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Ferroptosis in Cardiovascular Disease: Mechanisms and Pharmacological Targets

Devunuri Sravani, Polepaka Keerthi, Verpula Nikhitha, M. Rakesh, Syeda Nishat Fathima

Department of Pharmacology, Jayamukhi College of Pharmacy, Narsampet, Warangal-506332, Telangana, India

Email: edupharma.hub@gmail.com

ABSTRACT

Loss of cardiomyocytes, endothelial cells, and vascular smooth muscle cells underlies myocardial infarction, heart failure, cardiomyopathies, and vascular disease. For decades, apoptosis and necrosis dominated explanations for this loss, but the recognition of ferroptosis, an iron-dependent form of regulated cell death driven by uncontrolled peroxidation of membrane phospholipids, has opened a new mechanistic and therapeutic perspective. The heart is especially exposed to this process because cardiomyocytes are rich in mitochondria, depend on a continuous supply of iron for oxidative metabolism, and operate under high oxidative load. This review summarizes the molecular machinery of ferroptosis, including iron handling, polyunsaturated phospholipid metabolism, and the glutathione peroxidase 4 (GPX4), ferroptosis suppressor protein 1 (FSP1), and related defense systems. It then examines evidence for ferroptosis in ischemia–reperfusion injury, heart failure, anthracycline cardiotoxicity, diabetic and septic cardiac injury, iron-overload cardiomyopathy, and atherosclerosis. Finally, it evaluates pharmacological strategies, including radical-trapping antioxidants, iron chelators, inhibitors of lipid-remodeling enzymes, and activators of endogenous defenses, with attention to pharmacokinetic limitations, biomarker needs, and safety concerns such as cardiac iron deficiency and tumor-protective effects in cardio-oncology. Ferroptosis is a promising but still incompletely validated target, and rigorous translational work will be required to move inhibitors from experimental models to patients.

Keywords: ferroptosis; lipid peroxidation; iron metabolism; GPX4; myocardial ischemia–reperfusion; heart failure; cardiotoxicity; pharmacological targets

1. Introduction

Cardiovascular disease remains the leading cause of death worldwide, and a common feature of its major forms is the irreversible loss of specialized cells. The adult human heart has very limited regenerative capacity, so each cardiomyocyte lost to ischemia, toxins, or chronic stress reduces contractile reserve and promotes fibrotic remodeling. Similarly, death of endothelial cells and vascular smooth muscle cells contributes to plaque instability, vessel wall weakening, and loss of barrier function. Limiting regulated cell death has therefore been a long-standing therapeutic aim, yet clinical attempts to block apoptosis or necrosis have produced modest benefit. This gap suggests that additional death programs participate in cardiac injury and that they may offer unexploited drug targets.

Ferroptosis was named in 2012 to describe a form of cell death that differs from apoptosis, necroptosis, and autophagic death in its morphology, biochemistry, and genetic dependencies. It is triggered by the small molecule erastin, is suppressed by iron chelation and lipophilic antioxidants, and culminates in lethal accumulation of lipid hydroperoxides (Dixon et al., 2012). The Nomenclature Committee on Cell Death subsequently recognized it as a distinct regulated process (Galluzzi et al., 2018), and the field has since expanded rapidly to link ferroptosis with metabolism, redox biology, and disease (Stockwell et al., 2017; Jiang et al., 2021). A decade after its description, the concept has matured to encompass roles in development, immunity, neurodegeneration, cancer, and organ injury, together with early efforts toward therapeutic modulation (Stockwell, 2022).

Several features make the cardiovascular system a plausible arena for ferroptosis. Cardiomyocytes contain a dense mitochondrial network that consumes iron-containing heme and iron–sulfur proteins at high rates, and they must import, store, and export iron with precision. Too little iron impairs oxidative phosphorylation, whereas too much catalyzes free radical formation. Disturbed iron balance is a recognized feature of heart failure, anthracycline toxicity, hemochromatosis, and thalassemia, and the biology of cardiac iron has been reviewed in depth (Sawicki et al., 2023). Ischemia–reperfusion subjects the myocardium to oxygen shifts, calcium overload, and reactive oxygen species at the same moment that iron is released from damaged stores, creating

conditions in which lipid peroxidation can propagate. Ferroptosis is also considered an especially inflammatory form of death, and it can spread among neighboring cells in synchronized waves, as shown in renal tubules (Linkermann et al., 2014), which suggests that it could amplify tissue damage beyond the initial insult.

From the perspective of a pharmacologist, ferroptosis is attractive because its execution depends on identifiable enzymes, transporters, and metabolites, many of which can be modulated by existing or investigational drugs. These include iron chelators already used in thalassemia and cardio-oncology, radical-trapping antioxidants, and inhibitors of lipid-metabolizing enzymes. At the same time, the pharmacology is complicated by the fact that iron and polyunsaturated lipids are essential for normal cardiac function, that the same pathway protects against cancer, and that no validated biomarkers allow clinicians to identify ferroptosis in patients. A comprehensive account of the cardiovascular implications has been provided by Fang et al. (2023); the present review builds on it by emphasizing mechanisms that can be drugged. It proceeds by describing the molecular machinery of ferroptosis, then the evidence for its involvement in specific cardiovascular conditions, then the pharmacological opportunities and obstacles, and finally the major unanswered questions.

2. Molecular Machinery of Ferroptosis

The chemical basis of lipid peroxidation. Ferroptosis is fundamentally a failure of lipid redox control. Membrane phospholipids that contain polyunsaturated fatty acyl chains are vulnerable because the bis-allylic hydrogen atoms between double bonds are easily abstracted by radicals, initiating chain reactions that generate phospholipid hydroperoxides. Redox-active iron propagates these reactions, either through Fenton-type chemistry that converts hydrogen peroxide and lipid hydroperoxides into highly reactive radicals or through iron-containing enzymes (Conrad & Pratt, 2019). When the cell cannot reduce hydroperoxides to harmless alcohols or terminate radical chains, oxidative damage alters membrane structure and permeability, ultimately causing rupture. The precise biophysical events that convert peroxidized membranes into cell death are still debated (Feng & Stockwell, 2018), but the requirement for lipid peroxidation is well established, since lipophilic radical-trapping antioxidants such as ferrostatin-1 and liproxstatin-1 prevent death by intercepting propagating radicals rather than by inhibiting a specific enzyme (Zilka et al., 2017).

The glutathione–GPX4 axis. The central defense is glutathione peroxidase 4, a selenoprotein that uniquely reduces phospholipid hydroperoxides within membranes, using reduced glutathione as the electron donor. Inhibition or deletion of GPX4 induces ferroptosis in many cell types, and the small molecule RSL3 acts by inactivating this enzyme (Yang et al., 2014). Inducible deletion of Gpx4 in adult mice leads to acute organ failure, which was shown to be preventable with ferroptosis inhibitors (Friedmann Angeli et al., 2014). Because GPX4 contains selenocysteine, its function depends on selenium availability and on the machinery that incorporates this amino acid; impaired selenocysteine use renders cells sensitive to hydroperoxide-induced death (Ingold et al., 2018). This dependence is pharmacologically relevant since selenium status varies among populations and may modify cardiac vulnerability, a point echoed by the long-recognized association between selenium deficiency and cardiomyopathy in some regions.

Glutathione supply in turn relies on cysteine, which many cells obtain by importing cystine through system x_c^-, a heterodimer of SLC7A11 and SLC3A2. Erastin, sulfasalazine, and sorafenib inhibit this transporter, depleting glutathione and sensitizing cells to ferroptosis (Dixon et al., 2012; Dixon et al., 2014). The glutathione–GPX4 axis is therefore regulated at several levels: cystine uptake, glutathione synthesis, selenocysteine incorporation, and enzyme activity. Each of these nodes represents a possible drug target in either direction, inhibition to induce ferroptosis in tumors or support to prevent it in ischemic tissue.

Phospholipid composition and lipid-oxidizing enzymes. Because only certain lipids are susceptible, the cellular lipidome strongly influences ferroptotic sensitivity. Acyl-CoA synthetase long-chain family member 4 (ACSL4) preferentially activates arachidonic and adrenic acids, and lysophosphatidylcholine acyltransferase 3 (LPCAT3) esterifies them into phosphatidylethanolamines. Loss of ACSL4 confers resistance to ferroptosis, and oxidized arachidonoyl and adrenoyl phosphatidylethanolamines have been identified as pro-ferroptotic signals (Doll et al., 2017; Kagan et al., 2017). Genetic screens independently highlighted the roles of these lipid-metabolism genes (Dixon et al., 2015). Conversely, exogenous monounsaturated fatty acids displace polyunsaturated species from membranes and promote a ferroptosis-resistant state (Magtanong et al., 2019), which illustrates how diet and lipid metabolism could modify risk.

The enzymes that initiate peroxidation remain a matter of discussion. Lipoxygenases, particularly ALOX15 in complex with the scaffold protein PEBP1, can generate hydroperoxy-phospholipid signals that drive ferroptosis (Wenzel et al., 2017; Yang et al., 2016). Other work argues that non-enzymatic autoxidation, catalyzed by iron, is sufficient for propagation and that lipoxygenases act primarily to initiate it (Shah et al., 2018). Both views support the same practical point: reducing the availability of oxidizable substrate, the initiating enzymes, or the catalytic iron can all delay death.

Parallel suppressor systems. GPX4 is not the only barrier. Ferroptosis suppressor protein 1 (FSP1, encoded by *AIFM2*) is recruited to the plasma membrane by myristoylation and reduces coenzyme Q10 to its lipophilic hydroquinone form, which traps radicals independently of glutathione (Bersuker et al., 2019; Doll et al., 2019). A non-canonical vitamin K cycle can also be fueled by FSP1 to protect membranes (Mishima et al., 2022). The GTP cyclohydrolase 1–tetrahydrobiopterin pathway supplies another radical-trapping lipid antioxidant and alters phospholipid composition (Kraft et al., 2020), while mitochondrial dihydroorotate dehydrogenase regenerates ubiquinol within the inner mitochondrial membrane (Mao et al., 2021). A genome-scale analysis further revealed a surveillance pathway that is independent of GPX4 and influenced by sex hormones, through enzymes that incorporate monounsaturated fatty acids into membrane lipids (Liang et al., 2023). The existence of multiple, partly redundant defenses explains why different tissues vary in susceptibility and suggests that the heart, with its distinct metabolic profile, may rely on specific combinations that remain to be mapped.

Iron metabolism. Iron enters cells mainly as transferrin-bound iron via transferrin receptor 1, is reduced and released from endosomes, and enters a labile pool that supplies mitochondria and iron-dependent enzymes or is sequestered in ferritin. Excess iron is exported through ferroportin, whose abundance is controlled by the hormone hepcidin. Ferroptosis is sensitive to each step of this cycle (Chen et al., 2020). Transferrin and glutaminolysis are required for the death induced by serum, linking extracellular iron delivery and amino acid metabolism to ferroptotic execution (Gao et al., 2015). Selective autophagy of ferritin, termed ferritinophagy and mediated by the cargo receptor NCOA4, releases stored iron and increases ferroptotic sensitivity (Mancias et al., 2014; Hou et al., 2016). Heme catabolism by heme oxygenase-1 supplies additional free iron, a mechanism that is especially pertinent to the heart, which contains abundant heme proteins.

Transcriptional and signaling control. The transcription factor NRF2 upregulates numerous anti-ferroptotic genes, including those encoding SLC7A11, ferritin subunits, ferroportin, and enzymes of glutathione metabolism, and its activation through the p62–KEAP1 route protects cells from ferroptosis (Sun et al., 2016; Dodson et al., 2019). NRF2 also induces heme oxygenase-1, which illustrates how a protective program can become harmful when heme is abundant. The tumor suppressor p53 can sensitize cells by repressing SLC7A11 (Jiang et al., 2015). Autophagy, mitochondrial metabolism, and endoplasmic reticulum stress all intersect with the process, and an extensive survey of regulators has been compiled by Chen et al. (2021a). Mitochondria contribute differently depending on the trigger: they are required for ferroptosis caused by cysteine deprivation but are dispensable when GPX4 is directly inhibited (Gao et al., 2019), which implies that the cardiac consequences of a given stress depend on how it engages mitochondrial metabolism.

Propagation and inflammatory consequences. Ferroptotic death can spread between adjacent cells, in part through an osmotic mechanism that does not require classical membrane rupture (Riegman et al., 2020), and damaged cells release oxidized lipids and other damage-associated molecules that influence inflammation and immunity (Chen et al., 2021b). In the myocardium, where cells are electrically and mechanically coupled and where the inflammatory response determines scar formation, such propagation and signaling could be important determinants of infarct size and remodeling.

Cardiac-specific determinants of susceptibility. Several features of cardiac biology plausibly shape how these general principles apply in the heart. Cardiomyocytes depend on mitochondrial oxidation of fatty acids and other substrates for most of their ATP, which supplies both the electrons that fuel radical generation and the polyunsaturated phospholipids, notably in mitochondrial membranes, that serve as targets. They can import non-transferrin-bound iron through L-type calcium channels when circulating iron saturation is high (Oudit et al., 2003), and they depend on transferrin receptor for physiological iron supply (Xu et al., 2015). Their reliance on specific iron-handling proteins is evident from the severe phenotypes that follow tissue-restricted deletion of ferritin H or ferroportin (Fang et al., 2020; Lakhal-Littleton et al., 2015). Moreover, because mitochondria participate differently in ferroptosis depending on the trigger (Gao et al., 2019), stresses that damage mitochondrial function, such as ischemia and anthracyclines, may produce a distinct ferroptotic signature compared with stresses that primarily inhibit GPX4. Defining this cardiac-specific wiring is a prerequisite for rational drug selection.

3. Evidence for Ferroptosis in Cardiovascular Disease

Myocardial ischemia–reperfusion injury. Some of the earliest evidence for ferroptosis in the heart came from ischemia–reperfusion models. Glutaminolysis inhibitors reduced injury in perfused hearts subjected to ischemia followed by reperfusion, supporting a role for the pathway in tissue damage (Gao et al., 2015). Mice with experimental myocardial infarction showed a decline in GPX4 abundance in cardiomyocytes, and the damage correlated with markers of ferroptosis (Park et al., 2019). Ferrostatin-1 and iron-lowering interventions reduced infarct-related injury and improved functional outcomes in mouse models of ischemia–reperfusion (Fang et al., 2019). Mechanistic work has identified the lipid arm: oxidized phosphatidylcholines were shown to trigger ferroptosis in cardiomyocytes during reperfusion (Stamenkovic et al., 2021), and Alox15 together with its product 15-hydroperoxyeicosatetraenoic acid was found to promote cardiomyocyte ferroptosis and worsen reperfusion injury, with inhibition of the enzyme conferring protection (Cai et al., 2023). Nutrient-sensing pathways appear to modulate vulnerability, because mechanistic target of rapamycin activity protected cardiomyocytes from excess iron and ferroptosis (Baba et al., 2018). Taken together, these findings indicate that reperfusion engages multiple ferroptotic inputs: iron release, glutaminolysis, lipid oxidation, and loss of antioxidant defenses. They also suggest a clinically attractive therapeutic window, because reperfusion is a defined, monitored event during which an adjunctive drug could be administered.

Heart failure and cardiac iron homeostasis. Chronic heart failure presents a paradox. On one hand, iron deficiency is common in patients and is associated with worse symptoms; on the other, experimental data connect excess or mislocalized iron with ferroptotic damage. Genetic models clarify the delicate balance. Deleting the iron exporter ferroportin in cardiomyocytes caused fatal cardiomyopathy through intracellular iron accumulation (Lakhal-Littleton et al., 2015), whereas deleting cardiac hepcidin, which raises ferroportin activity, caused cellular iron deficiency and cardiac dysfunction (Lakhal-Littleton et al., 2016). Mice lacking transferrin receptor in cardiomyocytes developed lethal cardiomyopathy associated with mitochondrial dysfunction (Xu et al., 2015). Thus, both too much and too little cardiomyocyte iron can be injurious, and any therapy that modifies iron availability must respect this narrow window. Loss of cardiac ferritin H made hearts vulnerable to injury through a mechanism involving SLC7A11 and ferroptosis, particularly under conditions of iron challenge (Fang et al., 2020), underscoring the protective role of iron storage.

The clinical trial literature is consistent with this duality. Intravenous ferric carboxymaltose improved symptoms and functional capacity in patients with heart failure and iron deficiency (Anker et al., 2009), and after hospitalization for acute heart failure it reduced subsequent heart failure admissions, although the primary composite endpoint did not reach statistical significance (Ponikowski et al., 2020). These results show that correcting systemic iron deficiency can help patients, but they do not contradict the ferroptosis hypothesis, since systemic iron stores, cardiomyocyte labile iron, and mitochondrial iron are different compartments. A central challenge is to distinguish a heart that is deprived of usable iron from one that has misdistributed, redox-active iron.

Anthracycline cardiotoxicity. Doxorubicin and related anthracyclines are effective chemotherapeutics but cause dose-dependent cardiomyopathy. Inhibition of topoisomerase 2β in cardiomyocytes was proposed as a major mechanism (Zhang et al., 2012), and doxorubicin was also shown to cause cardiotoxicity through accumulation of iron in mitochondria, an effect reversed by manipulating the mitochondrial iron exporter ABCB8 and by the iron-chelating cardioprotectant dexrazoxane (Ichikawa et al., 2014). Subsequent work linked doxorubicin to ferroptosis by showing that heme degradation through heme oxygenase-1 released free iron and that ferrostatin-1 and dexrazoxane attenuated cardiomyopathy (Fang et al., 2019). Further mechanistic studies reported that doxorubicin intercalates into mitochondrial DNA and disrupts heme synthesis, driving ferroptosis and cardiotoxicity (Abe et al., 2022), and that mitochondrial lipid peroxidation is a principal event in this injury (Tadokoro et al., 2023). Doxorubicin cardiotoxicity thus offers the strongest convergence of mechanistic, genetic, and pharmacological evidence for a ferroptotic component, and the already established clinical use of dexrazoxane provides a precedent for iron-directed cardioprotection.

Diabetic and septic cardiac injury. Metabolic stress and systemic inflammation are other settings in which ferroptosis has been implicated. In diabetic hearts subjected to ischemia–reperfusion, endoplasmic reticulum stress was linked to ferroptosis, and inhibiting the process lowered injury (Li et al., 2020). In sepsis-induced cardiac dysfunction, ferritinophagy-mediated ferroptosis was found to contribute to damage, and ferroptosis inhibition improved cardiac function in experimental models (Li et al., 2021). These findings are consistent with the interpretation that diverse stresses converge on a limited number of lipid-peroxidation and iron-handling checkpoints, although most data derive from rodent models and inhibitors with limited specificity.

Iron-overload cardiomyopathy. In hereditary hemochromatosis and transfusion-dependent thalassemia, iron accumulation in the myocardium produces cardiomyopathy, arrhythmia, and heart failure (Gujja et al., 2010; Murphy & Oudit, 2010). L-type calcium channels provide a major route for non-transferrin-bound iron entry into cardiomyocytes, which suggests one pharmacological entry point (Oudit et al., 2003). Cardiac iron chelation, guided by magnetic resonance imaging of iron burden, has substantially improved outcomes in thalassemia major (Pennell et al., 2013). While the extent to which ferroptosis, rather than other mechanisms, mediates damage in these conditions has not been fully established, the consistent protection afforded by chelation and the vulnerability of iron-loaded cells to lipid peroxidation make it a reasonable working model.

Atherosclerosis and vascular disease. In the vasculature, oxidized lipoproteins, iron deposition in plaques, and endothelial dysfunction create a setting where lipid peroxidation is prominent. Oxidized low-density lipoprotein induced ferroptosis in cultured endothelial cells, and ferroptosis inhibition reduced endothelial dysfunction and lesion development in atherosclerosis-prone mice (Bai et al., 2020). Reviews summarize the potential involvement of macrophages, endothelial cells, and smooth muscle cells in plaque biology (Ouyang et al., 2021), and cigarette smoke extract was shown to induce ferroptosis in vascular smooth muscle cells, linking an environmental risk factor to this death pathway (Sampilvanjil et al., 2020). Evidence in human plaques and in other vascular diseases, such as aneurysm and pulmonary hypertension, is still sparse, and the relative contribution of ferroptosis compared with other death mechanisms and with non-lethal oxidative signaling has yet to be determined.

Inflammation, remodeling, and interaction with other forms of cell death. Death of cardiomyocytes is rarely an isolated event; it initiates inflammatory signaling that determines scar quality and subsequent remodeling. Ferroptotic cells release oxidized lipids and other danger signals that can activate innate immune cells (Chen et al., 2021b), and the capacity of ferroptosis to propagate across adjacent cells (Riegman et al., 2020) could enlarge the zone of injury at the border of an infarct. Whether ferroptosis acts mainly as an initiator, an amplifier, or a bystander in these processes is unknown. It is also likely to coexist with other forms of regulated death. Ferroptosis and necroptosis have been implicated together in synchronized tubular death in the kidney (Linkermann et al., 2014), and similar cross-talk probably occurs in the heart. This overlap complicates interpretation of inhibitor studies, because a protective effect of ferrostatin-1 does not prove that ferroptosis is the only or dominant pathway, and it argues for experimental designs that combine pharmacological and genetic tools and quantify several death markers in parallel.

4. Pharmacological Targets and Therapeutic Strategies

Radical-trapping antioxidants. The first ferroptosis inhibitors were lipophilic antioxidants discovered by screening. Ferrostatin-1 prevented erastin-induced death at nanomolar to low micromolar concentrations (Dixon et al., 2012), and further ferrostatins and liproxstatin-1 protected cells and animals in diverse disease models (Skouta et al., 2014; Friedmann Angeli et al., 2014). Mechanistic studies established that these compounds function as radical-trapping antioxidants within membranes, and that this action, not inhibition of lipoxygenases, accounts for most of their activity (Zilka et al., 2017). In cardiac models, ferrostatin-1 and liproxstatin-1 are the standard tools that demonstrated the role of ferroptosis in ischemia–reperfusion and anthracycline injury (Fang et al., 2019). However, the parent compounds suffer from poor metabolic stability and unfavorable pharmacokinetic properties, which limit their direct clinical use. Medicinal chemistry efforts have produced analogues with improved potency, plasma stability, and in vivo efficacy (Hofmans et al., 2016; Devisscher et al., 2018). Edaravone, a free-radical scavenger approved in some countries for stroke and amyotrophic lateral sclerosis, was reported to inhibit ferroptosis in vitro (Homma et al., 2019), which raises the possibility of repurposing clinically available agents. Key pharmacological questions for any radical-trapping antioxidant include tissue distribution to the myocardium, partitioning into the relevant membrane compartment, rate of consumption, and the potential for pro-oxidant behavior of the oxidized species.

Iron chelation and iron-handling modulators. Chelators are the most clinically mature class. Dexrazoxane, which hydrolyzes to a metal-binding species, attenuates anthracycline cardiomyopathy, and its protective effect has been interpreted in light of mitochondrial iron and ferroptosis (Ichikawa et al., 2014; Fang et al., 2019). Deferoxamine, deferiprone, and deferasirox are used to treat transfusional iron overload, and cardiac outcomes have improved with optimized chelation regimens (Pennell et al., 2013). Applying chelators to common cardiovascular indications, such as infarction, requires caution. Systemic chelation may worsen iron deficiency in patients with heart failure, and the genetic work described above shows that cardiomyocytes tolerate neither severe iron loss nor excess (Lakhal-Littleton et al., 2016; Xu et al., 2015). Strategies that could address this concern include chelators

targeted to mitochondria or to the labile iron pool, short, time-limited administration at the moment of reperfusion, and modulation of upstream regulators such as the hepcidin–ferroportin axis, NCOA4-dependent ferritinophagy, or heme oxygenase-1 activity. Because heme oxygenase-1 can be cytoprotective in some contexts and harmful in others, the direction of modulation will depend on disease and timing.

Targeting lipid metabolism and oxidation. Inhibitors of ACSL4 reduce the supply of oxidizable phospholipids, and the thiazolidinedione class, including rosiglitazone, was identified as inhibiting ACSL4 and protecting against ferroptosis in experimental systems (Doll et al., 2017). This is intriguing because these drugs are already in clinical use, but thiazolidinediones carry a known risk of fluid retention and heart failure, so any cardiac application would require selective analogues or different delivery. Lipoxygenase inhibitors offer another route, and suppression of Alox15 reduced cardiac injury in a reperfusion model (Cai et al., 2023). An unconventional strategy is to modify fatty acid substrates themselves; polyunsaturated fatty acids deuterated at bis-allylic positions resist peroxidation and prevent ferroptosis, as do exogenous monounsaturated fatty acids that alter membrane composition (Yang et al., 2016; Magtanong et al., 2019). Whether dietary or pharmacological manipulation of the cardiac lipidome can be achieved safely is unknown, since cardiolipin and other polyunsaturated phospholipids are essential for mitochondrial function.

Reinforcing endogenous antioxidant defenses. Rather than blocking an injurious pathway, a complementary approach is to strengthen innate protection. Activation of NRF2 increases glutathione synthesis, SLC7A11 expression, and iron-sequestering proteins (Dodson et al., 2019), although its simultaneous induction of heme oxygenase-1 must be considered in heme-rich tissue. Selenium supplementation increases GPX4 expression through a transcriptional adaptive program and has protected against ferroptosis-related injury in a stroke model (Alim et al., 2019), and selenoprotein biosynthesis is a requirement for GPX4 activity (Ingold et al., 2018). These observations suggest that restoration of selenium status in deficient individuals, or pharmacological enhancement of GPX4 expression, merits study. Direct small-molecule activators of GPX4 are not yet established clinical agents. Enhancing parallel systems, such as FSP1, coenzyme Q10 recycling, or tetrahydrobiopterin synthesis, is conceptually possible, although specificity and tissue selectivity are unresolved (Bersuker et al., 2019; Kraft et al., 2020). Likewise, supporting cysteine supply could help maintain glutathione, but increasing cystine uptake may be double-edged in settings in which glutamate export or cystine reduction depletes cellular reducing equivalents.

Mitochondria-directed and pathway-selective approaches. Because mitochondria are central to anthracycline toxicity and to certain forms of ferroptosis (Gao et al., 2019; Tadokoro et al., 2023), compounds directed to the inner mitochondrial membrane may offer greater precision. These could include mitochondria-targeted radical-trapping antioxidants, activators of DHODH-dependent ubiquinol regeneration, and drugs that restore heme synthesis or normalize mitochondrial iron export (Abe et al., 2022; Ichikawa et al., 2014; Mao et al., 2021). Pathway-selective strategies could match the intervention to the trigger, for instance iron-directed therapy for anthracyclines, lipoxygenase inhibition for ischemia–reperfusion, and ferritinophagy inhibition for sepsis, rather than treating ferroptosis as a single entity.

Drug delivery and pharmacokinetic design. Beyond the choice of target, the pharmacokinetics of cardioprotective ferroptosis modulators will determine success. A compound intended for ischemia–reperfusion must reach therapeutic concentrations in the area at risk within minutes of reperfusion, which favors intravenous administration, rapid distribution, and adequate stability in plasma, the very properties that early ferrostatins lacked (Hofmans et al., 2016; Devisscher et al., 2018). For prophylaxis against cardiotoxicity or in chronic heart failure, oral bioavailability, duration of action, and the absence of accumulation in tissues that need physiological iron handling become more important. Radical-trapping antioxidants are consumed as they quench radicals, so their effective duration depends on oxidative flux, which differs between healthy and injured myocardium. Formulation strategies, such as nanoparticle carriers, cardiac-homing peptides, or mitochondria-targeting moieties, are conceptually attractive for achieving tissue selectivity, although they remain largely experimental for this indication. Dose selection will need to be informed by exposure–response models that incorporate target engagement markers rather than relying on doses that were efficacious in rodents.

Pharmacodynamic and safety considerations. Several concerns specific to ferroptosis modulation deserve attention. First, ferroptosis has tumor-suppressive functions, because p53 and other factors drive sensitivity in transformed cells (Jiang et al., 2015), and many anticancer agents may exert part of their effect through this pathway. In cardio-oncology, systemic ferroptosis inhibition could theoretically reduce the efficacy of chemotherapy, so cardiac-selective delivery or confirmation that tumor responses are unaffected will be essential. Second, complete and sustained GPX4 loss is lethal in adult tissues such as the kidney (Friedmann Angeli et al., 2014), which cautions against global enhancement of ferroptosis in any context, and highlights that chronic inhibitor therapy may disturb physiological roles that remain poorly characterized. Third, sex hormones and diet influence ferroptotic defenses (Liang et al., 2023; Magtanong et al., 2019), implying that efficacy and toxicity may differ by sex and nutritional state, an important consideration for clinical trial design. Finally, drugs already in clinical use, including sorafenib and sulfasalazine, inhibit system xc^- (Dixon et al., 2014), and their cardiovascular effects should be reconsidered in light of this mechanism.

5. Challenges, Future Directions and Conclusions

Defining ferroptosis in patients. The most immediate barrier to clinical translation is the absence of validated biomarkers. Evidence in the heart relies on a combination of genetic perturbation, inhibitors, and surrogate readouts such as lipid peroxidation products, iron content, and expression of GPX4 or related proteins, none of which is specific, and recommendations for rigorous demonstration emphasize using multiple independent criteria (Galluzzi et al., 2018; Jiang et al., 2021). Lipidomic signatures of oxidized phospholipids, circulating markers of iron handling, and imaging of myocardial iron by magnetic resonance could be combined into composite pharmacodynamic indicators, which would also enable patient enrichment in trials. Without such tools, a negative trial cannot distinguish an ineffective drug from a mismatched population.

Specificity of tools and model limitations. Much of the supporting data relies on ferrostatin-1, liproxstatin-1, and chelators, which are antioxidants or metal binders with effects beyond ferroptosis, so complementary genetic models, such as cardiomyocyte-specific manipulation of *Gpx4*, *Slc7a11*, *Acsl4*, or *Fth1*, are needed to confirm conclusions. Rodent hearts differ from human hearts in metabolic rate, lipid composition, and response to ischemia, and comorbidities such as diabetes, hypertension, advanced age, and kidney disease alter iron and redox status. Large-animal models and human tissue, including engineered heart tissue derived from induced pluripotent stem cells, should be used to test the most promising targets. The relationship of ferroptosis to other death pathways also needs clarification. Necroptosis, pyroptosis, apoptosis, and ferroptosis can be activated simultaneously, and blocking one may shift cells toward another (Linkermann et al., 2014), which could blunt benefit from single-pathway inhibitors and argue for rational combinations.

Pharmacological optimization and trial design. Future drug development should apply standard pharmacological principles that have so far been underused in this field. Candidate agents require characterization of absorption, cardiac exposure, metabolic stability, and dose–response relationships across relevant models, ideally with measurement of target engagement. For ischemia–reperfusion, trials should align dosing with the reperfusion window; for cardiotoxicity, prophylactic regimens begun before chemotherapy are logical; for heart failure, any iron-directed therapy must be stratified by iron status and likely requires compartment-specific approaches. Combination with established therapies, including reperfusion strategies, neurohormonal blockade, and standard cardioprotective agents, should be studied for additive or antagonistic interactions. Repurposing of approved drugs with anti-ferroptotic properties could shorten development timelines, but each candidate must be shown to act on the target at achievable human exposures.

Population heterogeneity and precision approaches. Patients who might benefit from ferroptosis-directed therapy are heterogeneous. Sex hormones modify ferroptotic defenses (Liang et al., 2023), age, diet, and genetic variation in iron-handling or selenoprotein genes may influence baseline susceptibility, and comorbid conditions alter both iron distribution and oxidative load. A precision approach would stratify patients by iron status, imaging of myocardial iron, lipid peroxidation signatures, and perhaps selenium status, and match therapy to the dominant mechanism. Such stratification would also help separate patients who need iron repletion from those who might benefit from compartment-specific chelation, a distinction at the heart of the current paradox in heart failure (Anker et al., 2009; Ponikowski et al., 2020). Pharmacogenomic and pharmacometric approaches, which are routine for established cardiovascular drugs, have not yet been applied to this field and offer an opportunity to define dose, timing, and combination strategies before large trials are undertaken.

Emerging technologies. Technical advances could accelerate progress. Spatial lipidomics and single-cell methods may map where and when peroxidized lipids accumulate in infarcted or failing hearts. Unbiased genetic and chemoproteomic screens have already uncovered the FSP1 and DHODH defenses (Bersuker et al., 2019; Doll et al., 2019; Mao et al., 2021), and comparable screens in cardiomyocytes could reveal heart-specific suppressors and vulnerabilities. Human induced pluripotent stem cell-derived cardiomyocytes and engineered heart tissue permit manipulation of these genes in a human context, providing a bridge between rodent studies and clinical testing.

Conclusions. Ferroptosis integrates iron metabolism, lipid biochemistry, and antioxidant defense into a single cell-death framework that aligns closely with the vulnerabilities of the heart and vasculature. Experimental evidence supports a contribution to ischemia–reperfusion injury, anthracycline cardiomyopathy, iron-overload disease, and diabetic and septic cardiac dysfunction, with emerging but less certain evidence in heart failure and atherosclerosis. The pathway offers multiple pharmacological entry points, including radical-trapping antioxidants, chelators, modulators of lipid-metabolizing enzymes, and reinforcement of the GPX4, FSP1, and NRF2 systems. At the same time, the narrow tolerance of cardiomyocytes for both iron deficiency and iron excess, the tumor-suppressive role of ferroptosis, the poor drug-like properties of many inhibitors, and the lack of clinical biomarkers mean that the target remains unvalidated in humans. Progress will depend on precise mechanistic mapping in human tissue, development of pharmacokinetically suitable and cardiac-selective agents, and trials designed around pharmacodynamic biomarkers. If these obstacles can be overcome, ferroptosis-directed therapy could complement existing cardiovascular treatments by preserving the cells on which cardiac and vascular function depend.

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