3A2) heterodimer (system Xc^-) serves as a crucial gatekeeper, functioning as an upstream regulator of ferroptosis.[7] Its primary function is to supply the cell with cystine. Once imported, cystine is converted into cysteine, a critical precursor for producing the intracellular antioxidant GSH.[38] The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) upregulates the system Xc^- transporter by binding to the antioxidant response element in the SLC7A11 promoter region, thereby increasing cellular resistance to ferroptosis.[39] Ozone pretreatment activates the NRF2 transcription factor, thereby simultaneously upregulating SLC7A11 and GPX4—two key molecules in the ferroptosis pathway. This approach enhances cellular antioxidant capacity while directly strengthening lipid peroxide clearance, thereby synergistically inhibiting ferroptosis in cardiomyocytes. This mechanism was validated in both in vivo ischemia-reperfusion (I/R) models simulating clinical conditions and in vitro H9c2 cardiomyocyte (H/R) models for in-depth mechanistic studies.[40]

GPX4: The Ultimate Defense Against Lipid Peroxidation

As a cornerstone of antioxidant defense, GPX4 is the only glutathione peroxidase capable of utilizing GSH to reduce lipid peroxyl radicals within cells. This enzyme was first isolated and identified from pig liver in 1982.[37] Early studies provided preliminary evidence for GPX4's critical role in ferroptosis: neurodegeneration and non-apoptotic cell death were observed in hippocampal neurons following the selective knockout of the GPX4 gene.[41] Subsequently, the Stockwell team provided a key evidence establishing GPX4 as a central upstream regulator of ferroptosis in 2014.[36] In the presence of GSH, GPX4 continuously clears LOOHs; however, GSH depletion, GPX4 inhibition RSL3 or GPX4 gene deletion impedes LOOHs clearance, leading to its accumulation. Accumulated LOOHs undergoes decomposition catalyzed by intracellular Fe^{2+}, triggering LPO reactions that cause irreversible membrane damage and ultimately result in ferroptosis.[42] A progressive experimental model spanning cells, mice, and patients robustly demonstrates that the active site of GPX4 contains a critical selenocysteine residue; selenium supplementation significantly enhances GPX4 function and suppresses ferroptosis by boosting the activity of this residue.[43] As a key transcriptional regulator of the intracellular antioxidant response, NRF2 not only regulates SLC7A11 but also directly upregulates GPX4 expression, thereby promoting glutathione synthesis and function while mitigating ferroptosis and oxidative stress damage.[44] In a stress-overloaded hypertrophic cardiomyopathy model, NRF2 transcribes and activates key enzymes in the pentose phosphate pathway (PPP), generating abundant NADPH and nucleotides. NADPH provides reducing equivalents for glutathione reductase, sustaining the regeneration of the core antioxidant GSH. This indirectly enhances GPX4's ability to scavenge lipid peroxides, ultimately inhibiting ferroptosis in cardiomyocytes and synergistically exerting cardioprotective effects.[45] Therefore, the suppression of ferroptosis and the maintenance of intracellular redox homeostasis are dependent on the preservation of adequate GSH levels and fully functional GPX4 enzyme activity.

Imbalance of the GSH-GPX4 Axis in Myocardial Infarction

The development of CVDs involves processes such as cell death, inflammation, oxidative stress, and LPO. Studies indicate that in atherosclerosis models, overexpression of GPX4 suppresses LPO in foam cells, thereby delaying plaque progression.[46] MI is a clinically prevalent high-risk cardiovascular disease. Quantitative proteomics analysis revealed that left anterior descending artery ligation reduces GPX4 protein levels in cardiomyocytes, inducing early accumulation of lipid peroxides and ultimately triggering ferroptosis in cardiomyocytes.[47] These findings indicate that GPX4 holds potential as a therapeutic target for preventing or treating related cardiovascular diseases.

Lipid Metabolism and Enzyme-Driven Processes

Dysregulated lipid metabolism is a hallmark of ferroptosis, with the core mechanism being the peroxidation of PUFAs. By acting sequentially, the enzymes acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) drive the integration of PUFAs into cell membranes. This process effectively enriches phospholipids with PUFAs, thereby producing the metabolic precursors necessary for LPO. These subsequently trigger LPO through enzymatic or non-enzymatic pathways.[48] Notably, monounsaturated fatty acids (MUFAs) also

inhibit ferroptosis.[49] Although both PUFAs and MUFAs serve as potential substrates for peroxidation, their regulatory mechanisms in ferroptosis differ significantly: PUFAs promote oxidative damage, while MUFAs exert protective effects by competitively integrating into phospholipids. The specific mechanisms underlying this paradoxical phenomenon warrant further investigation.

Synergistic Effects of ACSL4 and LPCAT3

The primary substrate driving ferroptosis is phosphatidylethanolamine (PE), which is rich in PUFAs. Among these, arachidonic acid and adrenic acid are two key PUFAs that induce ferroptosis. During biosynthesis, ACSL4 first catalyzes the binding of PUFAs to coenzyme A, forming PUFA-CoA. Subsequently, LPCAT3 esterifies PUFA-CoA onto PE, yielding PUFA-PE. The oxidation products of these PUFA-PE molecules directly induce ferroptosis by disrupting cell membrane structure.[50] Studies demonstrate that ACSL4 knockout mice exhibit significant resistance to ischemia-reperfusion injury.[51] Furthermore, certain antidiabetic drugs, such as rosiglitazone, mitigate ferroptosis precisely by inhibiting ACSL4.[50]

Parkin, a gene first linked to Parkinson's disease, encodes an E3 ubiquitin-protein ligase that operates within the ubiquitin–proteasome degradation pathway.[52] Recent studies indicate that iron overload in MIRI-induced cardiomyopathy leads to depletion of Parkin protein. Notably, Parkin overexpression can rescue ferroptosis by ubiquitinating ACSL4. The p53-Parkin-ACSL4 signaling axis has been identified as a novel defense mechanism against ferroptosis. Specifically, p53 upregulation may mediate Parkin loss under iron overload conditions, significantly expanding our understanding of the ferroptosis regulation. Recent studies indicate that iron overload leads to Parkin protein depletion in MIRI, while Parkin overexpression rescues ferroptosis by ubiquitinating ACSL4. Furthermore, an increase in p53 expression could be the mechanism by which iron overload leads to Parkin depletion. Collectively, these findings not only define the p53-Parkin-ACSL4 pathway as a novel regulatory axis that suppresses ferroptosis but also provide fresh perspectives on the complexity of its regulatory network.[53]

The Catalytic Role of Lipoxygenase

Members of the lipoxygenase (LOX) family generate LOOHs by specifically oxidizing the double bond sites of PUFAs.[54] Studies indicate that 12-LOX participates in the p53-dependent ferroptosis pathway: when p53 is activated, it promotes 12-LOX expression, thereby increasing LPO levels and ultimately mediating ferroptosis.[55] Furthermore, during ferroptosis, 15-LOX interacts with phosphatidylethanolamine-binding protein 1, significantly enhancing LPO.[56] Notably, accumulation of 15-LOX metabolites is observed in ferroptotic cardiomyocytes. ML351, a specific inhibitor of 15-LOX, effectively suppresses ferroptosis in cardiomyocytes within an I/R model, mitigates myocardial injury, and promotes cardiac function recovery.[57]

The Protective Effects of Monounsaturated Fatty Acids

MUFAs including oleic acid, reduce the oxidative susceptibility of membrane phospholipids by competitively inhibiting ACSL4-mediated PUFAs incorporation.[49] The protective mechanism of MUFAs involves their ability to prevent the accumulation of ROS-dependent lipids on the plasma membrane and to competitively displace PUFAs from these sites. Research reveals that the enzyme ACSL3 is required for this protective effect when MUFAs are supplied externally, whereas it is dispensable for the lipotoxic effects caused by saturated fatty acids. Thus, ACSL3-mediated MUFA metabolism serves as a crucial regulatory pathway in ferroptosis,[49,58] Regarding dietary interventions, the MUFAs-rich Mediterranean diet correlates with reduced cardiovascular disease risk,[59,60] with this protective effect partially attributable to its ferroptosis-inhibitory properties.

Dysregulation of Lipid Metabolism in CVDs

Dyslipidemia plays an important role in the onset and progression of CVDs. Although high-density lipoprotein (HDL) and low-density lipoprotein (LDL) are widely used as CVDs risk markers in clinical practice, lipidomics research reveals that they represent only a small fraction of lipid-derived risk factors. Beyond the well-known pathogenic factor oxidized LDL (ox-LDL), the Bruneck study employed lipidomics techniques to identify 28 specific lipid molecules from cholesterol esters, lysophosphatidylcholine, phosphatidylcholine, PE, sphingomyelin, and triglycerides.[61] It is noteworthy

that while PUFAs may promote oxidative damage and ferroptosis in cardiomyocytes at the molecular level, epidemiological and clinical studies consistently demonstrate that moderate intake of PUFAs—particularly omega-3 PUFAs—reduces cardiovascular disease risk. Extensive research confirms a strong association between PUFA levels and the development of various CVDs, including myocardial infarction, ischemic heart failure, and cardiomyopathy.[62–64] Therefore, the effects of PUFAs on cardiovascular health are dual-sided. However, through appropriate dietary and medical interventions, their benefits can be maximized while minimizing associated risks.

The Death Regulation Network and Key Regulatory Factors in Iron Homeostasis

Energy Sensing and Metabolic Reprogramming by AMPK

Functioning as a master regulator, AMP-activated protein kinase (AMPK) is responsible for sensing the energy levels within the cell, regulating adaptive responses under energy stress. Previous study have demonstrated that energy stress activates AMPK and inhibits its downstream target acetyl-CoA carboxylase, thereby reducing fatty acid synthesis and suppressing ferroptosis.[65] Furthermore, AMPK pathway-induced FoxO3a activity plays a unique role in energy stress responses and ROS regulation. Recent studies reveal that energy stress-mediated AMPK activation suppresses ferroptosis via a FoxO3a/CYCs-dependent mechanism.[66] However, earlier research proposed conflicting findings: AMPK may directly block system Xc^- activity by phosphorylating BECN1, thereby promoting ferroptosis.[67] AMPK exhibits a dual role in ferroptosis regulation—both promoting and inhibiting it—which profoundly reflects its highly context-dependent function. This apparent contradiction stems from fundamental differences in the downstream pathways activated by distinct stressors. Under energy stress, AMPK inhibits ferroptosis by phosphorylating and suppressing acetyl-CoA carboxylase, thereby limiting polyunsaturated fatty acid biosynthesis and reducing substrates for lipid peroxidation at the source. Conversely, under direct oxidative stress, AMPK preferentially phosphorylates BECN1, promoting its binding to SLC7A11—a core component of the system Xc^-—to directly block cysteine uptake. This intensifies intracellular oxidative stress and drives lipid peroxidation, ultimately executing pro-ferroptotic pathways. Thus, AMPK's role is not fixed but determined by the nature of the initial stress signal. By precisely selecting different substrates, it mediates distinctly different—even opposing—cellular fates.

p53 Participates in the Regulation of Ferroptosis

The p53 protein is a transcription factor that regulates target gene transcription through direct, sequence-specific DNA binding. This binding occurs at DNA sites that moderately match the p53 response element consensus sequence, thereby activating or suppressing gene expression.[68] Under non-stress conditions, p53 protein levels and activity are maintained at extremely low levels by its negative regulator murine double minute 2 (MDM2). As an E3 ubiquitin ligase, MDM2 ubiquitinates p53 and directs it for proteasomal degradation. This reduction in p53 levels constitutes a protective mechanism against ferroptosis, maintaining cellular homeostasis.[69] However, when cells encounter severe or irreversible damage (such as intense reactive oxygen species stress or metabolic crisis), p53 promotes ferroptosis through multiple mechanisms: On one hand, it reduces cysteine uptake by inhibiting transcription of the SLC7A11, thereby limiting production of the primary intracellular antioxidant GSH and significantly increasing cellular sensitivity to ROS-induced ferroptosis.[70] On the other hand, p53 can also activate the expression of lipoxygenases like ALOX12/15, promoting LPO and thereby driving ferroptosis.[55,71] Furthermore, recent studies have revealed that p53 enhances cellular susceptibility to ferroptosis by regulating Yes-associated protein 1 (YAP1) to increase ACSL4 expression, which elevates the content of PUFAs in the cell membrane.[72] In summary, this decision-making shift from "promoting repair" to "promoting clearance" is precisely regulated by the nature and intensity of stress signals, as well as cell-specific post-translational modification states. This ensures that p53 can both maintain tissue integrity and effectively eliminate cells that pose potential threats.

Non-Canonical Pathways of FSP1-CoQ10

The inhibition of ferroptosis was originally thought to be solely mediated by the GSH/GPX4 pathway. This view was revised with the discovery of a parallel mechanism: ferroptosis suppressor protein 1 (FSP1), which can effectively prevent lethal LPO and ferroptosis even when GPX4 is absent.[73] FSP1 belongs to the type II NADH, whose primary

function is to reduce coenzyme Q10(CoQ10) using NADH. In resisting ferroptosis, FSP1 directly scavenges lipid radicals by terminating the lipid auto-oxidation chain reaction through the reduction of ubiquinone to ubiquinol.[74] FSP1 synergizes with CoQ10 synthesis mechanisms to counter ferroptosis via the same pathway that inhibits LPO. This indicates that the FSP1-CoQ10 pathway constitutes an independent ferroptosis suppression pathway distinct from the GPX4 antioxidant system, specifically counteracting LPO.[75]

Regulation of Ferroptosis by Mitochondria

Mitochondria, as a vital organelle in organisms, play a pivotal role in cellular death processes. Clear evidence indicates that mitochondria are deeply involved in multiple cell death pathways, including apoptosis, necrosis, and pyroptosis.[76] Whether mitochondria directly participate in ferroptosis remains under investigation, but a growing body of research suggests that mitochondrial iron metabolism, ROS and energy metabolism are closely linked to the ferroptosis process (Figure 2).

Unique Mechanisms of Mitochondrial Iron Metabolism

Mitochondria contain approximately 20–50% of the cell's total iron content. Ferritin within mitochondria serves as an essential cofactor in electron transfer during enzymatic redox reactions. Mitochondrial iron is taken up via Mitoferrin1

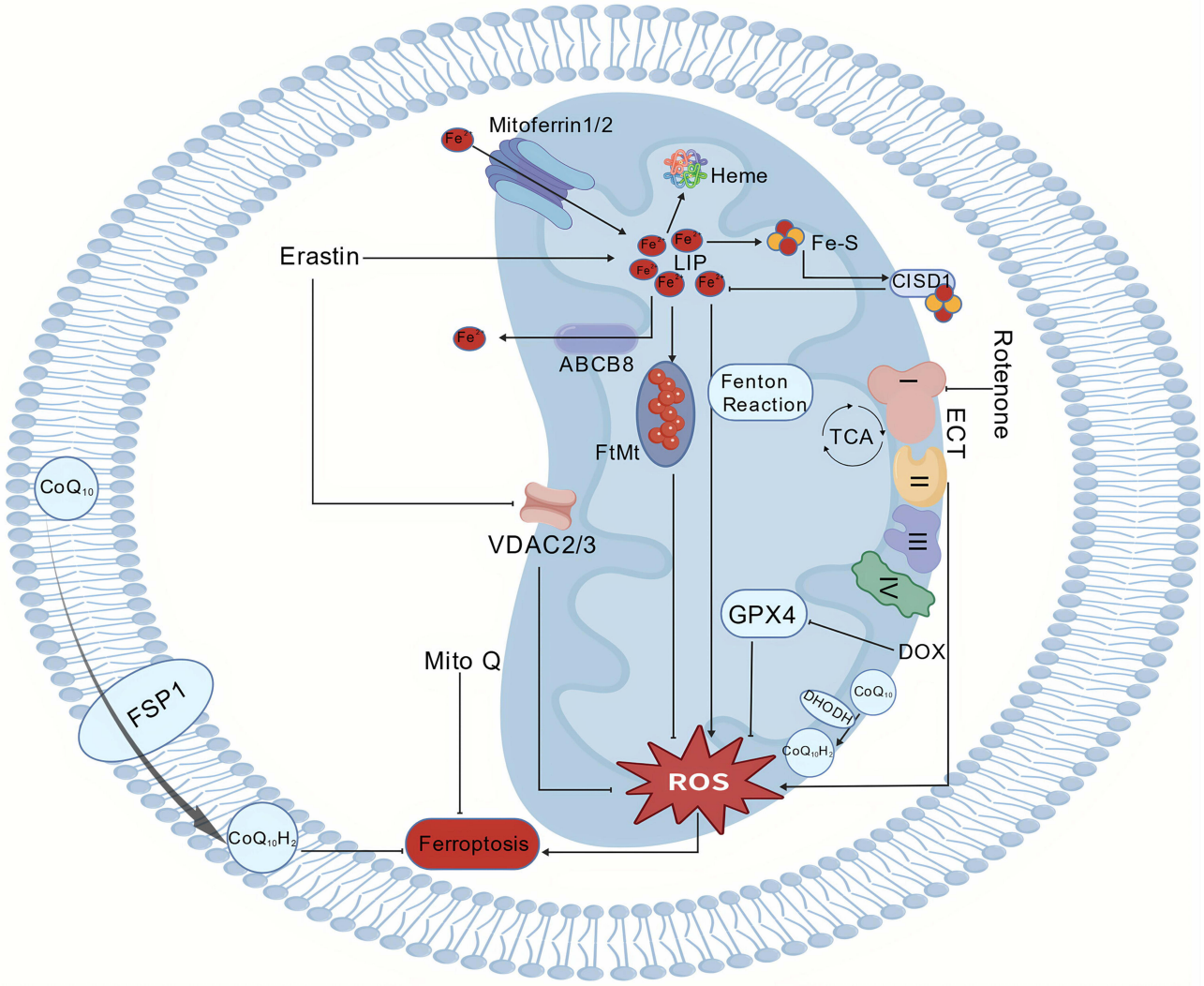

Figure 2 Role of Mitochondria in Regulating Ferroptosis in CVDs the key mechanisms by which mitochondria contribute to ferroptosis through iron metabolism, ROS production, and energy metabolism pathways. The pattern was created with BioGDP.com.[19]

Abbreviations: ABCB8, ABC protein-B8; CISD1, CDGSH iron sulfur domain 1; DHODH, dihydroorotate dehydrogenase; ETC, electron transport chain; Fe-S, iron-sulfur cluster; FtMt, mitochondrial ferritin; mGPX4, mitochondrial GPX4; MitoQ, mitoquinone mesylate; mtROS, mitochondrial reactive oxygen species; SLC25A37, solute carrier family 25 member 37 (Mitoferrin1); SLC25A28, solute carrier family 25 member 28 (Mitoferrin2); VDAC, voltage-dependent anion channel.

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(Slc25A37) and Mitoferrin2 (Slc25A28), binding to mitochondrial ferritin (FtMt). Mitoferrin1 primarily supports heme synthesis in erythrocyte precursors, while Mitoferrin2 dominates iron uptake in highly metabolically active tissues like heart.[77] Uptaken mitochondrial iron is utilized for heme and iron-sulfur cluster (Fe-S) synthesis. Defects in Fe-S clusters lead to mitochondrial iron overload. Once overloaded, mitochondrial iron can elevate mtROS levels via the Fenton reaction, activating mitochondrial nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4) and 15-lipoxygenase, resulting in phospholipid peroxidation and ferroptosis.[78,79] Overexpression of FtMt in SH-SY5Y cells improved mitochondrial iron homeostasis and suppressed Erastin-induced ferroptosis.[79] ABC protein-B8 (ABCB8), a transporter localized to the inner mitochondrial membrane, maintains mitochondrial iron homeostasis by mediating iron ion efflux.[80] Studies indicate that ABCB8 overexpression in the heart significantly reduces mitochondrial iron levels and maintains mitochondrial structural integrity, effectively mitigating DOX-induced cardiomyopathy,[81] suggesting a critical role for mitochondrial iron efflux in cardiac protection. CDGSH iron sulfur domain 1 (CISD1) is an iron-sulfur cluster-binding protein that resides on the outer membrane of mitochondria. Downregulation of this protein increases iron-mediated LPO in mitochondria. Conversely, CISD1 overexpression reduces mitochondrial iron uptake and LPO while inhibiting erastin-induced ferroptosis.[82] These findings collectively demonstrate that mitochondrial iron metabolism plays a crucial role in both lipid oxidation and ferroptosis.

Mitochondrial ROS and Energy Metabolism

ROS is closely associated with the ferroptosis process. As one of the primary sources of ROS, mitochondria play a crucial role in ferroptosis. The primary mechanism by which ferroptosis induces cell death is the generation of large amounts of lipid peroxides, ultimately leading to damage to the cell membrane. A key step in this process is the inhibition of GPX4, as illustrated by the action of the ferroptosis inducer RSL3. During RSL3-induced ferroptosis in HT22 cells and mouse embryonic fibroblasts, addition of the mitochondria-targeted antioxidant mitoquinone mesylate (MitoQ) enhances mitochondrial integrity, thereby reducing ferroptosis occurrence.[83] Another ferroptosis activator, erastin, accelerates oxidative processes and induces endogenous ROS accumulation by inhibiting voltage-dependent anion channels (VDAC2/VDAC3). When erastin or RSL3 induces ferroptosis in SK-Hep1 ρ^{+} cells, a significant increase in mitochondrial ROS levels is observed; however, adding MitoQ markedly suppresses ferroptosis.[84] Collectively, these studies indicate that elevated mitochondrial ROS promotes ferroptosis, while scavenging mitochondrial ROS effectively inhibits this process.

Furthermore, mitochondrial energy metabolism is also linked to ferroptosis. As the core of intracellular energy conversion, mitochondrial respiratory chain function involves multiple enzymes, including key enzymes in the tricarboxylic acid (TCA) cycle. These enzymes could promote LPO by modulating the production of mitochondrial ROS, thereby influencing the ferroptosis. For instance, mitochondrial electron transport chain (ETC) inhibitors like rotenone suppress ferroptosis by reducing superoxide production.[85] CoQ10, a vital electron carrier in the ETC, also functions as a lipophilic antioxidant. FSP1 can reduce CoQ10, thereby inhibiting cellular ferroptosis.[75]

The Protective Role of mGPX4 and DHODH

Mitochondrial GPX4 and mitochondrial LPO play key roles in DOX-induced ferroptosis of cardiomyocytes. Studies indicate that DOX induces excessive LPO by simultaneously downregulating GPX4 expression and forming DOX-Fe^{2+} complexes within mitochondria, ultimately leading to mitochondrial-dependent ferroptosis. This ferroptotic process is considered the primary mechanism of DOX cardiotoxicity.[86] Another study by the same team further supports the central role of mGPX4: they found that upregulating mGPX4 expression conferred ferroptosis resistance to ρ□ cells depleted of mitochondrial DNA.[84]

It is well established that antioxidant systems such as GPX4, NRF2, and FSP1 constitute the primary cellular defense mechanisms against ferroptosis,[36,44,75] Recent work by Mao and colleagues confirmed the existence of an additional ferroptosis defense pathway—mitochondrial dihydroorotate dehydrogenase (DHODH) constitutes a mitochondria-specific antioxidant system. This study demonstrated that DHODH synergizes with mGPX4 to jointly inhibit mitochondrial LPO, thereby defending against ferroptosis.[87] However, further research is needed to determine the in vivo function of

DHODH, particularly its role in cardiac protection, and to elucidate the ferritin deposition mechanisms regulating other mitochondrial enzymes.

Interactions Between Autophagy and Ferroptosis

To maintain cellular health, eukaryotes utilize an intrinsic recycling mechanism known as autophagy. This self-degradative system primarily operates through three conserved pathways: macroautophagy, microautophagy, and chaperone-mediated autophagy.[88] Macroautophagy is the one that has received the most research attention. In fact, it's so predominant in studies involving mammalian cells and diseases that it's typically just called "autophagy." This process involves the encapsulation of cytoplasmic and organellar components through subcellular membrane rearrangement, followed by their transport to lysosomes or vacuoles for degradation and recycling, Autophagy activity is precisely regulated by enzymes such as kinases, phosphatases, and guanosine triphosphatases. For it to work correctly, two core mechanisms are essential: one involves the ubiquitin-like protein conjugation system, and the other depends on protein complexes that help the dock and fuse with lysosomes or vacuoles to enable degradation.[89] As a survival mechanism, Selective autophagy comes into play by specifically eliminating damaged or dysfunctional parts of the cell under certain conditions, thereby helping cells to counteract ferroptosis. This process helps limit LPO and maintain cellular homeostasis, thereby playing a key role in ferroptosis regulation. As the final executors of autophagic degradation, lysosomes are indispensable intracellular organelles that maintain an acidic pH environment and are primarily responsible for degrading substrates delivered by the autophagy pathway.[90] Although a broad consensus from existing research points to a pro-ferroptotic role for lysosomes,[91–93] certain lysosomal components, like specific proteins or breakdown products including cysteine and selenium, have been shown to suppress ferroptosis.[94] This highlights the complex and highly context-dependent nature of the relationship between autophagy and ferroptosis.

Ferritinophagy

Ferritin is a cytoplasmic protein involved in iron storage, composed of two subunits: FTH1 and FTL. As a receptor for ferritin autophagy, Nuclear receptor coactivator 4 (NCOA4) plays a pivotal role in maintaining iron homeostasis.[95] Under iron deficiency or oxidative stress conditions, NCOA4 targets ferritin for degradation in autophagic lysosomes, releasing Fe^{2+}.[96] This released Fe^{2+} further exacerbates LPO.[97] Additionally, FTH1 deficiency disrupts cardiac iron homeostasis, significantly elevates LPO levels, thereby promoting ferroptosis and ultimately inducing myocardial injury.[98] Studies indicate that hypoxia,[99] overexpression of the E3 ubiquitin ligase family member tripartite motif-containing protein 7[100] and overexpression of HECT domain and RCC1-like domain-containing E3 ubiquitin protein ligase 2[101] reduce NCOA4 expression, thereby inhibiting ferritin autophagy-dependent ferroptosis. Cardiac cell-specific knockout of NCOA4 suppresses iron overload and LPO, mitigating stress-induced cardiac remodeling including hypertrophy, dysfunction, chamber dilation, and fibrosis; conversely, NCOA4 overexpression exacerbates cardiac injury.[78] Given that ferritin autophagy may interact with fundamental processes such as iron metabolism, redox regulations,[102] exploring these connections will contribute to comprehensively understanding their functions in health and disease.

Lipophagy

Lipid autophagy is the cellular process of clearing lipid droplets (LDs). As storage organelles for neutral lipids, LDs associate with autophagy components like LC3-labeled autophagosomes during nutrient deprivation, forming macrolipophagy.[103] Through autophagy, the contents of LDs are delivered to lysosomes for degradation, releasing fatty acids for cellular utilization. Typically, LDs reduce free fatty acid levels by storing neutral lipids, thereby inhibiting LPO, as indicated by malondialdehyde (MDA). However, during lipophagy, the degradation of LDs releases PUFAs, which paradoxically promote LPO and subsequently drive ferroptosis.[104] Thus, exploring how lipophagy and ferroptosis interplay sheds light on the sophisticated regulatory networks that connect lipid metabolism with cell death.

Clockophagy

The circadian clock, our internal time-keeping mechanism, orchestrates the timing of numerous cellular processes.[105] A central player in this rhythm is the transcription factor ARNTL (aryl hydrocarbon receptor nuclear translocator-like protein 1)/BMAL1 (brain and muscle ARNT-like 1).[106,107] Notably, the degradation of ARNTL/BMAL1 is associated

with ferroptosis. The selective autophagic degradation of ARNTL, termed "clockophagy", occurs during ferroptosis induced by class II ferroptosis inducers such as GPX4 inhibitors RSL3 and FIN56. This autophagy-mediated degradation of ARNTL promotes the expression of EGLN2 (prolyl hydroxylase EGLN family member, also known as PHD1 or HPH3). Elevated EGLN2 levels destabilize the HIF1A (hypoxia-inducible factor 1 subunit α), thereby facilitating LPO and ferroptosis. It is important to note that class I ferroptosis activators, such as erastin, do not alter basal ARNTL expression levels.[108] Collectively, these findings identify clockophagy as a molecular bridge that links specific ferroptosis triggers to the execution of cell death.

Mitophagy

Damaged or aged mitochondria are cleared from within cells through a specialized process called mitophagy. The PTEN-induced kinase 1 (PINK1)/Parkin (PRKN) pathway serves as a central regulatory mechanism for mitochondrial quality control, maintaining cellular homeostasis through the clearance of compromised mitochondria. This pathway is particularly critical in cardiac tissue, where its impairment can lead to mitochondrial DNA (mtDNA) leakage, activating the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, and subsequent inflammatory responses and cardiac hypertrophy.[109] Additionally, knockdown of dynamin-related protein 1 (Drp1) induces mitochondrial filamentation and inhibits BAY 87–2243–induced cell death, a selective HIF-1 inhibitor.[110] Furthermore, FTMT mitigates ferroptosis by suppressing reactive ROS production.[111] Although mitophagy seems to facilitate ferroptosis, the precise mechanisms by which it regulates the duration and intensity of LPO during ferroptosis remain to be fully elucidated.

Ferroptosis in Cardiovascular Disease

Clinical investigations indicate that patients with CVDs exhibit aberrant overexpression of ferritin within atherosclerotic lesions and coronary arterial tissues,[112,113] suggesting that myocardial iron overload may facilitate CVDs pathogenesis through the induction of oxidative stress, insulin resistance, and iron-mediated cytotoxicity.[114] Ferroptosis has been conclusively linked to various CVDs, including coronary atherosclerosis, MIRI, cardiomyopathies, heart failure, arrhythmias, and SARS-CoV-2-associated cardiac damage.

Atherosclerosis

Atherosclerosis (AS) constitutes the primary pathological substrate underlying coronary artery disease, characterized by chronic low-grade inflammation, lipid core formation, foam cell apoptosis, and vascular remodeling. The pathogenesis involves dysfunction or aberrant apoptosis of vascular endothelial cells (VEC), macrophages, and vascular smooth muscle cells (VSMC), which are pivotal in disease initiation and progression.[115–117] Recent investigations reveal that ferroptosis plays a significant role in AS development, evidenced by marked iron accumulation, decreased GPX4 expression, and elevated ROS.[46,118,119] Studies by Vinchi and others demonstrated that in iron-overloaded ApoE$^{-/-}$ murine models, there is pronounced iron deposition within VEC and VSMC, persistent endothelial activation, and accelerated formation of macrophage-derived foam cells, concomitant with dyslipidemia and heightened inflammatory responses, collectively promoting the formation and instability of atherosclerotic plaques.[118] Furthermore, ox-LDL induces ferroptosis in VEC, while treatment with ferroptosis inhibitors like Fer-1 significantly reduces cell death, corroborating the involvement of ferroptosis in AS pathology.[120] Recent studies indicate that the antiproliferative drug paclitaxel significantly inhibits ferroptosis in macrophages by activating the Sirt1/Nrf2/GPX4 signaling pathway. This mechanism not only reduces intracellular lipid peroxidation levels and abnormal iron accumulation but, more importantly, enhances plaque stability and delays the progression of atherosclerosis by maintaining macrophage survival and normal function. Specifically, following paclitaxel intervention, expression of the key antioxidant protein GPX4 is upregulated in macrophages, iron metabolism-related indicators normalize, lipid metabolism disorders improve, and ultimately, an anti-atherosclerotic effect is exerted at the systemic level.[121] Furthermore, is dietary iron restriction and iron chelation therapy have demonstrated substantial anti-atherosclerotic effects in animal models, further supporting the critical role of iron homeostasis imbalance and ferroptosis in AS.[118,120] Consequently, targeting ferroptosis pathways

presents a promising therapeutic strategy for AS prevention and intervention. The accumulated evidence underscores a close association between ferroptotic cell death in plaque constituents and the progression of atherosclerosis.

Myocardial Ischemia-Reperfusion Injury

As a critical form of programmed cell death in the early stages of MIRI, ferroptosis perpetuates cellular damage during reperfusion.[57] Oxidative redox reactions between PUFAs and phospholipids within cardiomyocytes during ischemia lead to pronounced oxidative injury upon reperfusion[122] Consequently, ferroptosis plays a pivotal role in MIRI pathogenesi. Studies indicate that MIRI induces non-heme iron accumulation and abnormal expression of FTH and FTL,[15,123] resulting in mitochondrial iron overload and disruption of ETC complex functions, thereby causing TCA cycle impairment and explosive ROS generation.[123] Simultaneously, oxidized phosphatidylcholines (OxPCs) produced during reperfusion directly target mitochondrial bioenergetic systems, interfering with calcium ion transport channels and ATP synthase activity, which triggers irreversible cardiomyocyte death.[124] During this process, the collapse of antioxidant defense mechanisms further amplifies injury: GPX4 activity is markedly reduced in early reperfusion, mediated by mechanisms such as miR-1224 binding to the GPX4 mRNA 3'-UTR to inhibit translation,[125] and NOX2-dependent ROS consumption of GSH impairs its reductive capacity.[126] In MIRI, miR-199a-5p enhances ferroptosis sensitivity by blocking the Akt/eNOS signaling pathway.[127] Additionally, in ischemic cardiomyopathy, the transcription factor BTB domain and CNC homolog 1 promotes LPO and ferroptosis through co-regulation of GSH metabolism and intracellular LIP.[128] Cardiac transplantation remains the definitive treatment for end-stage heart failure; however, post-transplant MIRI can lead to severe complications, including primary graft dysfunction and increased mortality risk.[129] Glutathione-S-transferases are a class of enzymes that catalyze glutathione conjugation. As one subtype, microsomal glutathione-S-transferases 1 (MGST1) can eliminate cytotoxic substances by catalyzing GSH conjugation,[130] and exerts protective effects against oxidative stress damage and even ferroptosis.[131] Recent studies indicate that MGST1 exerts cardioprotective effects in post-transplant MIRI by inhibiting mitochondrial dysfunction and ferroptosis, with its expression regulated via epigenetic mechanisms mediated by DNA methyltransferase 1.[132] Furthermore, verbascoside, a water-soluble phenylethanoid glycoside extracted from plants, exhibits anti-inflammatory, antioxidant, and cardioprotective properties. Research demonstrates that VB significantly suppresses ferroptosis induced by MIRI following cardiac transplantation through the GDF15/GPX4/SLC7A11 pathway.[133,134]

Recent advances in targeted therapeutic strategies addressing ferroptosis regulation within myocardial MIRI have been achieved. Study demonstrates that mitochondrial-specific iron chelator 2,2′-bipyridyl effectively mitigates mitochondrial free iron, thereby inhibiting Fenton chemistry and markedly improving TCA cycle function, whereas conventional iron chelator DFO, lacking mitochondrial targeting capacity, remains ineffective.[123] The small-molecule ferroptosis inhibitor liproxstatin-1 (Lip-1) confers cardioprotection in MIRI by decreasing VDAC1 expression, restoring GPX4 levels, and reducing mitochondrial ROS generation.[135] Similarly, Fer-1 attenuates ferroptosis, diminishes LPO, and interrupts TLR4/Trif/Type I interferon signaling pathways, thereby alleviating MIRI and neutrophil-mediated inflammatory responses.[136] Notably, the natural compound resveratrol exhibits multi-target protective effects: it alleviates cardiomyocyte ferroptosis via inhibition of the USP19/Beclin-1 autophagy pathway and reduces iron overload and LPO through modulation of VDAC1/GPX4 signaling.[137,138] These findings not only offer novel therapeutic avenues for MIRI but also underscore the clinical potential of targeting ferroptosis pathways.

Cardiomyopathy

Cardiomyopathies constitute a heterogeneous group of disorders characterized by genetic or non-genetic etiologies, manifesting primarily as mechanical and electrical dysfunctions of the myocardium. These conditions often present with ventricular hypertrophy, dilation, or restrictive physiological alterations.[139,140] Epidemiological studies indicate that progression to symptomatic heart failure imposes a substantial global health burden and is a leading cause of sudden cardiac death.[141] Recent evidence increasingly implicates ferroptosis as a significant pathogenic factor across various cardiomyopathy subtypes. This section systematically explores the mechanistic role of ferroptosis in the pathogenesis and progression of cardiomyopathies progression of cardiomyopathies.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the predominant form of primary cardiomyopathy.[142] Studies have shown that ferroptosis plays a key role in its pathological progression. Specifically, FTH plays a preventive role in HCM by maintaining cardiac iron homeostasis and inhibiting the SLC 7A11-dependent ferroptosis pathway.[98] Under iron overload, cardiomyocyte-specific deletion of FTH down-regulates SLC7A11 expression, leading to GSH depletion and lipid peroxide accumulation, ultimately triggering ferroptosis.[98] Genetic evidence further supports this mechanism: System Xc antagonizes angiotensin II (Ang II)-induced cardiac hypertrophy by promoting cystine uptake to maintain GSH synthesis, effectively inhibiting LPO and ferroptosis; conversely, deletion of the SLC7A11 gene activates ferroptosis, exacerbating Ang II–induced cardiac fibrosis, hypertrophy and dysfunction.[143] Meanwhile, NCOA4-mediated ferritin autophagy drives the ferroptosis process by releasing free iron, and inhibition of NCOA4 reduces myocardial damage caused by pressure overload.[78] Of particular note, interferon regulatory factor 3 (IRF3) inhibits ferroptosis by regulating transcription of SLC7A11, providing a protective advantage to the endothelial system under stress overload. Therefore, targeting IRF3 may be an effective strategy for treating cardiac hypertrophy and heart failure.[144] However, whether ferroptosis is involved in the pathogenesis of hypertrophic cardiomyopathy remains to be determined.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a form of primary myocardial disease. It is marked by the key findings of ventricular dilation and concomitant systolic dysfunction.[140] DCM is the second most common cause of cardiac arrest after coronary artery disease.[145] Despite advances in drug and interventional therapy, DCM has a 10-year mortality rate of 40%,[146] highlighting the urgent need for novel treatment strategies.

Previous direct evidence for an association between DCM and ferroptosis was limited, but recent studies have gradually revealed the role of this cell death mode in its pathogenesis. One study showed for the first time that IL-27 deficiency disrupts the iron homeostasis of cardiomyocytes, causing intracellular iron overload and LPO, thereby inducing ferroptosis and ultimately DCM; inhibition of ferroptosis can reverse this pathological process to some extent.[147] In addition, another study pointed out that after activation of Hippo signaling pathway, it promotes the formation of YAP-YY 1 complex, inhibits YAP-TEAD 1 (TEA-domain family member) complex, and then binds to Cysteine desulfurase NFS1 gene promoter region to inhibit its transcription, triggering mitochondrial iron overload and LPO, which ultimately leads to myocardial ferroptosis and promotes DCM progression.[148] These findings suggest that molecules such as IL-27 and NFS1 may serve as potential targets for DCM therapy, restoring its function or inhibiting the ferroptosis pathway, with important clinical translational prospects.

Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DbCM) is a major cause of heart failure in diabetic patients. It directly damages myocardial tissue through microvascular complications and metabolic disorders, triggering specific myocardial fibrosis and hypertrophy independently of traditional cardiovascular risk factors.[149] Recent studies indicate that ferroptosis plays a pivotal role in the pathological progression of DbCM. Advanced glycation end-products, a core pathological factor in diabetes, reduce ferritin and SLC7A11 expression in cardiomyocytes, leading to intracellular free iron accumulation and GSH depletion. Iron overload generates ROS via the Fenton reaction, while GSH deficiency weakens cellular antioxidant capacity. Together, these factors trigger significant LPO and elevated markers such as MDA, ultimately inducing ferroptosis.[150] Furthermore, the hyperglycemic environment impairs mitochondrial biogenesis, manifested by decreased mtDNA/nDNA ratios and reduced expression of respiratory chain complexes. This leads to insufficient ATP synthesis and ROS accumulation, further exacerbating ferroptosis.[151] Intervention studies validate the importance of regulating ferroptosis in DbCM: Ferroptosis inhibitors like CoQ10 and vitamin E demonstrate significant cardioprotective effects in diabetic animal models, effectively alleviating oxidative stress, diastolic dysfunction, myocardial hypertrophy, fibrosis, and cell death.[152,153] Their mechanisms involve multifaceted coordinated actions, including scavenging lipid radicals, reducing LPO, lowering cardiac ROS levels, and maintaining key signaling pathways such as Akt/SERCA2a and protein kinase C. Natural compounds like sulforaphane inhibit LPO and ferroptosis by activating the AMPK/NRF2 pathway to upregulate SLC7A11 and ferritin expression, restore GSH levels, and reduce free iron, thereby alleviating cardiac

inflammation, oxidative damage, and hypertrophy.[150] Curcumin directly suppresses ferroptosis by activating the Nrf2 pathway to mitigate high-glucose-induced GPX4 loss.[154] Notably, non-coding RNAs such as lncRNA-ZFAS1 promote ferroptosis by downregulating Cyclin D2 (CCND2), thereby accelerating DbCM progression,[155] offering novel therapeutic strategies for DbCM. In summary, ferroptosis serves as a pivotal link connecting diabetic metabolic disorders, oxidative stress, and cardiomyocyte injury/death, constituting a key mechanism in DbCM pathogenesis. Targeting its pathways demonstrates significant potential for preventing and treating DbCM.

Iron Overload Cardiomyopathy

The duality of iron—being essential yet potentially toxic—is well-documented. Although it supports vital bodily functions, excessive intake may cause problems, particularly in individuals with hereditary hemochromatosis or those who undergo frequent blood transfusions due to conditions such as sickle cell disease and beta thalassemia.[156] The heart is one of the primary target organs for iron deposition, which can further progress to iron overload cardiomyopathy (IOC).[157] IOC is not only a major cause of morbidity and mortality in both primary and secondary iron overload patients but also frequently manifests as cardiomyopathy and life-threatening arrhythmias. However, the underlying iron-related cardiac toxicity mechanisms remain incompletely understood.[158,159]

Under iron overload conditions, excess free iron can enter cardiomyocytes through L-type calcium channels and T-type calcium channels, subsequently promoting ROS generation via the Haber-Weiss reaction and Fenton reaction,[160,161] Excessive ROS delays calcium channel inactivation, leading to increased calcium influx and resulting in impaired myocardial diastolic function. As iron overload intensifies, competitive inhibition between iron and calcium ions within calcium channels paradoxically reduces calcium influx, ultimately causing contractile dysfunction.[158] Concurrently, excessive ROS depolarizes the mitochondrial membrane potential ($\Delta\Psi m$), causing mitochondrial dysfunction. The mitochondrial calcium uniporter (MCU) plays a pivotal role in this process. Thus, inhibiting MCU activity may serve as an effective strategy to prevent iron overload-induced cardiac mitochondrial damage in thalassemia patients.[162] Furthermore, iron chelators such as DFO, deferiprone, and deferasirox (DFX)—particularly when combined with N-acetyl cysteine—significantly alleviate iron overload-induced myocardial structural and functional impairment by reducing cardiac iron burden, suppressing oxidative stress, and improving mitochondrial function, offering new directions for clinical treatment.[163,164] Nevertheless, numerous critical questions remain to be explored in depth, including the regulatory network of mitochondrial iron metabolism, the specific mechanisms of MCU in ferroptosis, and the subcellular localization of LPO reactions.

Doxorubicin-Induced Cardiomyopathy

Anthracycline drugs like DOX are widely used in cancer treatment, but their severe cardiotoxicity limits clinical application. DOX induces myocardial ferroptosis through multiple mechanisms, leading to cardiomyocyte death. A 2014 study indicated that DOX downregulates the mitochondrial iron efflux protein ABCB8, causing mitochondrial iron accumulation. This triggers elevated ROS, LPO, and cell death—a process highly consistent with ferroptosis mechanisms. The use of iron chelators such as dexrazoxane significantly mitigates DOX-induced cardiac injury.[81] Recent studies further revealed that the mitochondrial outer membrane protein FUN14 domain-containing 2 promotes ferroptosis by regulating mitochondrial glutathione levels, playing a crucial role in doxorubicin-induced cardiomyopathy (DIC).[165] Furthermore, studies have for the first time definitively established mitochondrial-dependent ferroptosis as the core mechanism of DOX cardiotoxicity, emphasizing that GPX4 downregulation and DOX-Fe^{2+} complex-mediated LPO as critical steps, providing a theoretical basis for developing cardioprotective strategies such as chelators targeting mitochondrial Fe^{2+} or GPX4 agonists. This suggests that targeting mitochondrial iron metabolism and antioxidant defense systems may be effective strategies for preventing and treating DIC.[86] On one hand, protein arginine methyltransferase 4 inhibits Nrf2 nuclear translocation and transcriptional activity, thereby downregulating GPX4 expression, promoting ferroptosis and exacerbating DIC.[166] On the other hand, Sorting nexin 3 promotes the recycling of transferrin receptor 1 (TFRC) to the cell membrane by directly binding to it, thereby increasing iron uptake, leading to ferroptosis and ultimately exacerbating DIC.[167] In contrast, Protosappanin A (PrA) directly binds ACSL4 and FTH1, dual-inhibiting LPO and iron release to suppress ferroptosis, thereby protecting against DIC and MIRI. As a novel dual-target ferroptosis

inhibitor, PrA demonstrates potential clinical translational value.[168] Collectively, these studies indicate that DIC is closely associated with mitochondrial iron overload and subsequent ferroptosis. Targeting ferroptosis pathways may represent a novel strategy for preventing and treating DIC.

Sepsis-Induced Cardiomyopathy

Among the various complications that can worsen a patient's outcome during sepsis, one of the most notable is sepsis-induced cardiomyopathy (SIC). This form of cardiac impairment is strongly linked to increased morbidity and is a major factor behind the high mortality rates associated with the condition. Although the condition exhibits some reversibility, the death of terminally differentiated cardiomyocytes remains a key pathological feature in its cardiac injury process.[169] In vivo studies demonstrate that sepsis degrades ferritin via NCOA4-mediated ferritinophagy. The released free iron is transported to mitochondria via sideroflexin1, triggering mitochondrial iron overload and LPO. This ultimately activates ferroptosis, leading to myocardial injury.[170] Inhibiting ferroptosis or targeting its upstream pathways significantly improves cardiac function and survival rates in septic mice.[170] Furthermore, agents such as melanin nanoparticles and ceria nanozyme coordination with curcumin, leveraging their dual functions of iron chelation and ROS scavenging, effectively inhibit lipopolysaccharide (LPS)-induced ferroptosis in cardiomyocytes, thereby improving cardiac function and survival rates in septic mice.[171,172] In contrast, transmembrane protein 43 (TMEM43) exhibits downregulated expression in septic myocardial tissue. In vitro studies demonstrate that TMEM43 overexpression suppresses LPS-induced LPO and cardiomyocyte injury, while its knockout exacerbates LPS-induced ferroptosis, leading to worsened cardiac dysfunction, inflammatory response, and cardiomyocyte death.[173] The above in vivo studies collectively indicate that ferroptosis is a key driver of LPS-induced SIC, making targeting ferroptosis a potential therapeutic strategy for septic myocardial injury.

Viral Myocarditis

Viral myocarditis (VMC) represents a significant cause of acquired heart disease in the pediatric and adolescent population, with Coxsackievirus B3 (CVB3) being the primary pathogen responsible for VMC. In CVB3-induced myocarditis, the virus activates the classical complement pathway by promoting direct binding between TFRC and complement C4, thereby inducing ferroptosis in cardiomyocytes and exacerbating myocardial inflammatory responses. Treatment with the ferroptosis inhibitor Fer-1 or modulation of complement activity effectively mitigates VMC-associated myocardial injury.[174] In addition, enteroviruses such as CVB3 and certain coronaviruses promote viral replication and release through ACSL4-mediated ferroptosis, thereby inducing or exacerbating myocarditis. Inhibiting ACSL4 or the ferroptosis pathway significantly reduces viral load, offering novel therapeutic targets and drug repurposing opportunities for treating such viral myocarditis.[175] A recent study demonstrated for the first time that exosomes derived from human umbilical cord mesenchymal stem cells, through their let-7a-5p effectively suppress CVB3-induced ferroptosis in cardiomyocytes by regulating the SMAD2/ZFP36 signaling pathway.[176] These studies provide novel strategies and theoretical foundations for the prevention and treatment of viral myocarditis.

Heart Failure

Heart failure primarily manifests as cardiac remodeling, cardiomyocyte hypertrophy, and reduced ventricular compliance. These alterations collectively mark it as the end-stage of numerous cardiovascular disease pathways. Heart failure represents the terminal stage of various cardiovascular diseases, primarily characterized by cardiac remodeling, cardiomyocyte hypertrophy, and reduced ventricular compliance.[177] Multiple studies indicate that disrupted iron homeostasis within cardiomyocytes can induce ferroptosis by promoting LPO and ROS accumulation, thereby exacerbating cardiac dysfunction. SLC7A11 and GPX4 play core roles in suppressing ferroptosis. Their functional loss or downregulation in heart failure diminishes antioxidant capacity, leading to lipid peroxide accumulation and subsequently promoting cardiomyocyte ferroptosis and cardiac dysfunction.[98,143]

In vivo and in vitro models of cardiac hypertrophy, pyrroloquinoline quinone exhibits anti-ferroptotic effects by triggering YAP expression, thereby upregulating GSH and GPX4.[178] Similarly, Levosimendan enhances GPX4 levels, promotes GSH production, reduces oxidative stress, and exerts therapeutic effects on heart failure with preserved ejection

fraction (HFpEF) by regulating connexin 43.[179] Nuciferine (NF) exhibits antioxidant, anti-inflammatory, and lipid metabolism-regulating effects. In vivo and in vitro cardiac remodeling models induced by stress overload, NF alleviates oxidative stress, mitochondrial damage, and iron metabolism disorders via the SENP1-ACSL4 axis, thereby improving cardiac function and reducing myocardial hypertrophy and fibrosis.[180] Furthermore, ACSL4 enhances cellular susceptibility to ferroptosis by promoting PUFAs incorporation into membrane phospholipids, thereby increasing LPO substrate availability, and its expression is upregulated in cardiac hypertrophy.[181,182] Cagrelin suppresses ferroptosis by reducing ACSL4 expression, demonstrating a mitigating effect on ferroptosis-induced HFpEF.[183] Research is increasingly building a case for ferroptosis as a promising therapeutic target. Inhibiting this process could lead to new strategies for treating cardiac remodeling and heart failure.

Cardiac Arrhythmia

Emerging evidence implicates ferroptosis in the initiation and progression of arrhythmias, particularly atrial fibrillation (AF). Iron overload not only disrupts cardiac electrophysiological properties by interfering with calcium, sodium, and potassium channel function,[184] but also induces mitochondrial dysfunction through mechanisms such as excessive ROS production, mitochondrial calcium overload, and impaired energy metabolism, and then promotes electrophysiological remodeling of cardiomyocytes and the onset of arrhythmias.[185] Among GST subtypes, GSTP1 serves as a key factor in the ferroptosis pathway, exhibiting antioxidant and cytoprotective functions.[186,187] In an AngII-induced AF model, Fer-1 intervened in AF development while GSTP1 expression was significantly reduced in atrial tissue and cells. Further studies revealed that GSTP1 overexpression suppressed AngII-induced atrial electrical remodeling, oxidative stress, and ferroptosis, thereby reducing AF susceptibility. This study first revealed that GSTP1 exerts a protective role in AngII-induced AF by inhibiting ferroptosis, providing a new theoretical basis and potential target for AF prevention and treatment.[188] Additionally, animal experiments indicate that electrocardiographic abnormalities such as PR-interval and QRS-prolongation can be observed in iron-overloaded gerbils.[189] Chronic iron overload can also trigger various arrhythmias, the manifestations can range from premature ventricular contractions to more sustained issues like supraventricular tachycardia and recurrent ventricular tachycardia. Iron chelators such as DFX effectively alleviate arrhythmias and improve cardiac structural and functional abnormalities caused by iron overload.[190] Therefore, targeting the ferroptosis pathway may offer novel therapeutic strategies for arrhythmia prevention and treatment, though the specific mechanisms require further investigation.

COVID-19 Associated Arrhythmias

Investigations indicate that Coronavirus disease 2019 (COVID-19) may trigger multiple cardiovascular complications.[191,192] Arrhythmias represent one of the most common cardiac manifestations of COVID-19: In addition to tachyarrhythmias such as AF and polymorphic ventricular tachycardia, patients in the acute phase may also develop bradyarrhythmias like atrioventricular block.[193,194] A 2022 study systematically demonstrated for the first time that DFO can directly infect sinus node-like pacemaker cells differentiated from embryonic stem cells, inducing ferroptosis characterized by downregulated GPX4 expression and ROS accumulation and lead to pacemaker dysfunction. This potentially explains persistent bradycardia and other arrhythmias observed in COVID-19 survivors.[195] The iron chelator DFO effectively inhibits SARS-CoV-2 infection and its induced ferroptosis, demonstrating potential therapeutic value.[196]

Discussion

Ferroptosis, as a key mechanism regulating programmed cell death, plays a pivotal role in the pathogenesis of various cardiovascular diseases. This review summarizes the complex molecular mechanisms driving ferroptosis—iron metabolism dysregulation, the GSH-GPX4 axis, and peroxyl lipid metabolism—which collectively induce ferroptosis. It also elucidates the mitochondrial specificity of ferroptosis and its regulatory interactions with selective autophagy. The accumulation of lipid peroxides driven by redox imbalance and iron overload positions ferroptosis as a central driver of myocardial injury, vascular dysfunction, and adverse remodeling. Compelling preclinical evidence—particularly the consistent cardioprotective effects of ferroptosis inhibitors like ferroptosis inhibitor-1 and lipid peroxidation inhibitor-1 across diverse disease models—highlights the therapeutic potential of targeting this pathway.

The translational prospects are indeed encouraging, heralding a new paradigm beyond conventional cardioprotective strategies. Future research should prioritize developing precise, context-aware interventions, including designing organelle-specific drugs such as mitochondrial-targeted iron chelators and pharmacologically activating endogenous defense systems like the NRF2-GPX4 and FSP1-CoQ10 axes. Furthermore, elucidating cross-regulatory mechanisms between ferroptosis and other cell death forms is crucial for understanding cellular fate decisions in disease states and designing rational combination therapies. However, the path from mechanistic understanding to clinical application is fraught with significant challenges that demand rigorous attention. The primary translational bottleneck lies in the lack of sensitive, specific, and clinically viable biomarkers for ferroptosis detection. Current reliance on markers like MDA or tissue GPX4 activity fails to distinguish ferroptosis from general oxidative stress in human biofluids and lacks spatial information within the cardiovascular system. Developing validated biomarkers—potentially through advanced lipidomics or imaging techniques reflecting specific phospholipid peroxidation signatures—is critical for patient stratification in clinical trials, target combination evaluation, and treatment monitoring. Second, safety concerns stemming from off-target effects and pathway specificity pose significant barriers. The complex interactions between ferroptosis and other biological processes mean therapeutic inhibition may yield unintended consequences. For instance, systemic iron chelation therapy, while reducing the catalytic iron required for ferroptosis, may induce or exacerbate anemia—particularly in heart failure patients where functional iron deficiency is common. Similarly, broad-spectrum antioxidant strategies may disrupt critical redox-dependent signaling pathways. Furthermore, the duality and context-dependence of key regulators like p53 and AMPK complicate targeted therapies—their modulation may yield opposite effects across different cell types or disease stages. Third, the long-term safety of sustained ferroptosis regulation remains a major unknown. Cardiovascular diseases are predominantly chronic conditions requiring continuous treatment. The potential consequences of lifelong suppression of this conserved cell death pathway remain unclear. Theoretical risks include: impaired tumor surveillance (given ferroptosis's tumor-suppressing role), hindered clearance of damaged or infected cells, and disruption of normal tissue homeostasis and repair mechanisms. Comprehensive long-term toxicology studies in relevant preclinical models, coupled with rigorous post-marketing surveillance, are imperative. Finally, these scientific challenges directly impact clinical trial design. Identifying suitable patient populations, optimizing dosing regimens and treatment durations, selecting rational combinations with standard therapies, and defining clinically meaningful endpoints all represent complex challenges requiring deepened translational insights.

Conclusion

In summary, while ferroptosis presents an attractive novel therapeutic target for cardiovascular disease, overcoming these multidimensional challenges requires multidisciplinary collaboration for successful clinical translation. Future research must bridge the gap between mechanism discovery and clinical needs by developing reliable biomarkers, designing safer targeted therapies, and conducting rigorous clinical trials. Additionally, exploring interactions between ferroptosis and other forms of cell death to develop organelle-specific intervention strategies is essential. Only by resolving these translational challenges can anti-ferroptosis therapies fully realize their potential to effectively reduce the global burden of cardiovascular disease morbidity and mortality.

Abbreviation

CVDs, Cardiovascular diseases; MI, Myocardial infarction; I/R, Ischemia-reperfusion; RCD, Regulated cell death; GSH, Glutathione; ROS, Reactive oxygen species; LOOHs, Lipid hydroperoxides; GPX4, Glutathione peroxidase 4; DOX, Doxorubicin; DFO, Deferoxamine; Fer-1, Ferrostatin-1; LPO, Lipid peroxidation; PUFAs, Polyunsaturated fatty acids; TF, Transferrin; DMT1, Doublesex and mab-3 related transcription factor 1; STEAP3, Six-transmembrane epithelial antigen of prostate 3; FTH1, Ferritin heavy chain 1; FTL, Ferritin light chain; FPN1, Ferroportin; IRPs, Iron-regulatory proteins; LIP, Labile iron pool; MDA, Malondialdehyde; GSSG, Oxidized glutathione; L-OH, Lipid alcohols; SLC7A11, Solute carrier family 7 member 11; SLC3A2, Solute carrier family 3 member 2; NRF2, Nuclear factor erythroid 2-related factor 2; MIRI, Myocardial ischemia-reperfusion injury; ACSL4, Acyl-CoA synthetase long-chain family member 4; LPCAT3, Lysophosphatidylcholine acyltransferase 3; MUFAs, Monounsaturated fatty acids; PE, Phosphatidylethanolamine; LOX, Lipoxygenase; PEBP1, Phosphatidylethanolamine-binding protein 1; HDL, High-density lipoprotein; LDL, Low-density

lipoprotein; ox-LDL, Oxidized LDL; AMPK, AMP-activated protein kinase; YAP1, Yes-associated protein 1; FSP1, Ferroptosis suppressor protein 1; CoQ10, Coenzyme Q10; FtMt, Mitochondrial ferritin; NOX4, Nicotinamide adenine dinucleotide phosphate oxidase 4; ABCB8, ABC protein-B8; CISD1, CDGSH iron sulfur domain 1; MitoQ, Mitoquinone mesylate; VDAC, Voltage-dependent anion channels; TCA, Tricarboxylic acid; ETC, Electron transport chain; DHOD, Dihydroorotate dehydrogenase; NCOA4, Nuclear receptor coactivator 4; LDs, Lipid droplets; ARNTL, Aryl hydrocarbon receptor nuclear translocator-like protein 1; BMAL1, Brain and muscle ARNT-like 1; mtDNA, Mitochondrial DNA; cGAS-STING, Cyclic GMP-AMP synthase-stimulator of interferon genes; AS, Atherosclerosis; VEC, Vascular endothelial cells; VSMC, Vascular smooth muscle cells; OxPCs, Oxidized phosphatidylcholines; MGST1, Microsomal glutathione-S-transferases 1; Lip-1, Liproxstatin-1; HCM, Hypertrophic cardiomyopathy; Ang II, angiotensin II; IRF3, Interferon regulatory factor 3; DCM, Dilated cardiomyopathy; DbCM, Diabetic cardiomyopathy; CCND2, Cyclin D2; IOC, Iron overload cardiomyopathy; MCU, mitochondrial calcium uniporter; DFX, Deferasirox; DIC, Doxorubicin-induced cardiomyopathy; TFRC, Transferrin receptor 1; PrA, Protosappanin A; SIC, Sepsis-induced cardiomyopathy; LPS, Lipopolysaccharide; TMEM43, Transmembrane protein 43; VMC, Viral myocarditis; CVB3, Coxsackievirus B3; HFpEF, Heart failure with preserved ejection fraction; NF, Nuciferine; AF, Atrial fibrillation; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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Author Contributions

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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