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REVIEW

The Regulatory Landscape of Ferroptosis and Iron Homeostasis: Pathophysiological Mechanisms and Therapeutic Horizons in Cardiovascular Disease

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Abstract: Ferroptosis is an iron-dependent form of regulated cell death driven by unrestrained lipid peroxidation, morphologically and biochemically distinct from apoptosis, necrosis, and autophagy. It is increasingly recognized as a core pathophysiological mechanism across the full spectrum of cardiovascular diseases, including myocardial ischemia-reperfusion injury, heart failure, atherosclerosis, diabetic cardiomyopathy, and chemotherapy-induced cardiotoxicity. The initiation and progression of ferroptosis are governed by the dysregulation of iron homeostasis, lipid metabolic remodeling, and collapse of antioxidant defense systems, with extensive crosstalk with other regulated cell death modalities in cardiovascular pathophysiology. Preclinical studies have consistently demonstrated that targeting ferroptosis exerts robust cardioprotective effects via multiple mechanisms. However, clinical translation faces key hurdles, including the lack of specific biomarkers, off-target risks, and interindividual heterogeneity in therapeutic response. This review systematically summarizes the regulatory mechanisms of ferroptosis, its causal role in cardiovascular diseases, and the latest advances in targeted therapeutic strategies, with a focus on clinical translation prospects and challenges.

Keywords: ferroptosis, iron homeostasis, lipid peroxidation, cardiovascular diseases, myocardial injury, antioxidant therapy, GPX4, Nrf2, heart failure, ischemia–reperfusion injury, atherosclerosis, therapeutic targeting

Introduction

Cardiovascular diseases (CVDs) represent a leading cause of global mortality and morbidity, encompassing conditions such as coronary artery disease, myocardial infarction, hypertension, atherosclerosis, and heart failure.[1,2] Although conventional therapeutic strategies have improved patient outcomes to some extent, many individuals still face high risks of recurrence and adverse cardiovascular events. Thus, identifying novel molecular mechanisms and therapeutic targets has become a central focus in cardiovascular research.

The cardiovascular system is characterized by high metabolic activity and oxygen consumption, making it particularly susceptible to oxidative stress. The heart contains a dense mitochondrial network and primarily relies on oxidative phosphorylation for energy production; therefore, cardiomyocytes are highly vulnerable to disruptions in lipid oxidation and iron metabolism.[3,4] Furthermore, the limited regenerative capacity of cardiac myocytes means that irreversible injury—such as that caused by ischemia or toxic insults—can directly impair cardiac function and increase susceptibility to heart failure. Maintaining redox homeostasis and iron balance in cardiomyocytes is thus essential for preserving myocardial integrity and preventing pathological remodeling.[5] Dysregulation of iron homeostasis has emerged as a key driver of ferroptosis—a form of regulated cell death defined by iron-dependent lipid peroxidation.[6] Iron overload promotes the Fenton reaction, which generates reactive oxygen species (ROS) that induce lipid peroxidation and DNA damage, ultimately leading to cardiomyocyte death and fibrotic remodeling.[6] Notably, elevated levels of lipid peroxidation markers such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), along with reduced expression of glutathione peroxidase

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4 (GPX4), have been detected in post-mortem tissues from patients with acute myocardial infarction or chronic heart failure, suggesting that ferroptosis may play a significant role in human cardiovascular pathology.[7]

Ferroptosis, first identified in 2012, represents a newly classified mode of programmed cell death distinct from apoptosis, necrosis, and autophagy.[8] It is biochemically defined by the accumulation of lipid ROS, structural disruption of cellular membranes, and iron dyshomeostasis, culminating in loss of membrane integrity, mitochondrial dysfunction, and irreversible cell death.[9] Ferroptotic signaling is tightly controlled by multiple pathways, including the system Xc^-–GSH–GPX4 axis, lipid metabolic enzymes such as ACSL4 and lipoxygenases (LOXs), and redox-sensitive transcription factors such as Nrf2.[10] As our understanding of this process has expanded, ferroptosis has been increasingly recognized as a contributing mechanism in several cardiovascular pathologies, including myocardial ischemia–reperfusion injury, dilated cardiomyopathy, doxorubicin-induced cardiotoxicity, and atherosclerosis, where dysregulation of these control networks often occurs.[11]

Recent studies have demonstrated that pharmacological inhibition of ferroptosis can confer robust protection in preclinical models of cardiovascular disease. For example, specific ferroptosis inhibitors such as ferrostatin-1 (Fer-1) and liproxstatin-1 significantly reduce myocardial injury and improve cardiac function in murine models of ischemia–reperfusion.[12] Similarly, iron chelators such as deferoxamine (DFO) and deferiprone (DFP) protect against doxorubicin-induced cardiotoxicity by lowering labile iron levels and suppressing ROS generation.[12]

In addition to synthetic compounds, natural products have also shown promise in targeting ferroptosis. Molecules such as melatonin, vitamin E derivatives, curcumin, and resveratrol exert protective effects through various mechanisms, including activation of the Nrf2 pathway, upregulation of GPX4, and reduction of lipid ROS.[13,14] Notably, Nrf2, a master regulator of antioxidant responses, offers multi-target regulation of ferroptosis. Its activation enhances the expression of SLC7A11 and GPX4, thereby increasing cellular resistance to ferroptosis and providing new therapeutic insights into heart failure and myocardial injury.[15] Despite compelling evidence from basic science, clinical translation remains challenging.[16] First, most current findings derive from animal models and in vitro systems, with limited support from large-scale clinical data. Second, reliable and specific biomarkers of ferroptosis remain undefined. While markers such as MDA and 4-HNE offer some indication of lipid peroxidation, they lack specificity for distinguishing ferroptosis from other forms of oxidative stress-mediated cell death.[16] Moreover, ferroptosis may exhibit context-dependent roles: in certain diseases, it may be detrimental at one stage yet potentially beneficial at another. For instance, ferroptosis may act as a tumor suppressor in early-stage cancer but may be evaded during later stages,[16] suggesting that its role in cardiovascular disease must be carefully evaluated across different disease phases to enable precision intervention. Looking forward, future research should not only summarize the mechanisms and regulatory pathways of ferroptosis in CVDs but also explore novel therapeutic approaches based on emerging discoveries. Structural biology and artificial intelligence-driven drug discovery now allow for high-resolution modeling of key ferroptosis-related proteins—including ACSL4, LOXs, GPX4, and system Xc^- —enabling the design of small-molecule inhibitors with improved selectivity and pharmacokinetic properties.

Furthermore, cutting-edge technologies such as single-cell RNA sequencing, spatial transcriptomics, and organoid culture systems offer unprecedented opportunities to dissect the heterogeneity of ferroptosis across distinct cardiac and vascular cell types, including ventricular cardiomyocytes, sinoatrial node cells, conduction fibers, endothelial cells, and smooth muscle cells. These tools can help identify cell-specific markers of ferroptosis and inform targeted interventions tailored to distinct cell populations within the heart and vasculature. Strategies aimed at modulating ferroptosis—such as iron chelation, antioxidant supplementation, and gene editing to restore antioxidant defenses—are gradually transitioning from experimental models to clinical evaluation. By addressing these critical questions, we aim to establish ferroptosis modulation as a novel and effective strategy in the prevention and treatment of cardiovascular diseases. With continued advances in mechanistic understanding and therapeutic innovation, targeting ferroptosis holds strong potential to transform clinical cardiology and usher in a new era of precision medicine. To clarify the evolutionary trajectory of ferroptosis research and highlight the key breakthroughs that lay the foundation for our study, we summarized the critical time points in ferroptosis discovery (Figure 1).

Ferroptosis and Its Regulatory Mechanisms

Ferroptosis is an iron-dependent form of regulated cell death distinct from apoptosis, necrosis, and autophagy.[8] The process is primarily driven by the accumulation of reactive oxygen species (ROS), phospholipids containing polyunsaturated fatty acid chains (PUFA-PLs), and iron overload.[8] Moreover, inter- and intracellular signals, as well as environmental stressors, can

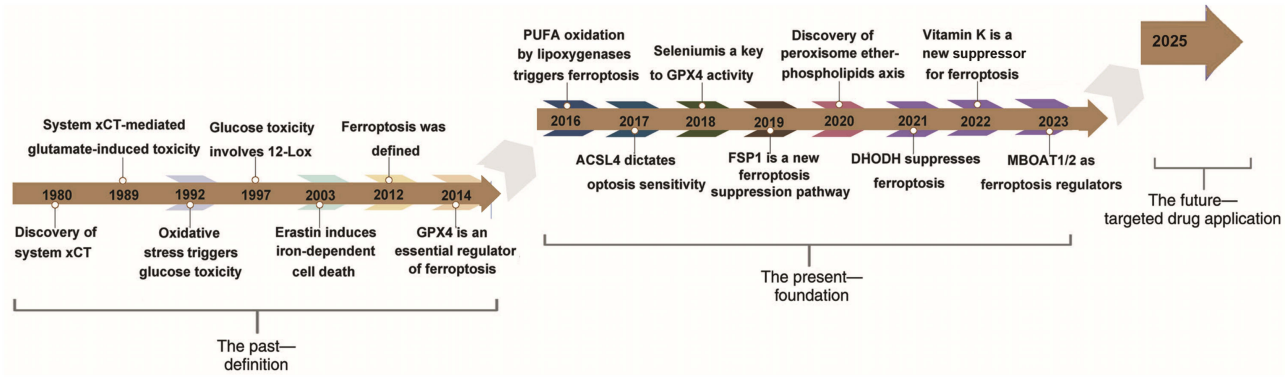

Figure 1 The key time points for the discovery of ferroptosis. (It outlines the complete historical trajectory of ferroptosis research: from the discovery of System xCT in 1980 and its formal naming and definition in 2012, through the in-depth elucidation of its multi-dimensional regulatory network (including lipid metabolism, antioxidant defense, iron homeostasis, and related pathways) since 2016, to the clinical application of targeted therapeutics in 2025 and beyond. It provides essential historical and theoretical context for understanding the role of the ferroptosis–iron homeostasis axis in cardiovascular diseases such as atherosclerosis. This figure was created with BioRender.

indirectly modulate ferroptosis by influencing cellular metabolism and ROS levels. Morphologically, ferroptosis is characterized by mitochondrial shrinkage, increased membrane density, loss or disappearance of cristae, and rupture of the outer mitochondrial membrane; nuclear morphology remains largely unchanged without chromatin condensation. At the biochemical level, ferroptosis is marked by elevated lipid peroxidation and ROS production.[10] The underlying mechanisms involve dysregulation of iron metabolism, amino acid antioxidant systems, and the accumulation of lipid peroxides.[10] Key events in ferroptosis include excessive intracellular iron deposition and lipid peroxidation, with multiple organelles—such as mitochondria and the endoplasmic reticulum—forming a regulatory network that governs redox balance and iron homeostasis.[16,17] As illustrated in Figure 1, three core conditions are necessary for the induction of ferroptosis: (1) excessive Fe^{2+} availability initiating redox reactions; (2) lipid peroxidation of PUFA-PLs; and (3) disruption of the antioxidant defense system responsible for neutralizing harmful lipid hydroperoxides.[18]

Role of Iron Metabolism in Ferroptosis

In the bloodstream, extracellular iron primarily exists in the Fe^{3+} form, with the vast majority bound to transferrin (TF) to form complexes that are transported via circulation to tissues with high iron demand, such as the liver and bone marrow. Excess iron is mainly stored in organs including the liver.[19] Cellular iron uptake is regulated through multiple pathways, the core of which include transferrin receptor-mediated internalization of transferrin-bound iron (TBI), endocytosis of other iron forms, and direct transmembrane uptake of non-transferrin-bound iron (NTBI) and heme iron.

Once inside the cell, Fe^{3+} is reduced to Fe^{2+} within lysosomes by STEAP3, a member of the six-transmembrane epithelial antigen of the prostate family and a key metalloreductase. The reduced Fe^{2+} has two primary destinations: it is released into the cytosol via ferroportin (FPN, encoded by SLC40A1) to form the intracellular labile iron pool (LIP), or sequestered and stored in ferritin. Ferritin is a heteropolymer composed of heavy-chain (FTH1) and light-chain (FTL1) subunits that provides a safe, biologically controllable storage mechanism for iron. This prevents free iron from causing damage through reaction with reactive oxygen species (ROS) and serves as a central molecule in maintaining cellular iron homeostasis.[11]

Precise regulation of iron homeostasis is essential for sustaining normal cellular physiological functions. When this balance is disrupted and iron metabolism becomes disordered, excess reactive Fe^{2+} triggers the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + \cdot OH$), generating large amounts of ROS and activating lipoxygenase (LOX), the key rate-limiting enzyme in membrane lipid peroxidation. The continuous accumulation of ROS causes extensive oxidative damage to cell membranes, organelles, and DNA, ultimately triggering ferroptosis.[16] Current studies have clearly defined the core quantitative thresholds for ferroptosis initiation: (1) At the free iron level, intracellular LIP concentration is maintained within a narrow physiological range of 0.2–0.5 μM; when LIP levels exceed physiological concentrations by 2–3 times, the Fenton reaction is significantly activated. When LIP exceeds 1 μM, irreversible lipid peroxidation cascade reactions are initiated, ultimately leading to ferroptosis. (2) At the lipid peroxidation product level, when phospholipid hydroperoxide (PLOOH) levels surpass 5 nmol/mg

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protein, their accumulation exceeds the clearance capacity of the endogenous antioxidant system, and ferroptosis enters an irreversible stage.

To systematically elucidate the fundamental biological processes of iron homeostasis, we have constructed a schematic diagram of systemic iron circulation and cellular iron metabolism patterns (Figure 2). This diagram comprehensively illustrates the dynamic flow of iron in the body as well as the complete regulatory network of iron uptake, storage, utilization, and export at the cellular level. It also highlights the critical concentration thresholds for ferroptosis occurrence, thereby laying a solid theoretical foundation for further exploration of the molecular mechanisms by which iron metabolic disorders drive ferroptosis.

Lipid Metabolism and Ferroptosis

Lipids perform diverse biological functions, including energy storage, signal transduction, and membrane structure maintenance. Among these, lipid peroxidation represents one of the defining features of ferroptosis, frequently resulting in oxidative damage to biomembranes and lipoproteins.[20] Phospholipids containing polyunsaturated fatty acids (PUFA-PLs) serve as primary substrates for lipid peroxidation. The enzymes acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) catalyze the esterification of free PUFAs and their subsequent incorporation into phospholipids. These PUFA-PLs are then oxidized by lipoxygenases (ALOXs) to generate phospholipid-hydroperoxides (PL-PUFA-OOH).

Initial lipid peroxidation products accumulate in the endoplasmic reticulum, although early peroxidation has also been observed in lysosomes, peroxisomes, and mitochondria.[21–24] Inhibition of ACSL4 or LPCAT3 expression reduces the cellular abundance of peroxidation-prone PUFA-PLs and suppresses ferroptosis.[25] Following GPX4 inhibition, lipid hydroperoxides first accumulate in the perinuclear membrane before spreading to the plasma membrane, ultimately causing structural membrane disruption and cell death.[26,27] Thus, ACSL4 and LPCAT3 regulate the formation of long-chain unsaturated fatty acid-containing PLs. During ferroptosis, these lipids become substrates for ROS-driven oxidation. Under conditions of impaired antioxidant defenses, PL-PUFA-OOH accumulates across organelle membranes and eventually propagates to the plasma membrane, leading to membrane destruction and ferroptotic cell death.

Redox Regulation of Ferroptosis

The cystine/glutamate antiporter system system Xc^-, composed of the light chain SLC7A11 and heavy chain SLC3A2, mediates the 1:1 exchange of extracellular cystine for intracellular glutamate.[28] Once inside the cell, cystine is converted into L-cysteine by glutamate–cysteine ligase (GCL) and glutathione synthetase (GS), forming reduced glutathione (GSH) —a central component of the cellular antioxidant machinery.[29] GSH serves as both a radical scavenger and a cofactor for glutathione peroxidase 4 (GPX4), playing a key role in redox regulation and stress resistance.[30,31] GPX4 is a crucial enzyme that counteracts Fenton reaction-driven ROS accumulation.[32] Utilizing GSH as a reducing agent, GPX4 converts toxic lipid hydroperoxides (L-OOH) into inert lipid alcohols (L-OH), thereby suppressing ferroptosis.[33]

Mitochondrial Regulation of Ferroptosis

Mitochondria play a critical dual regulatory role in the occurrence and development of ferroptosis, serving as both its core initiator and final executor. Their metabolic functions, iron-handling capacity, and structural homeostasis collectively participate in the precise control of the ferroptosis threshold.

As the core initiator of ferroptosis, mitochondria are the primary intracellular source of reactive oxygen species (ROS). Superoxide radicals generated during mitochondrial electron transport are converted by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2), thereby amplifying cellular oxidative stress. Hydrogen peroxide subsequently reacts with Fe^{2+} through the Fenton reaction to produce highly reactive hydroxyl radicals (·OH), which directly initiate the oxidation of polyunsaturated fatty acids (PUFAs) and constitute the central upstream event driving ferroptosis.[34,35] In addition, sustained activation of the mitochondrial tricarboxylic acid (TCA) cycle and electron transport chain provides the essential premise for basal intracellular ROS generation. Mitochondrial fatty acid β-oxidation directly supplies abundant substrates for lipid peroxidation reactions, while key enzymes such as citrate synthase (CS) and acyl-CoA synthetase family member 2 (ACSF2) regulate fatty acid activation and synthesis, thereby controlling the availability of lipid peroxidation substrates

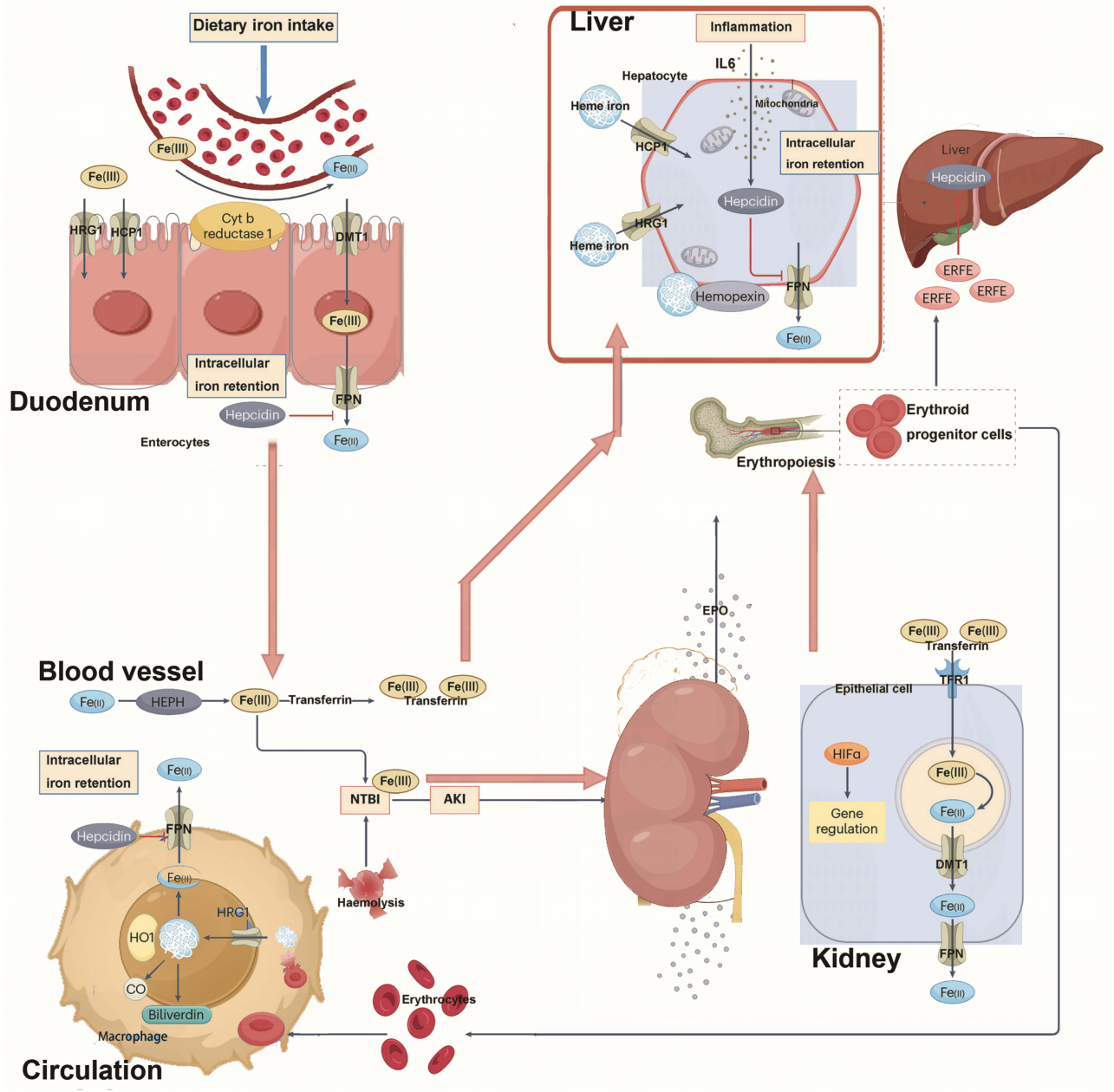

Figure 2 Schematic Diagram Illustrating the Core Regulatory Network of Systemic Iron Cycling and Cellular Iron Metabolism, and Its Association with Pathological Disorders. [Symbols present in the figure artwork are defined as follows: Lines terminating with a perpendicular bar (−|) represent inhibitory effects (e.g, hepcidin-mediated downregulation or degradation of ferroportin, FPN). Red arrows (→ or ↑) indicate the effects of iron metabolic pathways on organs or tissues (inter-organ regulatory influences). Black arrows represent signaling pathways. Solid arrows in other colors denote the direction of iron transport, uptake, release, or intracellular processes. In this figure, arrows of different colours represent the direction of iron transport, regulatory signals, cellular processes, or pathway flows (with distinct colours used to distinguish specific physiological or pathological routes). Red lines ending with a perpendicular bar (−|) denote inhibitory or negative regulatory actions. This schematic systematically integrates the physiological regulatory network of mammalian iron homeostasis with the mechanisms of its pathological dysregulation, providing a core theoretical framework for understanding how iron metabolic imbalance mediates ferroptosis and contributes to the onset and progression of cardiovascular diseases. Under physiological conditions, dietary iron is absorbed by duodenal enterocytes through divalent metal transporter 1 (DMT1) and cytochrome b reductase 1 (Cyt b reductase 1), then released into the circulation via ferroportin (FPN). It subsequently binds to transferrin and is distributed throughout the body. The liver serves as the central hub of systemic iron homeostasis by secreting hepcidin, which targets ferroportin for degradation, thereby negatively regulating intestinal iron absorption and macrophage iron release; this process is modulated by multiple physiological factors, including the inflammatory cytokine IL-6 and erythroferrone (ERFE). Macrophages maintain circulating iron pool homeostasis by phagocytosing senescent erythrocytes and recycling heme iron through heme oxygenase 1 (HO-1). The kidney participates in iron metabolism via hypoxia-inducible factor α (HIFα)-mediated gene regulation, while the EPO-ERFE axis coordinates erythropoiesis with iron supply. In pathological states, factors such as inflammation, hemolysis, and acute kidney injury (AKI) disrupt iron homeostasis, leading to accumulation of non-transferrin-bound iron (NTBI) and overload of the intracellular labile iron pool (LIP). This activates the Fenton reaction and the ferroptosis pathway, providing a critical pathological basis for the development of cardiovascular diseases including myocardial infarction, heart failure, and atherosclerosis. By comprehensively depicting the dynamic regulatory network of iron metabolism and its key pathological disruption points, the schematic establishes a solid theoretical foundation for research on cardiovascular disease prevention and treatment targeting the iron homeostasis–ferroptosis axis. The figure was created with BioRender.

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and modulating cellular susceptibility to ferroptosis.[12] Mitochondrial metabolism is deeply coupled to the ferroptosis process via the TCA cycle. Studies have confirmed that inhibition of glutaminolysis significantly modulates ferroptosis progression, and mitochondrial metabolic dysfunction further exacerbates cellular susceptibility to ferroptosis.[23]

As the ultimate executor of ferroptosis, mitochondrial iron homeostasis imbalance and structural disruption represent the core hallmarks of the execution phase. Mitochondria serve as the most important intracellular iron storage organelle besides ferritin, and their iron-handling capacity directly regulates the intracellular labile iron pool (LIP) level and the ferroptosis triggering threshold. Mitochondrial iron overload can directly initiate the Fenton reaction within the organelle, causing lipid peroxidation damage to the mitochondrial membrane system while releasing large amounts of ROS and free iron into the cytosol. This further amplifies whole-cell oxidative stress and the lipid peroxidation cascade, markedly lowering the ferroptosis triggering threshold. During the execution phase of ferroptosis, mitochondria undergo a series of characteristic morphological changes, including increased mitochondrial membrane density, cristae rupture and shrinkage, and outer membrane rupture. These structural disruptions directly lead to mitochondrial functional collapse, the release of pro-death molecules and metabolites, and ultimately the irreversible breakdown of cellular homeostasis, thereby completing the final execution of ferroptosis.

In summary, mitochondrial energy metabolism, iron handling, and lipid metabolism regulation are tightly coupled with both the initiation and execution of ferroptosis. To systematically elucidate the specific regulatory relationship between mitochondria and ferroptosis, we have constructed a core mechanistic diagram of mitochondrial involvement in ferroptosis (Figure 3). This diagram clearly depicts the dual regulatory pathways through which mitochondria function as both initiator and executor of ferroptosis and identifies the key molecular nodes at which mitochondrial metabolism and iron handling control the ferroptosis threshold, thereby offering new research perspectives for exploring targeted regulation of ferroptosis.

Alternative Pathways Regulating Ferroptosis

Beyond the canonical system Xc^-–GSH–GPX4 axis, other regulatory mechanisms have been identified that protect against membrane lipid peroxidation, including the FSP1–CoQ10–vitamin K and GCH1–BH2/BH4 pathways.

Regulation by the FSP1–$CoQH_2$ Axis

A novel ferroptosis-regulatory protein named ferroptosis suppressor protein 1 (FSP1) was found to operate independently of GPX4. FSP1 localizes to the plasma membrane and exerts protective effects by generating the reduced form of coenzyme Q10 ($CoQ10H_2$). $CoQ10H_2$ captures and neutralizes lipid peroxyl radicals, converting PLOOH into PLOH, thereby reducing ROS accumulation and blocking ferroptosis.[26] This pathway functions independently of GPX4 and offers an additional layer of protection against lipid peroxidation.

Regulation by the GCH1–BH4 Axis

GTP cyclohydrolase I (GCH1), another GPX4-independent regulator, plays a significant role in ferroptosis control.[28] GCH1 produces tetrahydrobiopterin (BH4), which can reduce ROS by facilitating the conversion of phenylalanine to tyrosine and contributing to the synthesis of CoQ10.[29] BH4 and its derivative BH2 provide redox-active molecules that counteract ferroptosis and support cellular survival under oxidative stress.

MBOAT1/2 in Ferroptosis Suppression

Membrane-bound O-acyltransferase domain-containing proteins 1 and 2 (MBOAT1/2) represent newly identified regulators of phospholipid remodeling. These enzymes are directly controlled by steroid hormone receptors and function by selectively incorporating monounsaturated fatty acids (MUFAs) into lyso-phosphatidylethanolamine (lyso-PE). By increasing the proportion of saturated fatty acid-containing phospholipids and decreasing PUFA-PLs in the membrane, MBOAT1/2 reduce substrate availability for lipid peroxidation and inhibit ferroptosis.[36,37]

Nrf2-Mediated Ferroptosis Control

Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the transcription of numerous antioxidant genes. It enhances ferroptosis resistance by upregulating GPX4 and SLC7A11, thereby promoting GSH synthesis and converting lipid hydroperoxides into non-toxic lipid alcohols.[30,31] Nrf2-mediated protection involves two main strategies: (1) direct reduction of

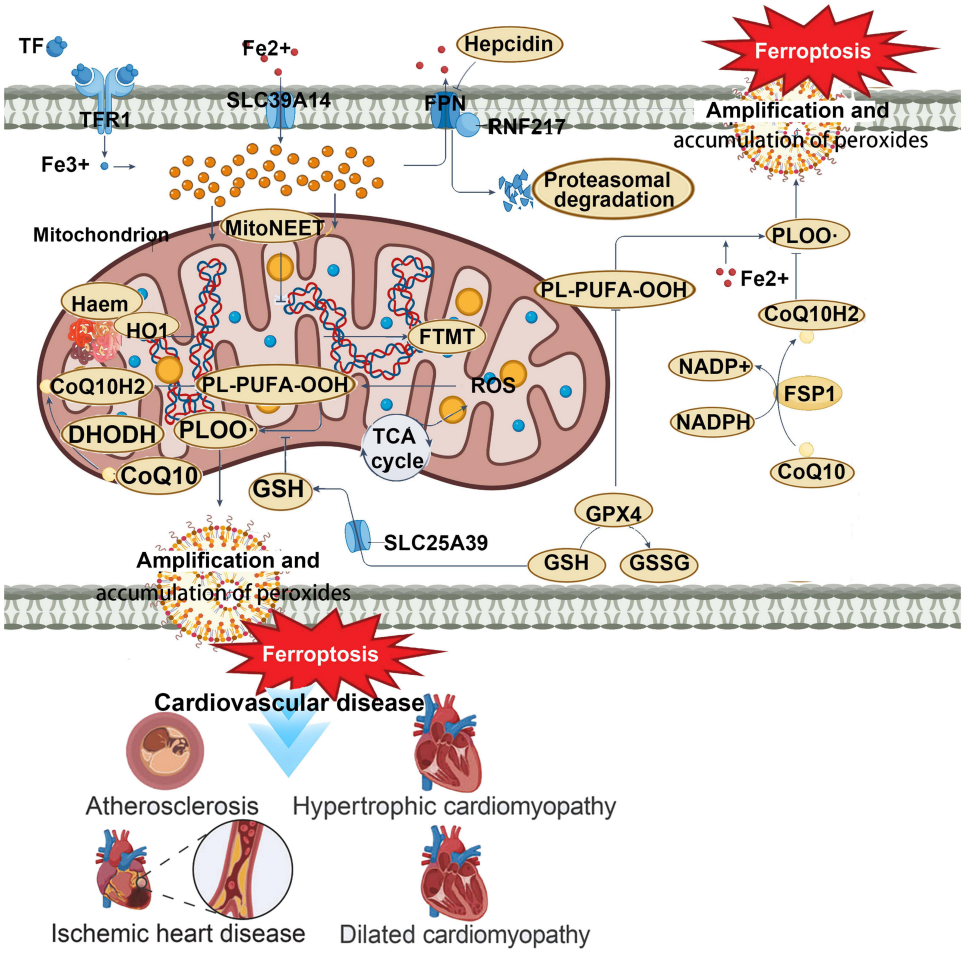

Figure 3 Schematic Diagram of the Core Mechanisms by Which Mitochondria Participate in the Pathogenesis and Progression of Cardiovascular Diseases. [Mitochondria serve as the central regulatory organelle in ferroptosis, exerting a dual critical role as both initiator and executor throughout its progression. Through the coordinated integration of energy metabolism, iron handling capacity, and lipid metabolic homeostasis, mitochondria precisely govern the triggering threshold of ferroptosis—including the critical concentrations of the intracellular labile iron pool (LIP) and phospholipid hydroperoxides (PLOOH)—and function as the key hub linking iron metabolic disorders to myocardial injury in cardiovascular diseases. As a primary initiator of ferroptosis, the mitochondrial tricarboxylic acid (TCA) cycle and electron transport chain (ETC) represent the principal intracellular sources of reactive oxygen species (ROS). Electrons leaking from the ETC are converted by superoxide dismutase (SOD) into hydrogen peroxide (H_2O_2), which reacts with free Fe^{2+} through the Fenton reaction to generate highly reactive hydroxyl radicals (·OH), thereby directly initiating the lipid peroxidation cascade in polyunsaturated fatty acids (PUFAs). At the same time, mitochondrial fatty acid β-oxidation supplies abundant substrates for lipid peroxidation, while metabolic enzymes such as citrate synthase (CS) and acyl-CoA synthetase family member 2 (ACSF2) regulate fatty acid activation and synthesis. The AMPK signaling pathway further amplifies PUFA production, collectively modulating cellular susceptibility to ferroptosis. Dysregulation of glutaminolysis additionally lowers the ferroptosis triggering threshold and exacerbates oxidative stress injury. As the ultimate executor of ferroptosis, mitochondrial iron overload directly drives the Fenton reaction in situ, amplifying whole-cell oxidative stress and lipid peroxidation. This is accompanied by the characteristic morphological changes of ferroptosis—increased mitochondrial membrane density, cristae rupture and shrinkage, and outer membrane rupture—ultimately leading to mitochondrial functional collapse and irreversible loss of cellular homeostasis. The figure comprehensively illustrates the full-chain regulatory network through which mitochondria participate in ferroptosis and delineates the key molecular nodes at which mitochondrial metabolism, iron handling, and oxidative stress control the ferroptosis threshold. It thereby provides an essential theoretical framework for understanding the pathological mechanisms of ferroptosis-mediated cardiovascular diseases, including myocardial ischemia-reperfusion injury, heart failure, atherosclerosis, and cardiomyopathy, as well as for developing novel prevention and treatment strategies targeting the mitochondria–ferroptosis axis. The figure was created with BioRender.

ROS via biosynthesis of reductive molecules, and (2) generation of antioxidants that react with lipid peroxides, offering multi-targeted regulation of ferroptosis.

Ferroptosis and Subcellular Organelles

Ferritinophagy, a selective autophagic degradation of ferritin, contributes to iron release and oxidative injury. This process is mainly executed by lysosomes, where ferritin—comprising FTH1 and FTL1 —undergoes proteolytic breakdown.[38] NCOA4, a conserved C-terminal domain-containing coactivator, recognizes FTH1 and facilitates its interaction with lysosomes, promoting ferritin degradation and iron mobilization,[39] which exacerbates oxidative damage. Lipophagy, a selective

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autophagic process involving lysosomal degradation of lipid droplets, also influences ferroptosis.[40] The small GTPase RAB7A, a member of the RAS oncogene family, is essential for this process. Lipid droplets store PUFAs in the form of triacylglycerols (TAGs), effectively segregating them from membrane phospholipids and preventing lipid peroxidation. Therefore, lipid droplet sequestration protects against ferroptosis. However, lipophagy-induced degradation of lipid droplets promotes PUFA release and enhances ferroptosis. Mitochondrial dysfunction is also closely associated with ferroptosis. Morphological changes—including mitochondrial shrinkage, cristae loss, and membrane permeabilization—are hallmarks of ferroptotic injury.[41] Notably, mitochondrial-targeting compounds such as XJB-5-131 and JP4-039 exhibit protective effects against ferroptosis. Moreover, mitochondrial metabolism actively participates in ferroptosis. The TCA cycle and electron transport chain enhance cystine deprivation-induced ferroptosis, whereas loss of fumarate hydratase activity inhibits this process.[42] Oligomerization of voltage-dependent anion channels (VDACs) leads to mitochondrial dysfunction and promotes ferroptosis.[43] In summary, Ferroptosis is a highly regulated and complex form of cell death governed by iron metabolism, lipid peroxidation, and redox control. Understanding the molecular determinants of ferroptosis—particularly the roles of iron-handling proteins, lipid-modifying enzymes, and redox-sensitive transcription factors—is critical for uncovering new therapeutic targets in cardiovascular diseases. As research continues to reveal the intricate crosstalk between ferroptosis and various subcellular compartments, it becomes increasingly evident that targeting ferroptosis may offer novel strategies for cardioprotection and vascular health. To clarify the key regulatory role of ferritinophagy in the ferroptosis pathway, we summarized the pathogenic mechanism of ferritinophagy in ferroptosis (Figure 4). This figure systematically illustrates the initiation, execution process of ferritinophagy and its molecular link with ferroptosis, providing a critical theoretical basis for exploring the targeted intervention of ferritinophagy to inhibit ferroptosis.

Role and Mechanisms of Ferroptosis in Cardiac Diseases

Emerging evidence indicates that ferroptosis plays a critical role in the development and progression of cardiovascular diseases (CVDs). This section focuses on the mechanistic involvement of ferroptosis in various cardiac pathologies, including heart failure (HF), myocardial ischemia–reperfusion (I/R) injury, diabetic cardiomyopathy (DCM), doxorubicin (DOX)-induced cardiotoxicity, sepsis-associated myocardial dysfunction, and arrhythmias.

Ferroptosis in Heart Failure

Heart failure (HF) is a severe clinical syndrome resulting from structural or functional impairments of the heart, often representing the end-stage manifestation of diverse cardiac diseases.[44] With increasing global aging and rising prevalence of metabolic comorbidities such as obesity, hypertension, and diabetes, the number of patients with heart failure with preserved ejection fraction (HFpEF) continues to grow, becoming the predominant HF subtype. Despite its high morbidity and mortality, effective therapeutic strategies remain limited due to the complex pathophysiology of HF.[44] Iron overload has been linked to increased reactive oxygen species (ROS) generation, which attacks genomic material, promotes lipid peroxidation (LPO), disrupts endogenous antioxidant defenses, and reduces glutathione (GSH) levels—hallmarks of ferroptosis.[15] These oxidative stress responses contribute to a systemic pro-inflammatory state that damages cardiomyocytes and impairs cardiac function. The interplay between inflammation, ferroptosis-related redox imbalance, and HF suggests a potential role for ferroptosis in disease progression. Indeed, iron dyshomeostasis can induce ferroptotic cell death through lipid peroxidation, oxidative stress, and inflammatory pathways, thereby contributing significantly to HF pathogenesis.[45]

Iron Dyshomeostasis and Heart Failure

Endothelial cell injury is a key initiating event in myocardial inflammation. Most HF patients exhibit impaired microvascular function in the coronary circulation,[46] and ferroptosis has been implicated in endothelial dysfunction. Iron overload contributes to ROS overproduction, leading to mitochondrial damage and compromised endothelial integrity.[47] Excess free Fe^{2+} in the cytoplasm increases ROS levels, impairing mitochondrial function and promoting endothelial dysfunction. Furthermore, studies have shown that iron overload not only induces apoptosis but also facilitates ferroptosis, accelerating endothelial calcification.[48] While ROS may serve physiological roles at low concentrations, excessive ROS production combined with inadequate antioxidant capacity promotes HF progression. As one of the primary sources of ROS, iron

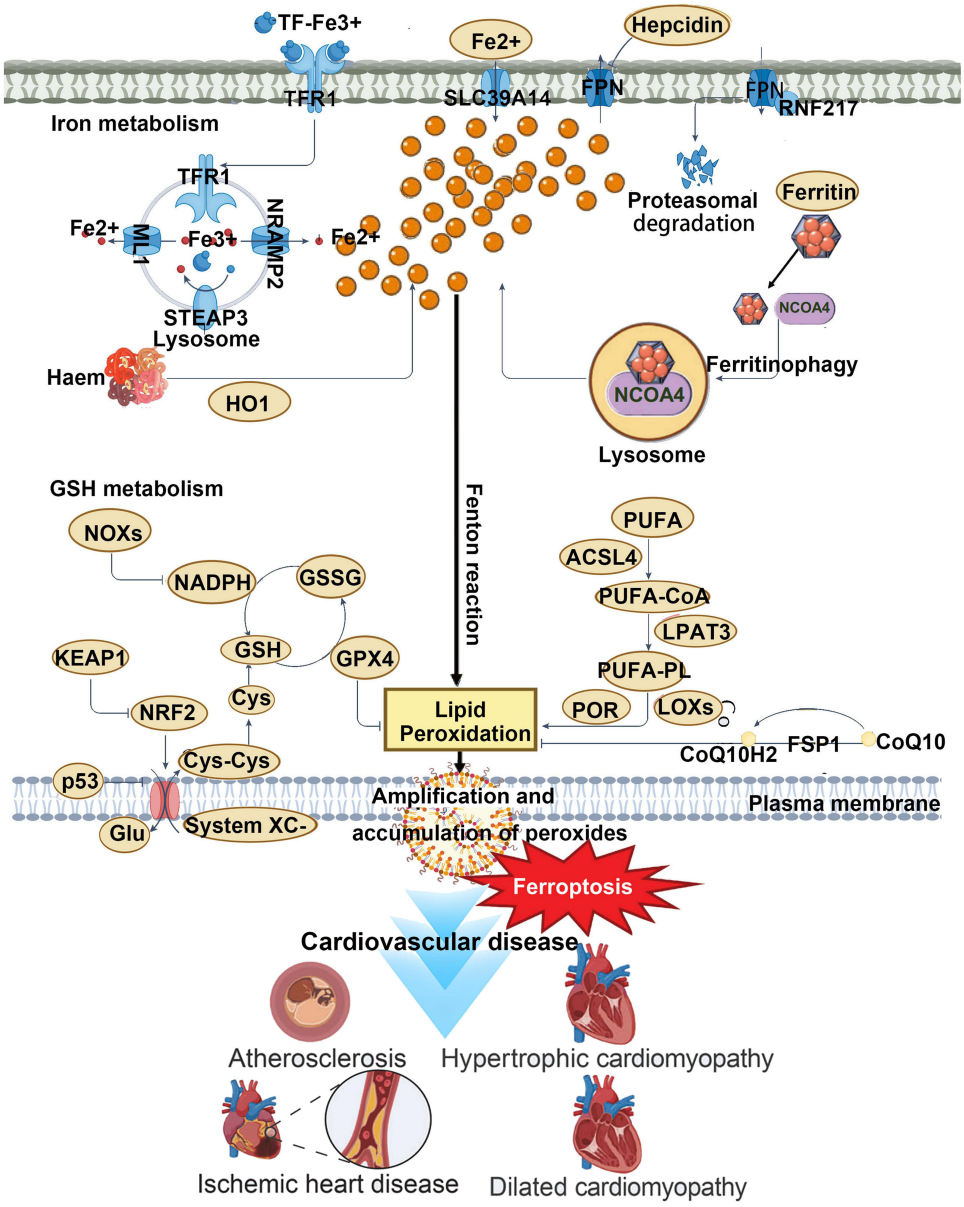

Figure 4 A Schematic Diagram Illustrating the Core Mechanism by Which the "Iron Metabolism–Antioxidant Defense–Lipid Metabolism Network" Regulates Ferroptosis and Mediates the Pathogenesis and Progression of Cardiovascular Diseases [The figure systematically integrates the three core regulatory pathways of ferroptosis—iron metabolism, antioxidant defense, and lipid metabolism—while providing a comprehensive illustration of the molecular mechanisms by which iron homeostasis imbalance drives ferroptosis and contributes to the onset and progression of various cardiovascular diseases. It thereby offers a central theoretical framework for understanding the multifaceted roles of ferroptosis in cardiovascular pathology. In the iron metabolism pathway, cells internalize transferrin-bound iron ($TF\text{-}Fe^{3+}$) via transferrin receptor 1 (TFR1), followed by reduction to Fe^{2+} by STEAP3. Additional iron uptake occurs through direct import of Fe^{2+} via SLC39A14 and heme degradation mediated by heme oxygenase 1 (HO1), collectively replenishing the intracellular labile iron pool (LIP). Hepcidin and RNF217 negatively regulate cellular iron export by promoting the degradation of ferroportin (FPN), while NCOA4-mediated ferritinophagy degrades ferritin to release Fe^{2+}, thereby further amplifying iron overload. Excess Fe^{2+} generates large amounts of reactive oxygen species (ROS) through the Fenton reaction, serving as the primary trigger of ferroptosis. The antioxidant defense pathway involves the cystine/glutamate antiporter (System Xc^-, negatively regulated by p53), which imports cysteine for glutathione (GSH) synthesis. GSH maintains the activity of glutathione peroxidase 4 (GPX4), the key enzyme that suppresses lipid peroxidation. The NRF2-KEAP1 pathway and NOXs-NADPH axis coordinately regulate the antioxidant system, while ferroptosis suppressor protein 1 (FSP1) provides an independent parallel defense by regenerating $CoQ_{10}H_2$. In the lipid metabolism pathway, polyunsaturated fatty acids (PUFAs) are activated by ACSL4 and esterified by LPCAT3 to form membrane-bound polyunsaturated fatty acid-containing phospholipids (PUFA-PLs). These undergo lipid peroxidation catalyzed by lipoxygenases (LOXs) and POR, constituting the core execution step of ferroptosis. When iron overload, antioxidant system impairment, and accumulation of lipid peroxidation substrates act synergistically, they trigger amplified lipid peroxidation cascades that ultimately initiate ferroptosis. Excessive activation of ferroptosis drives the onset and progression of multiple cardiovascular diseases, including atherosclerosis, hypertrophic cardiomyopathy, ischemic heart disease, and dilated cardiomyopathy. By clearly depicting the full regulatory network of ferroptosis and its pathological links to cardiovascular diseases, the figure establishes a solid theoretical foundation for the development of novel therapeutic strategies targeting the ferroptosis–iron homeostasis axis in cardiovascular disease. The figure was created with BioRender.

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generates hydroxyl radicals via Fenton chemistry and functions as a cofactor for several enzymes involved in LPO. Therefore, iron-induced endothelial dysfunction may be a key contributor to HF pathophysiology.

Macrophage Iron Overload Promotes Myocardial Inflammation and Fibrosis

Cardiac macrophages play a central role in maintaining iron homeostasis under normal conditions by phagocytizing aged erythrocytes and recycling iron.[49] During HF, injured cardiomyocytes release hemoglobin, increasing local iron availability and promoting macrophage iron uptake.[49] Iron-loaded macrophages exhibit altered polarization dynamics: they display elevated M1 markers and reduced M2 phenotypes, exacerbating inflammation and fibrotic remodeling.[50] Excess ROS generated by iron overload enhances the activity of p300/CBP acetyltransferase, leading to p53 acetylation and promoting M1 polarization of macrophages.[51] These findings reinforce the hypothesis that iron-overloaded macrophages drive myocardial inflammation and fibrosis, thus contributing to HF progression. Moreover, ferroptosis-related modulators and pharmacological agents have been shown to influence cardiac fibrosis. Mixed-lineage kinase 3 (MLK3) regulates oxidative stress through NF-κB/NLRP3 and JNK/p53 signaling, inducing ferroptosis and fibrosis during late-stage chronic HF.[52] These data underscore the importance of targeting ferroptosis to mitigate maladaptive remodeling in failing hearts.

Lipid Peroxidation and Heart Failure

Obesity and dysregulated lipid metabolism are major contributors to HF development. Adiponectin receptor agonists improve myocardial fatty acid oxidation and reduce fatty acid transport, thereby attenuating fibrosis and ameliorating HF progression in mouse models.[53] Lim et al demonstrated that elevated nitric oxide (NO) levels—driven by inducible nitric oxide synthase (iNOS) upregulation—induce nitrosative stress and promote lipid peroxidation, contributing to ferroptosis and HF pathology.[54] Further investigation revealed that the NO-driven Xbp1s-FoxO1 axis is crucial in HF pathogenesis. Genetic depletion of FoxO1 or overexpression of spliced Xbp1s improves diastolic dysfunction and exercise tolerance in HF mice, while reducing myocardial lipid accumulation.[55] Additionally, increased levels of H_2O_2 and MDA, a terminal product of LPO, were observed in obese HF rat models,[56] reinforcing the role of lipid peroxidation in HF progression. These findings suggest that LPO serves as a key driver in HF pathophysiology, linking iron metabolism, oxidative stress, and ferroptosis into a unified mechanism.

Targeting Ferroptosis as a Therapeutic Strategy for Heart Failure

Ferroptosis is characterized by iron overload, accumulation of lipid peroxidation products, and unsaturated fatty acid metabolism. Notably, this form of cell death cannot be inhibited by classical apoptotic or necrotic inhibitors, underscoring its unique molecular signature and therapeutic potential in HF.[57] The SGLT2 inhibitor empagliflozin exerts beneficial effects through multiple mechanisms, including suppression of inflammation, reduction of oxidative stress, improvement of endothelial and cardiomyocyte function, and attenuation of ventricular stiffness and remodeling.[58] Empagliflozin suppresses ferroptosis in DOX-treated mouse hearts by modulating NLRP3 and MyD88-related pathways, thereby improving myocardial inflammation and fibrosis and restoring cardiac function.[58] Similarly, the antidiabetic drug iglitin was found to enhance GPX4 expression, alleviate lipid peroxidation, and protect against ferroptosis in HF models.[59] Iglitin also reduces body weight, visceral fat deposition, and systemic inflammation while improving glucose tolerance, further supporting its dual benefits in HF treatment. Proteomic analysis by Ma et al showed that the SGLT2 inhibitor canagliflozin exerts its protective effect in HF rats primarily through inhibition of ferroptosis, suggesting that targeting ferroptosis may represent a novel and viable therapeutic approach.[60]

Modulation of Iron Metabolism for Heart Failure Therapy

Iron deficiency is a frequent comorbidity in HF patients. Supplementation with iron carboxymaltose improves ferritin levels, enhances endothelial function, and alleviates diastolic dysfunction, highlighting the importance of iron balance in HF management.[61] Fang et al further demonstrated that ferritin —a key regulator of cardiac iron homeostasis—protects cardiomyocytes from ferroptosis.[62] Given the role of cardiac fibrosis in diastolic dysfunction and HF progression, molecules like SIRT3 (silent information regulator 3) emerge as promising therapeutic targets. SIRT3 deletion exacerbates ferroptosis and reduces GPX4 expression in HF mice.[63] Conversely, apelin, an endogenous ligand of the APJ receptor, inhibits ferroptosis by modulating the IL-6/STAT3/GPX4 pathway, thereby protecting against angiotensin II–induced microvascular endothelial injury, fibrosis, and contractile dysfunction.[64] Additionally, long-term administration of levosimendan, a calcium sensitizer used in acute HF, reduces ferroptosis and improves cardiac function in animal models of metabolic syndrome, including obesity and hypertension.[64]

Antioxidants such as α-lipoic acid neutralize multiple ROS species, chelate transition metals, and regenerate endogenous antioxidants such as GSH, vitamin C, and vitamin E, offering protection against ferroptosis-mediated cardiac injury.[64] Lipocalin, a member of the adipokine family, interacts with various intracellular signaling pathways to regulate ventricular remodeling.[65] Studies show that adiponectin deficiency exacerbates susceptibility to diastolic HF and ventricular dysfunction,[66] indicating that lipid-binding factors may act as upstream regulators of ferroptosis and HF progression. In summary, ferroptosis plays a pivotal role in the pathogenesis of cardiovascular diseases. Targeting ferroptosis offers a promising avenue for developing novel therapies for HF and related cardiac disorders. As HF prevalence rises alongside increasing morbidity and mortality, few interventions have proven effective. However, emerging evidence demonstrates that ferroptosis inhibition via canagliflozin and other agents represents a new frontier in HF research. Understanding the causal relationship between ferroptosis and HF, and identifying precise regulatory mechanisms, will be essential for advancing targeted therapeutics in the clinic.

Ferroptosis in Myocardial Ischemia–Reperfusion Injury

Myocardial infarction is a leading cause of global mortality, driven by the pathophysiological process of coronary artery occlusion and subsequent myocardial ischemia.[67] Timely reperfusion through thrombolytic therapy or percutaneous coronary intervention (PCI) remains the most effective strategy for salvaging ischemic myocardium and limiting infarct size.[67] However, reperfusion itself can induce additional injury—termed myocardial ischemia–reperfusion (I/R) injury, which contributes to cardiomyocyte death via multiple mechanisms, including necrosis, apoptosis, autophagy, and increasingly recognized, ferroptosis.[68] Despite advances in treatment, effective interventions that mitigate I/R injury remain limited, making it a major focus in cardiovascular research. MI/R injury comprises four key pathological components: reperfusion arrhythmias (RA), myocardial stunning, microvascular obstruction (MVO), and lethal reperfusion injury, all primarily linked to oxidative stress, inflammation, calcium overload, mitochondrial permeability transition pore (mPTP) opening, and rapid pH normalization during reperfusion.[69] During early reperfusion, massive ROS production disrupts redox homeostasis and leads to various toxic effects. Excess ROS initiates lipid peroxidation, compromising membrane integrity and cellular function. Additionally, ROS activates NF-κB, triggering inflammatory cascades that amplify tissue damage.[70,71] Although several antioxidant therapies—including vitamin C/E, polyphenols, ascorbic acid, N-acetylcysteine, and deferoxamine (DFO) —have been tested clinically, their efficacy remains inconsistent, highlighting the need for more targeted approaches.[69] Inflammatory responses triggered by MI/R are typically sterile, initiated by damaged myocytes releasing chemokines that recruit neutrophils into the infarcted area.[70] Neutrophil activation results in the release of multiple cytokines and reactive species. While this response aids in clearing debris and initiating wound healing, it also exacerbates inflammation through damage-associated molecular pattern (DAMP) signaling, further damaging cardiac tissue. Activated neutrophils generate NADPH oxidase-derived ROS, respiratory bursts, and myeloperoxidase, contributing to oxidative injury and secondary cell death.[70] Calcium overload is another hallmark of MI/R injury. During ischemia, oxygen depletion forces cells to rely on anaerobic glycolysis, causing H^+ accumulation and Na^+/H^+ exchanger overactivation. This promotes excessive Na^+ influx, which subsequently drives Ca^{2+} entry via the Na^+/Ca^{2+} exchanger. Upon reperfusion, extracellular H^+ removal increases the transmembrane proton gradient, and sarcoplasmic reticulum Ca^{2+} pumps enhance cytosolic Ca^{2+} levels.[72] Elevated intracellular Ca^{2+} induces mitochondrial permeability transition pore (mPTP) opening, leading to mitochondrial depolarization, release of apoptogenic factors, and ultimately cardiomyocyte death. In parallel, Ca^{2+} overload activates calpains, proteases that degrade myofibrils and worsen myocardial injury.[72] The mPTP—a non-selective channel located between the inner and outer mitochondrial membranes—undergoes structural and functional changes upon opening, such as increased permeability, loss of membrane potential, disruption of the electron transport chain, matrix swelling, and membrane rupture.[69] Under normal ischemic conditions, mPTP remains closed but opens rapidly upon reperfusion in response to Ca^{2+} overload, oxidative stress, ATP depletion, and pH recovery. Pharmacological inhibition of mPTP—such as with the immunosuppressant cyclosporin A (CsA) —can reduce infarct size by approximately 40–50% when administered at the onset of reperfusion.[73] Moreover, strategies such as acidic buffer perfusion, Na^+/H^+ exchange inhibitors, or ischemic post-conditioning can effectively limit mPTP opening and Ca^{2+} overload, thereby reducing MI/R injury.[74]

Role of Antioxidant Systems in Ferroptotic Cell Death During MI/R Injury

Oxidized phospholipids, particularly oxidized phosphatidylethanolamine (PEox), serve as predictive biomarkers of ferroptosis. Using gas cluster ion beam secondary ion mass spectrometry (GCIB-SIMS), Sparvero et al directly detected PEox in H9C2 cells, providing direct evidence of ferroptosis in cardiomyocytes.[75] Experimental studies have confirmed that ferroptosis occurs during reperfusion and intensifies with prolonged reperfusion time,[76] while clinical data show that pre-reperfusion administration of deferoxamine (DFO) significantly reduces oxidative stress and improves cardiac function in both chronic coronary artery disease (CAD) and ST-segment elevation myocardial infarction (STEMI) patients.[77] These findings collectively indicate that ferroptosis plays a central role in MI/R injury, supported by both preclinical models and human clinical observations. As a critical upstream antioxidant enzyme, GPX4 regulates ferroptosis and oxidative stress. In rat MI/R models, Fe^{2+} and MDA levels rise progressively with reperfusion duration, whereas GPX4 expression declines.[76] Administration of liproxstatin-1, a specific ferroptosis inhibitor, elevates GPX4 levels and suppresses ferroptosis, attenuating reperfusion injury. The tumor suppressor p53 is upregulated during MI/R injury. p53 acts on SLC7A11, suppressing the system Xc^{-}–GSH–GPX4 axis and inducing ferroptosis.[77] The deubiquitinase USP22 counteracts p53 activity by modulating SIRT1, a NAD^{+}-dependent deacetylase, thereby inhibiting ferroptosis and offering protection against MI/R injury.[77] Another major regulator, Nrf2, functions as a master transcription factor in antioxidant defense. Activation of Nrf2-related pathways has shown protective effects in MI/R injury. For example, etomidate enhances nuclear translocation of Nrf2 and upregulates its downstream target heme oxygenase-1 (HO-1), activating the Nrf2/HO-1 pathway, increasing GSH activity, and restoring GPX4 expression to inhibit ferroptosis and reduce myocardial injury.[78] However, some studies suggest that HO-1 may paradoxically promote ferroptosis by increasing intracellular iron availability and facilitating erastin-induced lipid peroxidation in cancer cells.[79] This dual role underscores the complexity of redox regulation and highlights the importance of context-dependent modulation of ferroptosis in MI/R injury.

Iron Overload and Ferroptosis in MI/R Injury

Iron dyshomeostasis is a key contributor to ferroptosis in MI/R injury. DNA methyltransferase 1 (DNMT1) suppresses NCOA4-mediated ferritinophagy, thereby reducing intracellular iron levels and limiting ferroptotic damage.[80] Beyond ferritin, other iron-handling proteins contribute to MI/R injury. In hypoxia/reoxygenation (H/R) models, exosomal regulation of TFR1 has been observed. Exosomes inhibit TfR1 expression, reduce iron uptake, and alleviate H/R-induced cardiomyocyte injury.[81] In rat MI/R models, the USP7–p53–TFR1 axis is activated: I/R injury upregulates USP7, stabilizes p53 by reducing its ubiquitination, and enhances TFR1 expression, thereby promoting iron uptake and ferroptosis.[82] Hepcidin, an endogenous regulator of systemic iron homeostasis, controls ferroportin (FPN1) degradation and thus intracellular iron retention. Hepcidin expression is elevated under ischemic and hypoxic conditions, likely regulated by hypoxia-inducible factor (HIF) signaling.[83] These findings highlight the dynamic regulation of iron metabolism during MI/R injury and suggest that targeting hepcidin or iron transporters may offer therapeutic benefits.

Lipid Peroxidation and Ferroptosis in MI/R Injury

Lipid metabolic dysregulation is a core feature of MI/R injury. Key enzymes involved in lipid peroxidation, such as ACSL4 and LPCAT3, are significantly upregulated in I/R myocardial tissue.[84] Inhibition of ACSL4 ubiquitination and degradation markedly alleviates ferroptosis and protects against MI/R injury. Lipoxygenases (ALOX15) catalyze arachidonic acid (AA) oxidation, promoting lipid peroxidation and ferroptosis. ALOX15 is upregulated following I/R injury, generating 15-hydroperoxy-eicosatetraenoic acid (15-HpETE)—a critical intermediate in AA oxidation. 15-HpETE promotes PGC-1α ubiquitination, impairing mitochondrial lipid peroxidation, morphology, and function, ultimately triggering ferroptosis.[85] Targeted inhibition of ALOX15 significantly restores PGC-1α protein levels, suppresses ferroptosis, and improves cardiac function after reperfusion.

Endoplasmic Reticulum Stress in Ferroptosis During MI/R Injury

The endoplasmic reticulum (ER) serves as a central hub for protein synthesis, folding, and modification. Under ischemic and hypoxic conditions, accumulation of unfolded or misfolded proteins activates the unfolded protein response (UPR), a signaling cascade known as ER stress (ERS).[69] Artesunate (ART), a ferroptosis inducer, interacts with the ATF4-mediated UPR, enhancing ferroptosis through the ATF4–CHOP–PUMA–p53 pathway, which promotes lipid peroxidation and triggers

ferroptosis in liver cancer cells.[86] Recent findings demonstrate that ER stress is enhanced during MI/R injury and contributes to myocardial damage. Notably, ferrostatin-1 administration significantly reduces ERS and cardiomyocyte death, indicating a role for ERS in ferroptosis and cardiac injury.[87]

Inflammation and Ferroptosis in MI/R Injury

Following myocardial infarction, DAMPs activate the nod-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, which matures and releases pro-inflammatory cytokines such as IL-1β and IL-18, driving sterile immune activation.[71] Immunohistochemical staining of human coronary artery specimens shows that NLRP3 expression correlates positively with PTGS2 (COX-2) and ACSL4 levels, both of which are core mediators of ferroptosis.[88] Inhibiting ferroptosis with Ferrostatin-1 significantly reduces NLRP3 activation and myocardial injury.[89] A recent study in porcine models of post-cardiac arrest syndrome similarly found that NLRP3 inhibition decreases ferroptosis and limits myocardial damage, reinforcing the link between inflammation and ferroptosis.[90] DAMPs also signal through Toll-like receptor 4 (TLR4) to activate NF-κB, inducing a cascade of inflammatory cytokine release. Multiple studies have established that ferroptosis is tightly integrated with NF-κB signaling. Dimethyl fumarate (DMF), an Nrf2 activator, enhances the expression of HO-1, NQO1, and GPX4 through the Nrf2/ARE/NF-κB axis, increasing cellular resistance to ferroptosis.[91] These findings support the concept that anti-inflammatory and antioxidant strategies targeting ferroptosis can provide significant myocardial protection during I/R injury.

Ferritinophagy and Autophagy-Mediated Ferroptosis in MI/R Injury

Autophagy, particularly ferritinophagy, has emerged as a key mediator of ferroptosis in MI/R injury. Embryonic lethal abnormal vision-like protein 1 (ELAVL1) and AMP-activated protein kinase (AMPK) regulate ferritinophagy and ferroptosis during I/R.[92,93] ELAVL1, transcriptionally activated by forkhead box protein C1 (FoxC1), binds Beclin-1 mRNA and promotes autophagy, thereby accelerating ferroptosis and exacerbating myocardial injury.[91] AMPK similarly regulates Beclin-1 and induces autophagy in an mTOR-independent manner.[92] AMPK-mediated autophagy enhances iron mobilization and lipid peroxidation, worsening ferroptosis and reperfusion injury.[92] Moreover, mTOR signaling intersects with iron metabolism by modulating transferrin receptor 1 (TfR1) and iron export. Thus, these regulatory pathways not only influence autophagy but also affect iron handling and ferroptotic susceptibility. Collectively, these findings suggest that targeting autophagy-induced ferroptosis could represent a novel therapeutic approach for MI/R injury.

In summary, ferroptosis, a form of regulated cell death dependent on iron and lipid peroxidation, actively participates in myocardial ischemia–reperfusion (MI/R) injury through multiple interconnected mechanisms involving antioxidant defenses, iron metabolism, lipid peroxidation, ER stress, and inflammatory signaling.[67,93] Despite progress in understanding these processes, many questions remain regarding how best to intervene therapeutically. Key regulators such as Nrf2 exhibit dual roles in redox balance and ferroptosis control, necessitating further mechanistic exploration. Additionally, ferroptosis often overlaps with other forms of regulated cell death, emphasizing the need for selective targeting strategies. Future investigations should focus on: (1) Elucidating the causal relationship between ferroptosis and MI/R injury; (2) Identifying robust and specific ferroptosis biomarkers; (3) Developing tissue-targeted delivery systems for iron chelators and antioxidants; (4) Integrating multi-omics and AI-based drug discovery to identify novel ferroptosis modulators; (5) Exploring combinatorial therapies that synergistically inhibit ferroptosis and other death pathways. By dissecting the complex interplay among iron metabolism, lipid oxidation, and redox signaling, we can refine therapeutic strategies to improve outcomes in patients undergoing reperfusion therapy for acute myocardial infarction. To clarify the specific regulatory role of ferroptosis in myocardial I/R injury, we summarized the interaction mechanism between ferroptosis and myocardial I/R injury (Figure 5). This figure systematically illustrates the induction of ferroptosis during myocardial I/R and its pathological effects on myocardial tissue, providing a targeted direction for the prevention and treatment of myocardial I/R injury.

Ferroptosis and Atherosclerosis

Atherosclerosis (As) is a chronic inflammatory disease that serves as a common pathological basis for multiple cardiovascular and cerebrovascular disorders.[94] Its progression involves lipid deposition, immune cell infiltration, and sustained oxidative stress, culminating in the formation of fatty streaks, fibrous plaques, and advanced lesions characterized by intraplaque

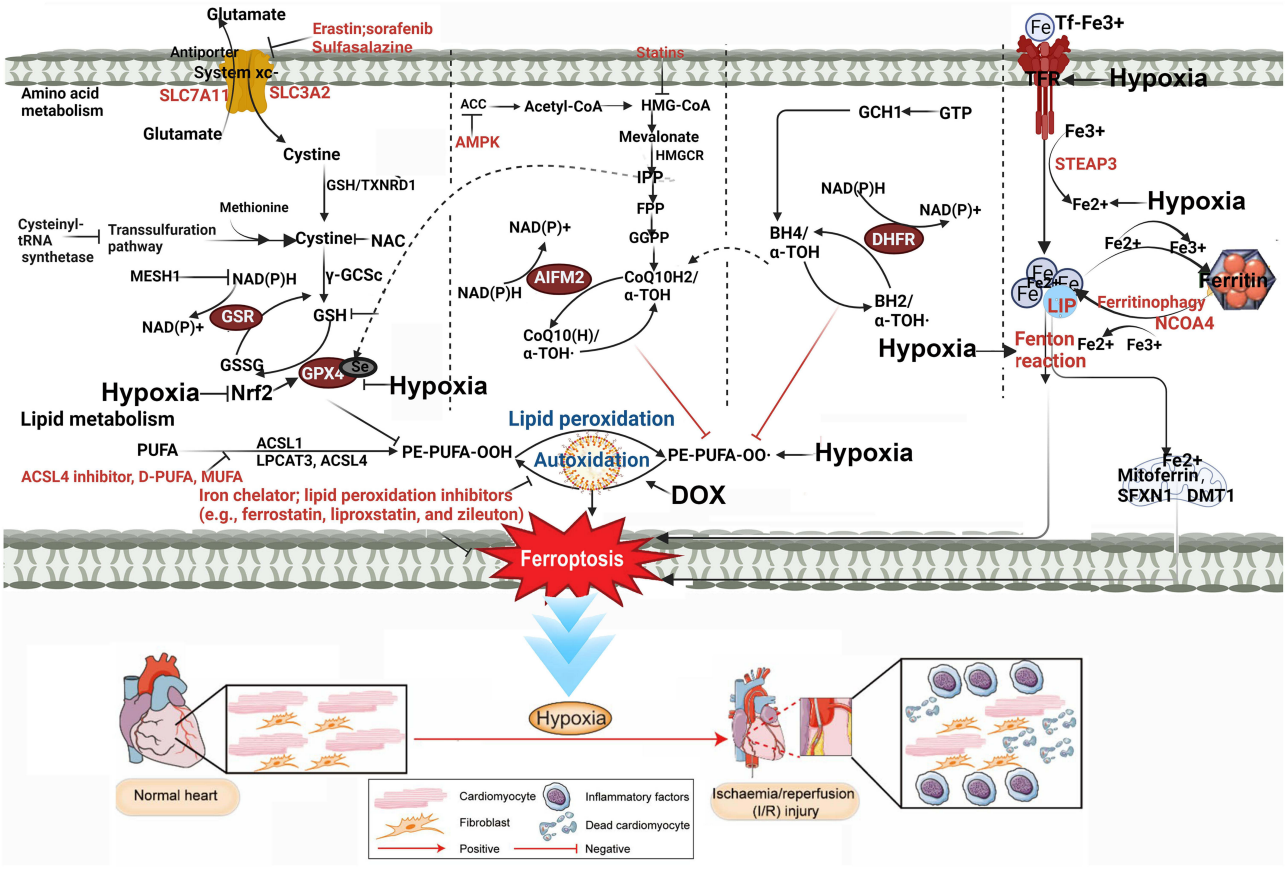

Figure 5 The role of ferroptosis in myocardial ischemia-reperfusion (I/R) injury. [Red lines terminating with a perpendicular bar (−|) represent inhibitory or negative regulatory effects (as shown in the lower panel inset legend). Red arrows (→) indicate positive regulation, activation, or promotion of pathological processes. Black solid arrows represent direct biochemical reactions, metabolic conversions, and molecular interactions within pathways. Dashed arrows denote indirect effects or regulatory relationships. The figure systematically illustrates the molecular mechanisms by which hypoxia regulates the four core pathways of ferroptosis through multiple dimensions—iron metabolism, cyst(e)ine/GSH/GPX4, FSP1/CoQ10, and GCH1/BH4/DHFR—thereby amplifying the lipid peroxidation cascade and triggering ferroptosis. It also delineates the complete pathological process through which the hypoxia–ferroptosis axis drives the transformation of the normal heart into myocardial ischemia-reperfusion (I/R) injury, while highlighting key targeted intervention nodes. In doing so, the figure provides a theoretical framework for understanding the role of ferroptosis in cardiovascular diseases and for developing preventive and therapeutic strategies against I/R injury. The figure was created with BioRender.

hemorrhage, rupture, and thrombosis. The interplay of various cellular and molecular mechanisms contributes to its complexity, posing major challenges for diagnosis and treatment.

Endothelial Cells and Ferroptosis

Endothelial dysfunction represents the initiating event in atherosclerosis development. Altered endothelial permeability facilitates the translocation of circulating low-density lipoprotein (LDL) into the subendothelial space, where iron overload —via ROS generation—converts LDL into oxidized LDL (ox-LDL), a key pathogenic factor in As.[95] Recent studies have demonstrated that ferroptosis is a critical regulator of endothelial function during atherogenesis. Bai et al showed that ox-LDL treatment of mouse aortic endothelial cells (MAECs) induces ferroptosis-like changes, including elevated expression of GPX4, SLC7A11, and increased lipid peroxidation, similar to Erastin-induced ferroptosis.[96] Administration of the specific ferroptosis inhibitor Ferrostatin-1 (Fer-1) significantly reduced iron content and lipid peroxidation levels, restored cellular viability, and decreased cell death rates, suggesting that ferroptosis inhibition can ameliorate endothelial dysfunction and delay As progression. Further evidence from PM2.5 exposure models also supports this link: PM2.5-treated endothelial cells exhibit features of iron overload, GSH depletion, and upregulated SLC7A11—hallmarks of ferroptosis—that were reversed by Fer-1 and iron chelators.[97] In vivo studies further confirm that ferroptosis mediates endothelial injury in As, while endothelial progenitor cells (EPCs) improve endothelial function and reduce AS risk.[98] In murine models, EPC-derived extracellular vesicles deliver miR-199a-3p to endothelial cells, suppressing specificity protein 1 (Sp1) and reducing GSH consumption,

ROS production, lipid peroxidation, and iron accumulation, thereby inhibiting endothelial ferroptosis and delaying atherogenesis.[98] These findings collectively suggest that endothelial ferroptosis contributes to As pathology, and that targeting this pathway may offer novel therapeutic opportunities.

Macrophages and Ferroptosis

Macrophages play a central role in As through their ability to polarize into distinct phenotypes under different microenvironmental stimuli. M1 macrophages are classically pro-inflammatory and accumulate around necrotic plaque cores, promoting disease progression.[99,100] Iron overload disrupts the balance between ROS generation and clearance, leading to excess ROS that promotes M1 polarization and accelerates inflammation. Notably, anti-inflammatory M2 macrophages often transition into M1 upon iron challenge, exacerbating inflammatory responses.[101] In vitro experiments demonstrate that coal dust-induced macrophage death is associated with elevated Fe^{2+} and malondialdehyde (MDA) levels, reduced GSH/GSSG ratios, and morphological signs of ferroptosis—all of which are mitigated by Fer-1.[102] Similarly, asbestos-exposed macrophages treated with excess iron show increased mortality and classic ferroptotic mitochondrial alterations identified via transmission electron microscopy.[103] Macrophages internalize ox-LDL via scavenger receptors, transforming into foam cells that drive plaque formation and instability.[104] Studies have shown that ox-LDL-induced foam cell death correlates with downregulation of SLC7A11 and GPX4, along with elevated ROS and MDA levels, indicating that foam cells undergo ferroptosis.[105] In late-stage As, inflammatory cytokines induce macrophage release of matrix metalloproteinases, which degrade collagen fibers in the fibrous cap, thinning it and increasing vulnerability to rupture.[106] These data highlight that macrophage ferroptosis is an integral component of As pathology, and that modulating this process may influence disease progression.

Vascular Smooth Muscle Cells and Ferroptosis

Vascular smooth muscle cells (VSMCs) are essential components of arterial walls, contributing to vessel stability through extracellular matrix synthesis and structural integrity maintenance.[107] Their proliferation and migration into the intima participate in early plaque formation. Experimental studies show that overexpression of antioxidant enzymes such as GPX3 and GPX4 enhances overall GPX activity, suppresses inflammation, and inhibits VSMC proliferation.[108] Smoking is an independent risk factor for As. Exposure of primary rat VSMCs to cigarette smoke extract leads to GSH depletion, GPX4 inactivation, and other ferroptotic markers—effects that can be reversed by Fer-1 and iron chelators.[109] This suggests that smoking may promote As through VSMC ferroptosis. ROS and lipid peroxidation products generated during ferroptosis alter VSMC behavior. Excess ROS induces oxidative stress and promotes a macrophage-like transformation of VSMCs, enhancing their migration into the intima and participation in unstable plaque formation.[110] Electrophilic end-products of lipid peroxidation, such as 4-hydroxynonenal (4-HNE) and acrolein, induce excessive autophagy in VSMCs, leading to cell death and fibrous cap thinning, which increases plaque fragility and rupture risk.[111] While these observations indicate that ferroptosis contributes to As lesion development and destabilization, definitive mechanistic links remain elusive. Some studies suggest that ferroptosis may slow As progression by inducing foam cell death, whereas others show that it accelerates As by damaging endothelial structure and function. These seemingly contradictory effects imply that ferroptosis exerts dual roles in As depending on disease stage. Whether these opposing outcomes arise from a single or multiple pathways remains to be determined.

Therapeutic Strategies Targeting Ferroptosis in Atherosclerosis

Given that ferroptosis is an iron-dependent form of regulated cell death driven by excessive lipid hydroperoxide accumulation and redox imbalance, iron chelators offer a promising strategy for intervention. Deferasirox, a clinically approved iron-lowering agent, has been used in hereditary hemochromatosis and Friedreich ataxia patients, where combined therapy with idebenone—a coenzyme Q10 analog—reduces cardiac hypertrophy, a major cause of mortality in Friedreich ataxia.[112] Another iron chelator, dexrazoxane, a cyclic derivative of EDTA, crosses the cell membrane and reduces labile iron pools, demonstrating cardioprotective effects in experimental models.[113] Tanshinone IIA, a compound derived from Salvia miltiorrhiza, protects vascular endothelial cells by activating the Nrf2 pathway, decreasing mitochondrial and cytosolic ROS, and slowing As progression.[114] Statins, widely used in cardiovascular medicine, also exert beneficial effects by inducing heme oxygenase-1 (HO-1) and suppressing hepcidin expression, thereby maintaining iron homeostasis and improving clinical outcomes.[115] Clinical trials have evaluated QXJYG (Qingxin Jieyu Granule), a traditional Chinese medicine formulation, showing reductions in cardiovascular events and inflammatory biomarkers in patients with stable coronary artery disease.[116]

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Mechanistically, QXJYG lowers LDL and triglyceride levels, stabilizes atherosclerotic plaques, and inhibits ferroptosis through activation of the GPX4/xCT signaling axis, reducing iron concentration and oxidative stress.[117] Moreover, angiotensin-converting enzyme 2 (ACE2) improves endothelial function and inhibits VSMC proliferation by modulating NF-κB, ERK1/2, and p38-MAPK pathways.[118] Simvastatin combined with resistance training more effectively improves cardiac function and reduces myocardial damage in heart failure patients than statin monotherapy alone—possibly through activation of the JAK/STAT3 pathway, reduction of mitochondrial injury, and suppression of inflammation.[119] Danggui Buxue Tang (DBT), a classical TCM formula, alleviates mitochondrial dysfunction, reduces ROS, and inhibits both ferroptosis and apoptosis via the HIF-1α signaling pathway, offering a novel approach to As management.[120] Collectively, these findings support the concept that targeting lipid peroxidation and redox imbalance may represent a new strategy for As prevention and treatment.

Therapeutic Potential of Ferroptosis Inhibitors in Atherosclerosis

Ferroptosis contributes to multiple pathological processes in As, making it an attractive target for therapeutic intervention. Based on their mechanism of action, ferroptosis inhibitors can be categorized into two major classes: (1) Iron Chelators: Agents such as deferoxamine mesylate, curcumin, and deferasirox inhibit ferroptosis by reducing intracellular Fe^{2+} levels and blocking Fenton reaction-driven ROS generation.[121,122] Deferoxamine and deferoxamine mesylate have been shown to alleviate As by regulating endothelial and macrophage ferroptosis,[123,124] while curcumin exhibits anti-inflammatory properties, inhibits VSMC proliferation and migration, and activates GPX4, offering dual protection against both inflammation and ferroptosis.[125] (2) Lipid Peroxidation Inhibitors: Small molecules such as Ferrostatin-1, Liproxstatin-1, and XJB-5-131 block lipid peroxidation and reduce ROS levels, thereby preventing ferroptosis and downstream vascular injury.[121] For example, Ferrostatin-1 suppresses lipid ROS and ox-LDL/Erastin-induced endothelial damage, reduces foam cell death, and ultimately attenuates As progression.[121] Beyond small molecule inhibitors, several regulatory proteins involved in ferroptosis have been implicated in As pathophysiology: (1) p53, a tumor suppressor gene, catalyzes glutaminolysis, depletes GSH, and sensitizes cells to ferroptosis.[126] Iron overload in macrophages induces M1 polarization via ROS-mediated acetylation of p53, reinforcing the idea that p53 acetylation is a potential therapeutic node for modulating macrophage polarization and As severity. (2) Stearoyl-CoA desaturase 1 (SCD1) inhibition disrupts the mevalonate pathway, impairs GPX4 synthesis, and promotes ferroptosis.[127] Additionally, SCD1 deficiency enhances lipid droplet–lysosome fusion via TFEB nuclear translocation, reducing foam cell formation.[128] Thus, pharmacological inhibition of SCD1 may offer a dual benefit by suppressing foam cell survival and promoting ferroptosis. (3) Heat shock protein 90 (HSP90), a key chaperone in HSP family, promotes ferroptosis by accelerating GPX4 degradation and lipid peroxidation.[129,130] Moreover, S-nitrosylation of HSP90 at Cys521, in conjunction with CDC37/NF-κB signaling, enhances endothelial adhesion and dysfunction, potentially driving As progression. Therefore, HSP90 emerges as a potential druggable target in As, although its exact role in ferroptosis modulation requires further investigation. In summary, Ferroptosis plays a multifaceted role in atherosclerosis, influencing endothelial dysfunction, macrophage polarization, foam cell death, and VSMC abnormalities. While iron overload and lipid peroxidation are well-documented triggers of ferroptosis in As, the detailed molecular mechanisms governing this process remain incompletely understood.

Current therapeutic strategies include iron chelation, lipid peroxidation suppression, and redox system restoration, with multiple compounds—including Fer-1, Liproxstatin-1, Nrf2 activators, and natural antioxidants like curcumin and tanshinone IIA—showing promise in preclinical models.[114–116,121,122] However, most of these interventions remain at the experimental stage, requiring further validation in human cohorts. Emerging evidence also highlights interactions between ferroptosis and other regulated cell death modalities, such as pyroptosis and autophagy, though no direct crosstalk has yet been reported in As.[126] Future studies should explore combinatorial approaches that integrate ferroptosis inhibition with modulation of autophagy or inflammasome signaling, aiming to develop multi-targeted therapies for As. By dissecting the intricate network linking iron metabolism, lipid oxidation, and antioxidant defenses, researchers can refine therapeutic strategies that specifically target ferroptosis and provide meaningful benefits for patients with atherosclerosis. To clarify the dynamic role of ferroptosis in AS progression, we summarized the regulatory mechanism of ferroptosis in each stage of atherosclerosis formation (Figure 6). This figure systematically illustrates the stage-specific association between ferroptosis and AS, providing a theoretical basis for developing stage-targeted ferroptosis inhibitors to prevent and treat AS.

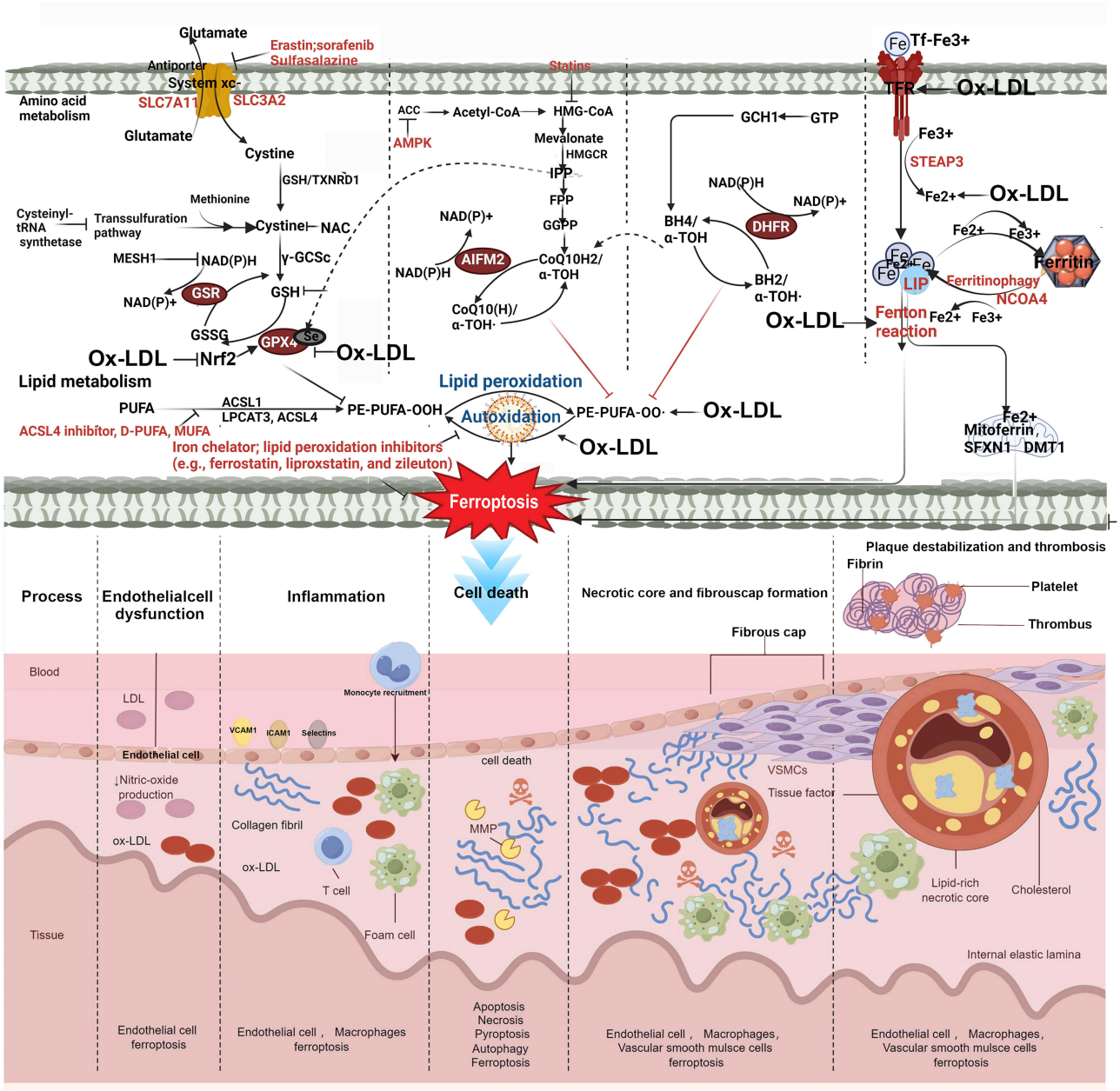

Figure 6 A Schematic Diagram Illustrating the Mechanisms by Which Oxidized Low-Density Lipoprotein (Ox-LDL) Mediates Ferroptosis Activation to Drive the Pathogenesis and Progression of Atherosclerosis [Red lines terminating with a perpendicular bar (−|) represent inhibitory or negative regulatory effects (as shown in the lower panel inset legend). Red arrows (→) indicate positive regulation, activation, or promotion of pathological processes. Black solid arrows represent direct biochemical reactions, metabolic conversions, and molecular interactions within pathways. Dashed arrows denote indirect effects or regulatory relationships. The figure systematically illustrates how oxidized low-density lipoprotein (Ox-LDL), a central pathogenic factor in atherosclerosis, perturbs the four core regulatory pathways of ferroptosis through multiple dimensions—iron metabolism, cyst(e)ine/GSH/GPX4, FSP1/CoQ10, and GCH1/BH4/DHFR—thereby amplifying the lipid peroxidation cascade and triggering ferroptosis. It further delineates the complete pathological progression mediated by ferroptosis in atherosclerosis, from endothelial dysfunction and inflammatory activation to foam cell formation, necrotic core development, and ultimately plaque instability with thrombus formation, while highlighting key targeted intervention nodes. Collectively, the figure provides a robust theoretical framework for understanding the role of the ferroptosis–iron homeostasis axis in atherosclerosis and for developing novel preventive and therapeutic strategies. The figure was created with BioRender.

Ferroptosis and Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is defined by myocardial dysfunction—particularly impaired systolic and/or diastolic function—in the presence of diabetes mellitus, independent of other known cardiovascular risk factors such as hypertension, coronary artery disease, or obesity.[131] Although DCM often coexists with these comorbidities, its pathophysiology involves intrinsic metabolic disturbances, including altered substrate utilization, mitochondrial dysfunction, oxidative

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stress, and fibrosis, which collectively contribute to cardiac remodeling and progressive heart failure.[132,133] In diabetic hearts, downregulation and aberrant translocation of glucose transporter 4 (GLUT4) impair glucose uptake and utilization, while increased fatty acid transport via cluster of differentiation antigen 36 (CD36) shifts myocardial metabolism toward excessive fatty acid oxidation. This metabolic imbalance leads to lipid accumulation and production of advanced glycation end products (AGEs),[134] which further exacerbate mitochondrial dysfunction, oxidative damage, and fibrotic remodelling. Excess AGEs activate inflammatory pathways and promote collagen crosslinking, increasing myocardial stiffness and impairing diastolic function. Additionally, AGEs disrupt calcium homeostasis by elevating ER Ca^{2+} levels and perturbing mitochondrial Ca^{2+} handling, thereby affecting sarcoplasmic reticulum Ca^{2+} reuptake and prolonging action potential duration.[135] These pathological changes ultimately lead to cardiomyocyte death, inflammation, and fibrosis, culminating in cardiac rigidity and heart failure. Although studies on ferroptosis in DCM are still limited, emerging evidence suggests that it contributes to disease progression through mechanisms involving cardiomyocyte death, oxidative stress, inflammation, and myocardial fibrosis.[136] Given the iron-dependent nature of ferroptosis and its interplay with lipid peroxidation and redox regulation, targeting this pathway offers a promising strategy for mitigating DCM-associated injury.

Ferroptosis and Metabolic Dysregulation in DCM

In diabetes, the primary energy substrate shifts from glucose to free fatty acids. However, fatty acid oxidation is less efficient than glucose metabolism, and when supply exceeds mitochondrial capacity, toxic lipid metabolites accumulate, leading to lipotoxicity and mitochondrial dysfunction.[137] Lipotoxicity directly impairs cardiomyocyte metabolism and promotes cell death, playing a central role in DCM development. Under conditions of iron overload and elevated lipoxygenase activity, polyunsaturated fatty acids (PUFAs) in cardiomyocyte membranes undergo peroxidation, initiating ferroptosis. Key contributors to this process include iron accumulation, ROS overproduction, lipid overload, and enhanced lipid peroxidation.[136] Zhang et al demonstrated that canagliflozin, an SGLT2 inhibitor, can alleviate lipotoxicity and inhibit ferroptosis in a high-glucose/high-fat (HG/HF) cardiomyocyte model (HL-1 cells).[137] In this model, reduced cell viability was accompanied by elevated Fe^{2+}, ROS, and MDA levels, increased mitochondrial membrane potential, and decreased GSH content. Treatment with ferrostatin-1 (Fer-1) reversed these effects, indicating that ferroptosis contributes to HG/HF-induced myocardial injury. Canagliflozin also activated the LKB1/TAK1/AMPK signaling axis, leading to restoration of cellular integrity and suppression of ferroptosis, highlighting its dual benefit in metabolic and oxidative stress regulation. Further studies have shown that curcumin, a natural compound derived from turmeric, alleviates ferroptosis and improves cardiac structure in streptozotocin (STZ)-induced DCM rabbits.[138] Histological analysis revealed myocardial edema, disarrayed myocytes, lipid accumulation, and increased collagen deposition—hallmarks of DCM—along with upregulated GPX4, suggesting active ferroptosis. Curcumin treatment restored GPX4 expression, suppressed lipid accumulation, and improved myocardial architecture in both in vivo and in vitro models. Persistent hyperglycaemia promotes AGEs deposition in the extracellular matrix, where they induce collagen cross-linking and myocardial stiffening. AGEs not only drive fibrosis but also interact with ferroptotic pathways. Wang et al established an engineered cardiac tissue (ECT) model of DCM and found that AGE accumulation led to elevated expression of ferroptosis markers such as PTGS2 (COX2) and MDA, along with reduced GSH and GSH/GSSG ratios.[139] Administration of Fer-1 and DFO significantly ameliorated these changes. Moreover, sulforaphane, an Nrf2 activator, inhibited ferroptosis in ECT and STZ-treated mice by enhancing ferritin and SLC7A11 expression, reinforcing the importance of antioxidant defenses in DCM. Recent findings indicate that glucolipotoxicity may promote ferroptosis by activating ACSL4 transcription, suppressing FSP1, and disrupting the Nrf2-regulated iron homeostasis network.[140] This molecular cascade enhances susceptibility to lipid peroxidation and ferroptosis, contributing to DCM progression.

Ferroptosis and Oxidative Stress in DCM

Chronic hyperglycaemia and insulin resistance alter cellular metabolism and increase ROS generation. The imbalance between ROS production and antioxidant defense results in mitochondrial damage, functional impairment, and contractile dysfunction.[141] Ferroptosis is closely linked to this oxidative environment. For instance, treating human pancreatic β-cells with Erastin —a classical inducer of ferroptosis—reduces glucose-stimulated insulin secretion and induces significant ROS

accumulation and oxidative damage, underscoring the role of ferroptosis in diabetes-related cell loss.[142] The heme oxygenase (HO) system, which catalyzes heme into biliverdin, carbon monoxide, and Fe^{3+}, also contributes to oxidative stress in DCM. Hana et al showed that HO activation in diabetic rats increases ROS and facilitates iron release into the ER, promoting iron overload and ferroptosis.[143] Wu et al demonstrated that 6-gingerol (6-G), a bioactive compound isolated from ginger, enhances GPX4 expression in both DCM mouse models and HG-palmitate-treated H9C2 cardiomyocytes, reducing oxidative stress and ferroptosis.[144] 6-G also activates Nrf2, thereby promoting nuclear translocation of antioxidant genes such as HO-1 and SOD, offering protection against ferroptosis and metabolic injury. Canagliflozin has also been shown to restore the system Xc^-–GSH–GPX4 axis in DCM mice, downregulating TfR1 and FTH1, thus limiting iron influx and storage.[145] Similarly, schisandrin B, a lignan from Schisandra chinensis, exerts cardioprotection by activating the Nrf2/HO-1/GPX4 pathway, attenuating oxidative stress and ferroptosis in diabetic hearts.[146] These data suggest that modulation of ferroptosis through antioxidant systems and metabolic regulators may represent a novel approach to preventing oxidative damage in DCM.

Ferroptosis and Inflammatory Responses in DCM

Inflammation plays a key role in DCM pathogenesis by promoting cardiomyocyte apoptosis, fibrosis, and hypertrophy, ultimately impairing contractility.[147] Ferroptosis itself can trigger necroinflammatory responses through lipid peroxidation and release of damage-associated molecular patterns (DAMPs). Targeting ferroptosis to suppress inflammation presents a new therapeutic opportunity in DCM. 6-G inhibits inflammation in diabetic hearts by modulating Nrf2/HO-1 signaling, reducing ferritin secretion and inflammatory cytokine production.[144] Zou et al demonstrated that deferiprone, a clinically approved iron chelator, alleviates myocardial fibrosis in STZ-induced DCM rats by downregulating NF-κB, COX2, tenascin C, and collagen type IV mRNA expression.[148] Masson's staining confirmed reduced collagen deposition and improved myocardial organization following 20 weeks of deferiprone administration. Myricitrin, another natural flavonoid, suppresses cardiac inflammation in diabetic mice by inhibiting the IκBα/NF-κB pathway and reducing the secretion of IL-1β, TNF-α, and IL-6, suggesting that anti-ferroptotic strategies may mitigate DCM progression by dampening inflammatory responses.[149]

Therapeutic Modulation of Ferroptosis in DCM

Targeting ferroptosis holds promise for delaying or reversing DCM pathology. GPX4 deficiency is associated with mitochondrial lipid peroxidation and cardiac hypertrophy in mice under high-fat diets, reinforcing its protective role in diabetic myocardium.[150] Antioxidants such as vitamin E and coenzyme Q10 improve diastolic dysfunction in diabetic animals, supporting their use in DCM management. Heat shock factor 1 (HSF1) regulates iron homeostasis in cardiomyocytes. By modulating TfR1, FTH, and SLC40A1 transcription, HSF1 preserves iron balance and reduces lipid peroxidation in palmitate-treated H9C2 cells.[150] Canagliflozin, a sodium–glucose cotransporter 2 (SGLT2) inhibitor, protects against ferroptosis in DCM models. In STZ-induced diabetic C57BL/6 mice, canagliflozin reduces myocardial disarray, lowers inflammation, decreases collagen deposition, and restores mitochondrial morphology. In high-glucose-induced H9C2 cells, canagliflozin reduces ROS, lipid ROS, and MDA levels; enhances SOD and GSH levels; suppresses total iron and Fe^{2+} accumulation; downregulates FTH; and upregulates SLC7A11. These effects highlight the ability of canagliflozin to rebalance cardiac iron homeostasis and inhibit ferroptosis via the SLC7A11–GPX4 axis.[137] Salidroside (SAL), a phenolic glycoside from *Rhodiola rosea*, reduces blood glucose (BG) and ameliorates DCM in db/db mice.[151] SAL also reshapes the gut microbiome, increasing beneficial bacterial strains and altering the Bacteroidetes/Firmicutes ratio, which correlates with improved BG control and myocardial protection. Curcumin, through activation of the Nrf2 pathway, mitigates ferroptosis-induced myocardial damage in DCM models.[152] In DM mice, curcumin restores Nrf2, GPX4, and HO-1 expression, reduces cardiomyocyte disarray, and reverses Erastin-induced injury, underscoring its multi-target protective mechanism. Sulforaphane, an AMPK/Nrf2 activator, prevents ferroptosis and cardiac damage in DCM.[153] In AGE-treated ECTs, sulforaphane increases cell viability, GSH levels, and Nrf2, SLC7A11, and ferritin expression, while decreasing COX2, MDA, and iron content. In high-fat diet and STZ-treated DM mice, sulforaphane activates AMPK/Nrf2 signaling, enhances SLC7A11 and ferritin, increases GSH/GSSG, and suppresses COX2 and MDA, demonstrating broad efficacy in DCM prevention. Resveratrol, a stilbenoid polyphenol, improves viability in H9C2 cells by upregulating HSF1, GPX4, and SLC7A11, while reducing MDA, ACSL4, and Fe^{2+}.[154] Through HSF1-mediated suppression of ferroptosis, resveratrol protects against high-glucose-induced cardiomyocyte injury. Schisandrin B also exhibits robust protection in STZ-induced diabetic mice by inhibiting ferroptosis and improving

myocardial function.[155] It increases left ventricular ejection fraction (LVEF) and fractional shortening (LVFS), decreases LVEDD, LVESD, fasting plasma glucose (FPG), heart weight, collagen volume fraction (CVF), and myocardial mortality, and reduces serum LDH, CK-MB, and cTnI, as well as myocardial MDA, ROS, and Fe^{2+} levels. Concomitant upregulation of SOD, GSH-Px, Nrf2, HO-1, and GPX4 at both mRNA and protein levels supports the hypothesis that schisandrin B mediates cardioprotection via ferroptosis inhibition and antioxidant enhancement, likely through activation of the Nrf2/HO-1/GPX4 pathway.[155] Iron chelators such as deferoxamine (DFO) and ferroptosis inhibitors like ferrostatin-1 have been shown to protect against cardiac injury in DCM models.[156] 6-G, a polyphenolic compound isolated from ginger, exhibits antioxidant, antitumor, lipid-lowering, and glucose-lowering activities. In STZ-induced diabetic mice, 6-G improves cardiac function, attenuates myocardial hypertrophy and interstitial fibrosis, and enhances ACSL4 degradation, GPX4 expression, and anti-inflammatory signaling.[157] Notably, 6-G activates Nrf2/HO-1/SOD signaling, enhances antioxidant defenses, and reduces MDA levels, reinforcing its role in ferroptosis inhibition and DCM improvement. In summary, ferroptosis contributes to the pathogenesis of diabetic cardiomyopathy through multiple interconnected mechanisms involving metabolic dysregulation, oxidative stress, inflammation, and mitochondrial dysfunction. Recent studies have demonstrated that interventions targeting ferroptosis—including GPX4 activation, iron chelation, Nrf2 induction, and AMPK stimulation —can significantly improve myocardial structure and function in experimental DCM models. Therapeutic compounds such as canagliflozin, curcumin, sulforaphane, resveratrol, salidroside, and schisandrin B exert protective effects by restoring redox balance, suppressing lipid peroxidation, and modulating iron homeostasis. These findings support the notion that targeting ferroptosis represents a novel and effective strategy for DCM intervention. Future research should focus on: (1) Identifying specific biomarkers of ferroptosis in DCM; (2) Developing targeted delivery systems for cardiac-specific ferroptosis inhibition; (3) Validating these findings in large-scale clinical cohorts; (4) Investigating the interplay between ferroptosis and other forms of regulated cell death in DCM. By integrating mechanistic insights with translational approaches, we can advance our understanding of ferroptosis in DCM and explore new avenues for precision therapy in diabetic heart disease.

Ferroptosis in Cardiotoxicity Induced by Anticancer Therapies

With advances in cancer therapy, patient survival has significantly improved; however, cardiotoxicity remains a major limitation of many anticancer drugs, occurring at an incidence rate of 3–26%.[158] This toxicity is the second leading cause of morbidity and mortality among long-term cancer survivors after tumor recurrence. The most common classes of cardiotoxic agents include chemotherapeutic drugs, such as anthracyclines (eg, doxorubicin), taxanes, platinum compounds, and fluorouracil, as well as molecularly targeted therapies, including trastuzumab and lapatinib, and immune checkpoint inhibitors.[158] Ferroptosis, a regulated form of iron-dependent cell death driven by lipid peroxidation, has emerged as a key mediator of cardiotoxicity during antitumor treatment.[159] Many anticancer strategies exploit ferroptosis to eliminate tumor cells by suppressing antioxidant defenses—particularly the system Xc^-–GSH–GPX4 axis —yet these interventions often lack tissue specificity and may inadvertently induce damage in non-malignant organs, particularly the heart.[159] Thus, ferroptosis represents a critical molecular mechanism underlying cardiac injury caused by antitumor therapies.

Cardiotoxic Mechanisms of Chemotherapeutic Agents via Ferroptosis

Doxorubicin (DOX) is one of the best-characterized inducers of ferroptosis in the myocardium. In both in vivo and in vitro models—including neonatal rat ventricular myocytes (NRVMs)—DOX reduces GPX4 expression and promotes mitochondrial lipid peroxidation through the formation of DOX–Fe^{2+} complexes, ultimately triggering mitochondrial-dependent ferroptotic death.[160] Mitochondrial E3 ubiquitin ligase (MITOL) plays a protective role by regulating GSH metabolism and GPX4 expression to suppress lipid peroxidation. DOX-induced downregulation of MITOL leads to increased susceptibility to ferroptosis in NRVMs.[161] Additionally, DOX activates Nrf2-mediated heme oxygenase-1 (HO-1) upregulation, which releases labile iron and contributes to rapid systemic iron accumulation in mice.[12] Protein arginine methyltransferase 4 (PRMT4) induces Nrf2 methylation and restricts its nuclear translocation, thereby suppressing GPX4 transcription and exacerbating DOX-induced cardiotoxicity.[162] Conversely, tripartite motif-containing protein 21 (TRIM21), an E3 ubiquitin ligase, mediates p62 ubiquitination, inhibiting the p62–KEAP1–Nrf2 antioxidant pathway. TRIM21 knockout mice exhibit resistance to DOX-induced ferroptosis, highlighting its role in redox regulation.[163] High mobility group box 1 (HMGB1), a damage-associated molecular pattern (DAMP) molecule, enhances DOX-induced ferroptosis and cardiac injury in rats.[164] Similarly, 5-fluorouracil (5-FU)

increases ROS levels in human cardiomyocytes, leading to oxidative stress and cellular damage.[165] In H9c2 cardiomyocyte models, 5-FU triggers ferroptosis characterized by reduced cell viability, elevated Fe^{2+} levels, and lipid peroxidation—effects associated with decreased ferritin heavy chain 1 (FTH1) and increased transferrin receptor 1 (TfR1) expression in both in vitro and in vivo settings.[166] Arsenic trioxide (ATO) also induces ferroptosis in H9c2 cells, marked by mitochondrial membrane potential loss, ER stress, and ROS overproduction. Importantly, ferrostatin-1 (Fer-1) can mitigate ATO-induced cardiac injury by reducing ROS generation, preserving mitochondrial function, and alleviating ER stress and autophagic damage,[167] suggesting that ferroptosis inhibition could serve as a viable cardioprotective strategy. Cyclophosphamide metabolites generate oxidative stress and lipid peroxidation in cardiomyocytes, while reducing glutathione peroxidase activity, further implicating ferroptosis in chemotherapy-related cardiac dysfunction.[168]

Cardiotoxic Mechanisms of Targeted Therapeutics via Ferroptosis

Sorafenib, a multikinase inhibitor, functions as a ferroptosis inducer by inhibiting system Xc^- activity.[169] Its efficacy in cancer models correlates with ACSL4 expression levels.[170] In murine cardiac tissues, sorafenib reduces anti-ferroptotic markers such as SLC7A11 and GPX4, increases MDA levels, and causes mitochondrial damage.[171] Fer-1 reverses sorafenib-induced lipid peroxidation and structural injury in H9c2 cells, supporting the involvement of ferroptosis in its cardiotoxic profile. Transcriptional activation of activating transcription factor 3 (ATF3) has been identified as a central mechanism linking sorafenib exposure to ferroptosis in the heart.[171] In contrast, ATF4 protects against ferroptosis by enhancing SLC7A11 expression in mouse myocardial tissue,[172] indicating a dual role for stress-induced transcription factors in modulating ferroptosis during targeted cancer therapy. Other tyrosine kinase inhibitors (TKIs) such as sunitinib and lapatinib also exert cardiotoxic effects mediated by ferroptosis. In H9c2 cardiomyocytes and mouse models, sunitinib decreases Nrf2 and GPX4 expression while increasing TfR1, pointing to a role for Nrf2-dependent ferroptosis in TKI-induced cardiac injury.[37] Lapatinib (LAP) impairs mitochondrial function via PI3K/AKT signaling, enhances oxidative stress and ferroptosis in H9c2 cells, and potentiates DOX-induced cardiotoxicity.[173] These findings suggest that targeting the PI3K/AKT/Nrf2 axis may offer protection against combination therapy-induced cardiac damage. Song et al demonstrated that imatinib mesylate (IMA) induces dose-dependent depletion of GSH, iron overload, and elevated MDA levels in mouse hearts.[173] Mitochondrial membrane potential was compromised, along with increased ROS and iron content in H9c2 cells. IMA also suppressed Nrf2, while promoting p53 and TfR1 expression, reinforcing its pro-ferroptotic effects. Trastuzumab alters gene expression profiles in cardiomyocytes, elevating oxidative and nitrosative stress markers.[174] Sun et al showed that trastuzumab reduces H9c2 cell viability, increases intracellular and mitochondrial ROS, and lowers GPX4 expression and GSH/GSSG ratios.[175] These changes were reversed by Fer-1, which also restored ACSL4 and cytochrome c expression. Ye et al further confirmed that trastuzumab impairs ErbB2/PI3K/AKT/Nrf2 signaling, resulting in reduced GPX4, elevated 4-HNE and MDA, mitochondrial dysfunction, and altered mitochondrial GSH/GSSG and iron homeostasis.[176] These studies collectively highlight the importance of ferroptosis in mediating cardiotoxicity from targeted therapies and suggest that modulation of this pathway may preserve cardiac integrity during cancer treatment. To clarify the specific regulatory mechanism of DOX-induced cardiomyocyte ferroptosis, we summarized the interaction between DOX and cardiomyocyte ferroptosis (Figure 7). This figure systematically illustrates the molecular mechanism of DOX-induced ferroptosis and its pathological effects on cardiomyocytes, providing a theoretical basis for developing ferroptosis-targeted strategies to mitigate DOX cardiotoxicity.

Therapeutic Strategies for Ferroptosis-Mediated Cardiotoxicity

Current therapeutic approaches targeting ferroptosis-induced cardiotoxicity remain largely preclinical but offer promising avenues for future clinical translation. These include direct scavenging of ROS or enhancement of endogenous antioxidant defenses.

The radical-trapping agent ferrostatin-1 (Fer-1) exhibits protective effects in various models of ferroptosis-associated cardiac injury, including atrial fibrillation,[43] post-transplant ischemia–reperfusion injury,[177] and cardiotoxicity induced by doxorubicin,[12] 5-FU,[166] sorafenib,[171] and ATO,[167] underscoring its broad applicability. The only FDA-approved iron chelator currently used clinically, dexrazoxane (DXZ), effectively neutralizes doxorubicin-induced iron overload and ROS production, offering established cardioprotection.[163] Antioxidants such as vitamin C, vitamin E, melatonin, sesamin, resveratrol, naringenin, and puerarin have shown promise in mitigating ferroptosis-related cardiotoxicity by reducing ROS and lipid peroxidation.[178]

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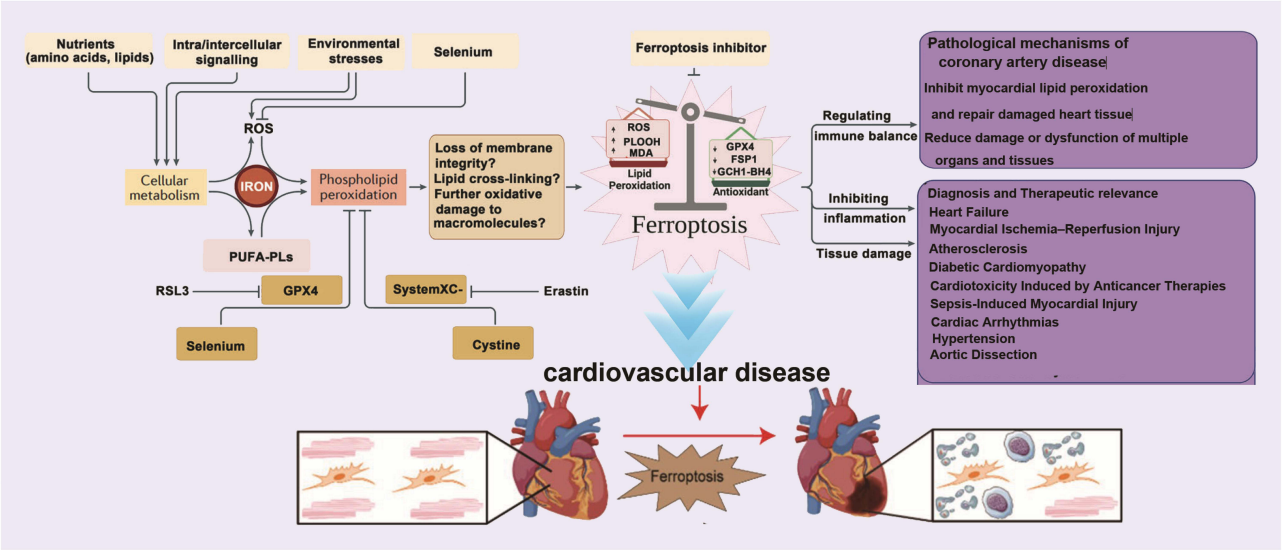

Figure 7 A schematic diagram of the core regulatory network of ferroptosis and its role and therapeutic prospects in cardiovascular diseases. [Lines terminating with a perpendicular bar (−|) represent inhibitory effects. Red arrows (→) indicate positive regulation, promotion of pathological processes, or disease progression. Black arrows represent molecular interactions, metabolic conversions, regulatory pathways, and signaling within the ferroptosis network. Ferroptosis upstream triggering factors and its core molecular regulatory network—centered on iron homeostasis imbalance-driven oxidative–antioxidant disequilibrium and the classical GPX4/System Xc^- pathway—are systematically illustrated. The mechanisms through which excessive ferroptosis activation drives the pathological transition from the normal heart to various cardiovascular diseases are elucidated. In addition, the multifaceted pathological roles of ferroptosis and its diagnostic and therapeutic translational prospects across conditions such as atherosclerosis, heart failure, myocardial ischemia-reperfusion injury, and diabetic cardiomyopathy are comprehensively reviewed. Collectively, these elements provide a panoramic theoretical framework for research on the prevention and treatment of cardiovascular diseases targeting the ferroptosis–iron homeostasis axis. The figure was created with BioRender.].

Moreover, advanced materials-based interventions, such as polyethylene glycol-coated dopamine nanoparticles (PDA NPs), have demonstrated cardioprotective effects in mouse models of myocardial I/R injury by reducing Fe^{2+} deposition, lipid ROS, and ferroptosis.[179] In summary, ferroptosis is increasingly recognized as a shared pathogenic mechanism in both oncology and cardiology. Numerous anticancer agents—including DOX, 5-FU, sorafenib, lapatinib, and IMA —induce cardiac injury through ferroptotic pathways. While some chemotherapeutics are designed to exploit ferroptosis for tumor suppression, their off-target effects on the heart pose significant risks. Therapeutic strategies targeting ferroptosis—such as iron chelation, radical trapping, and enhancement of Nrf2-GPX4 signaling —have demonstrated efficacy in preclinical models of drug-induced cardiotoxicity. However, current treatments lack tissue-specific delivery and may interfere with antitumor efficacy, necessitating further development of cardiac-selective antioxidants and ferroptosis inhibitors. Emerging evidence suggests that integrating nanomaterials, targeted drug delivery systems, and multi-omics approaches will be essential for developing safe and effective cardioprotective strategies alongside antitumor therapies. As personalized oncologic care continues to evolve, so too must our understanding of how to safeguard the cardiovascular system from unintended consequences of treatment. Ultimately, ferroptosis serves as a bridge between cancer biology and cardiac pathology. By identifying and validating ferroptosis-associated mechanisms in cardiotoxicity, we may uncover novel interventions that enable more effective and safer cancer therapies.

Pathogenic Mechanisms of Ferroptosis in Sepsis-Induced Myocardial Injury

Sepsis is a life-threatening systemic inflammatory syndrome characterized by multiorgan dysfunction, primarily driven by an excessive host response to infection.[180] It remains a leading cause of mortality among critically ill patients worldwide. A major complication of sepsis is sepsis-induced myocardial injury (SIMI), which contributes significantly to hemodynamic instability and poor clinical outcomes. SIMI manifests as reduced left ventricular ejection fraction and fractional shortening, and has gained increasing attention in intensive care medicine due to its impact on prognosis.[181] The pathophysiology of SIMI involves multiple cellular processes, including apoptosis, mitochondrial dysfunction, autophagy, pyroptosis, and oxidative stress.[182] Emerging evidence suggests that ferroptosis—a form of regulated cell death dependent on iron accumulation and lipid peroxidation —plays a pivotal role in the development of SIMI, making it a promising therapeutic target.[183] Studies have

demonstrated that ferroptosis via distinct pathways—including those involving GPX4 and ferroptosis suppressor protein 1 (FSP1) —contributes to cardiac damage during sepsis.[184,185] Pharmacological inhibition of ferroptosis has shown protective effects in experimental models. For instance, dexmedetomidine reduces lipopolysaccharide (LPS)-induced myocardial injury by suppressing heme oxygenase-1 (HO-1) and GPX4 downregulation.[186] Similarly, Huashi Baidu Decoction, a traditional Chinese herbal formula, modulates ferroptosis by targeting GPX4 and ACSL4, thereby ameliorating SIMI.[187] The specific ferroptosis inhibitor ferrostatin-1 (Fer-1) also improves myocardial function in septic models, potentially through suppression of the TLR4–NF-κB signaling pathway.[188] Zeng et al showed that resveratrol protects against LPS-induced ferroptosis in rat cardiomyocytes via activation of the SIRT1–Nrf2 axis, reducing oxidative damage and preserving cardiac integrity.[189] In LPS-treated models, elevated expression of prostaglandin-endoperoxide synthase 2 (PTGS2/COX-2) —a key enzyme in arachidonic acid metabolism—is closely associated with both inflammation and ferroptosis.[190] Downregulation of SLC7A11, a critical component of the system Xc^- cystine/glutamate antiporter, exacerbates ferroptotic vulnerability in these models, whereas its restoration alleviates SIMI.[191] These findings highlight the central role of ferroptosis in SIMI and suggest that targeting ferroptosis may represent a novel strategy for treating sepsis-related cardiac dysfunction.

Mitochondrial Dysfunction in Ferroptosis-Mediated SIMI

Mitochondria are central regulators of energy homeostasis and redox balance in cardiomyocytes. They coordinate oxidative phosphorylation, maintain iron metabolism, and contribute to ROS production and detoxification.[192] Dysregulation of mitochondrial iron handling, antioxidant defense, and membrane integrity has been linked to ferroptosis and myocardial damage during sepsis. Selective loss of mitochondrial proteins has been shown to induce mitochondrial iron overload, increase ROS generation, impair iron-sulfur cluster maturation, and promote cardiomyocyte death.[192] Mitochondria thus play a core role in regulating ferroptosis and overall cell fate. Mitochondria-targeted antioxidants have demonstrated efficacy in preventing ferroptosis-associated cardiac injury. Resveratrol exerts cardioprotection in LPS-induced SIMI by activating the SIRT1–GPX4 axis, reducing ROS levels, and mitigating mitochondrial damage.[189] Additionally, mitochondrial iron importers such as SLC25A37 and SLC25A28 —both involved in heme and iron-sulfur biogenesis—have been implicated in ferroptosis regulation. Notably, SLC25A28 knockout reduces erastin-induced ferroptosis, while its overexpression enhances susceptibility to this form of cell death.[193] Voltage-dependent anion-selective channel 2 (VDAC2), located on the outer mitochondrial membrane, plays a crucial role in mitochondrial bioenergetics. Persistent VDAC2 opening increases mitochondrial outer membrane permeability, disrupts metabolic and redox homeostasis, and promotes ferroptosis. Post-septic myocardium exhibits elevated malonylation of VDAC2, a post-translational modification that alters its conformation, impairs mitochondrial function, and facilitates ferroptosis.[194] In septic rats and patients, increased malonyl-CoA levels correlate with enhanced VDAC2 malonylation, contributing to mitochondrial dysfunction and myocardial injury. Targeting VDAC2 with TPP-conjugated nanoparticles (TPP-AAV) has been shown to inhibit ferroptosis and improve cardiac function in SIMI models,[194] underscoring the importance of maintaining mitochondrial iron homeostasis in preventing sepsis-induced cardiac damage.

Lipid Peroxidation and Ferroptosis in SIMI

In mammalian cells, lipid peroxidation of phospholipids containing polyunsaturated fatty acids (PUFA-PLs) is a hallmark of ferroptosis.[23] Acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the esterification of PUFAs into phospholipids, making them susceptible to oxidation and promoting ferroptosis. Lipoxygenases (LOXs), iron-containing enzymes, directly oxidize PUFA-PLs and drive the formation of toxic hydroperoxides, playing a central role in ferroptotic execution.[195] Excessive accumulation of lipid peroxidation products (LPO) indicates that endogenous antioxidant systems are overwhelmed. In septic hearts, this imbalance leads to membrane destruction and functional impairment. Studies show that LPS stimulation induces ferritinophagy, releasing free iron and triggering ferroptosis in cardiomyocytes.[189] Qi-Shen-Fu-Mai injection, a traditional Chinese medicine formulation, reduces iron overload and lipid peroxidation in LPS-treated cardiomyocytes by enhancing the system Xc^-–GPX4 axis. Treated SIMI rats exhibit reduced serum iron levels and suppressed markers of lipid peroxidation, accompanied by upregulated xCT and GPX4 expression.[196] Wang et al further confirmed that scavenging LPO effectively prevents ferroptosis and preserves myocardial structure, reinforcing the link between lipid oxidation and ferroptosis in septic myocardial injury.[197] These findings collectively support the view that lipid peroxidation and ferroptosis are key drivers of SIMI, and their modulation may yield significant therapeutic benefits.

Oxidative Stress and Inflammatory Responses in SIMI

Oxidative stress and inflammation are central mechanisms underlying sepsis-induced cardiac dysfunction. LPS binding to Toll-like receptors activates inflammatory cascades, leading to the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These mediators uncouple mitochondrial respiration, enhance ROS production, and activate ferroptosis, ultimately resulting in myocardial injury.[183] Several studies have explored anti-inflammatory and antioxidant interventions to mitigate LPS-induced cardiac damage. For example, leonurine, an alkaloid derived from Leonurus japonicus, suppresses LPS-induced oxidative stress by inhibiting NF-κB activation, offering cardioprotection.[198] Similarly, resveratrol attenuates LPS-triggered inflammation by modulating the PI3K/AKT/mTOR signaling axis, improving cardiac function in septic models.[199] Hydrogen sulfide donors such as NaHS (sodium hydrosulfide) protect against SIMI by activating the system Xc^-–GPX4 axis and suppressing oxidative stress.[200] These findings indicate that blocking oxidative stress and inflammatory signaling can effectively reduce ferroptosis and pyroptosis in septic cardiomyopathy.

Regulatory Factors Modulating Ferroptosis in SIMI

Annexin A1 (ANXA1) is a glucocorticoid-regulated protein widely expressed in human tissues and immune cells. It regulates diverse cellular processes, including proliferation, differentiation, and apoptosis.[201] ANXA1-derived peptides mimic the biological activity of full-length ANXA1 and have been shown to alleviate ferroptosis in H9C2 cardiomyocytes exposed to LPS. However, this protective effect is abolished in the presence of ferroptosis activators, indicating that ANXA1's cardioprotective effects are mediated through ferroptosis inhibition.[202] p53, a well-known tumor suppressor and "guardian of the genome", also participates in ferroptosis regulation. p53 deacetylation has been shown to reduce ferroptosis and attenuate SIMI.[203] As a transcriptional repressor of SLC7A11, p53 indirectly suppresses GSH synthesis and GPX4 activity, thereby increasing ROS and promoting ferroptosis. This mechanism supports the concept that modulating p53 acetylation status could serve as a viable approach for limiting ferroptosis in septic myocardium. Nuclear factor erythroid 2-related factor 2 (Nrf2) functions as a master regulator of redox homeostasis and ferroptosis. Under oxidative stress, Nrf2 positively regulates SLC7A11 expression, restoring GSH levels and GPX4 activity, and counteracting LPO accumulation.[204] Transmembrane protein 43 (TMEM43) is a recently identified regulator of ferroptosis in the heart. TMEM43 deficiency sensitizes cardiomyocytes to LPS-induced ferroptosis, whereas its overexpression protects against lipid peroxidation and cardiac injury.[205] TMEM43 inhibits ferroptosis by downregulating p53 and ferritin, while upregulating GPX4 and SLC7A11 expression. These findings position TMEM43 as a novel ferroptosis modulator and potential therapeutic target in SIMI. In summary, ferroptosis is emerging as a key molecular mechanism in sepsis-induced myocardial injury. Its involvement in SIMI is supported by extensive experimental data showing that iron overload, lipid peroxidation, and antioxidant system disruption converge to promote cardiomyocyte death and contractile dysfunction.

Therapeutic strategies targeting ferroptosis—such as iron chelation, radical-trapping antioxidants, activation of Nrf2–GPX4 signaling, and inhibition of VDAC2 malonylation —have shown promise in preclinical models of SIMI. Moreover, natural compounds like resveratrol, leonurine, and Qishen Fumai injection, along with regulatory proteins such as ANXA1 peptides and TMEM43, offer new avenues for cardioprotection by modulating ferroptosis. Despite these advances, the precise mechanisms linking ferroptosis to SIMI remain incompletely understood. Future research should focus on: (1) Identifying reliable biomarkers of ferroptosis in septic patients; (2) Developing targeted delivery systems for ferroptosis inhibitors; (3) Elucidating the interplay between ferroptosis, pyroptosis, and other forms of regulated cell death in septic myocardium; (4) Translating preclinical findings into clinical trials to assess the safety and efficacy of ferroptosis-targeted therapies. By integrating mechanistic insights with translational approaches, we can better define the role of ferroptosis in sepsis and explore innovative strategies for protecting the heart from inflammation-driven injury.

Ferroptosis and Cardiac Arrhythmias

Cardiac arrhythmia has emerged as a major public health burden globally, driven by aging populations and changing lifestyle patterns.[206] The pathophysiology of arrhythmogenesis involves multiple mechanisms, including alterations in myocardial electrophysiology, fibrosis, cardiac dilation, inflammation, oxidative stress, and autonomic imbalance. Clinically, arrhythmias present with variable severity—ranging from asymptomatic or mild palpitations to acute-onset life-threatening events such as hemodynamic collapse and sudden death. Notably, approximately 90% of fatalities in patients with acute heart disease are

attributed to arrhythmic complications. Recent studies have highlighted the role of ferroptosis, an iron-dependent form of regulated necrosis marked by lipid peroxidation and redox imbalance, in contributing to arrhythmia development. Dysregulated iron metabolism, lipid oxidation, and impaired antioxidant defenses are increasingly implicated in both structural and electrical remodeling of the heart, suggesting that ferroptosis may represent a novel mechanistic link between metabolic injury and cardiac rhythm disturbances.

Iron Dyshomeostasis and Ferroptosis in Arrhythmogenesis

Myocardial cells rely heavily on iron for metabolic function, yet they are highly sensitive to iron overload. Primary iron overload is often genetic (eg, hereditary hemochromatosis), while secondary forms arise from chronic transfusions, drug toxicity, or other acquired conditions.[207] When cellular iron storage capacity is exceeded, labile iron accumulates in cardiomyocytes, leading to toxic effects that disrupt normal cardiac physiology.[207] Epidemiological and clinical evidence supports a strong association between iron overload and arrhythmias. For instance, transfusion-dependent thalassemic patients exhibit higher rates of atrioventricular conduction abnormalities compared to non-transfusion-dependent counterparts.[208] Downregulation of ferroportin (FPN) increases intracellular iron levels and enhances oxidative stress, which correlates with increased susceptibility to atrial fibrillation; this can be mitigated by targeting ferroptosis.[209] Electrocardiographic changes further support this connection. Prospective studies show that iron-overloaded individuals display higher prevalence of low limb lead voltage and reduced atrial rhythm on ECG monitoring.[210] A Danish meta-analysis involving 20,261 subjects, including transfusion-dependent β-thalassemia patients, found that elevated iron stores are associated with prolonged QTc intervals in males,[211] with QTc >449 ms considered a critical threshold for identifying cardiac iron overload in adolescents.[212] Prolonged QTc and T-wave inversion are linked to increased risk of sudden cardiac death,[213] reinforcing the significance of iron homeostasis in maintaining cardiac rhythm. Iron influx into cardiomyocytes occurs via non-transferrin-bound iron (NTBI) pathways, particularly through L-type Ca^{2+} channels (LTCCs) and T-type Ca^{2+} channels (TTCCs).[214] Pharmacological inhibition of LTCCs by verapamil reduces myocardial iron accumulation and protects against arrhythmias.-[215] In chronic iron-overload murine models, Cav1.3—a specific LTCC isoform expressed in pacemaker cells—is selectively suppressed under high-iron conditions, with a ~40% reduction in Cav1.3 mRNA levels in atrial tissue. Genetic ablation of Cav1.3 induces PR interval prolongation, conduction block, and atrial fibrillation,[216] highlighting its dual role in iron handling and cardiac rhythm control. Inhibition of TTCC by efonidipine, a selective calcium channel blocker, significantly decreases cardiac iron uptake and improves left ventricular function and heart rate variability.[217] These findings underscore the importance of calcium channels in mediating iron entry and suggest that their modulation may serve as a protective strategy in iron overload-induced arrhythmias. Kuryshev et al were among the first to detect membrane currents in iron-loaded cardiomyocytes in vivo and in vitro, revealing that when iron concentrations reach those observed in cardiomyopathy, action potential overshoot and duration decrease—changes mediated by reductions in sodium current and enhancements in transient outward potassium current.[218] These alterations increase arrhythmic vulnerability, indicating that ion channel dysfunction contributes to ferroptosis-driven rhythm disturbances. Beyond direct effects on ion channels, emerging data suggest that iron overload influences autonomic activity,[219] potentially contributing to arrhythmogenesis. Collectively, these findings imply that iron dyshomeostasis plays a significant role in arrhythmia pathogenesis. However, some experimental models, such as iron-overloaded guinea pigs, do not develop arrhythmias despite hepatic fibrosis and ascites,[220] suggesting that arrhythmogenesis is not solely iron-dependent but rather results from complex interactions. Thus, while ferroptosis likely contributes to arrhythmia development, further investigation is required to clarify the precise mechanisms involved.

Lipid Metabolism and Ferroptosis in Arrhythmogenesis

Arachidonic acid (AA) and phosphatidylethanolamine (PE) are key phospholipids that undergo peroxidation during ferroptosis. These lipids influence membrane fluidity and promote lipid ROS formation via lipoxygenase-mediated oxidation, ultimately triggering ferroptotic signaling.[221] The downstream products of lipid peroxidation—including 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) —react with DNA and proteins, amplifying oxidative damage and accelerating cell death.[222] Elevated MDA levels are independently associated with post-myocardial infarction arrhythmias,[223] and growing evidence links lipid metabolism to arrhythmogenic remodeling. Obesity and hyperlipidemia are recognized independent risk factors for atrial fibrillation and other rhythm disorders,[224] yet the involvement of ferroptosis in this process remains incompletely understood.

ROS generated during ferroptosis directly impair ion channel function—enhancing late Na^+ current, L-type Ca^{2+} current, sarcoplasmic reticulum Ca^{2+} release, and Na^+/Ca^{2+} exchanger activity, while reducing peak Na^+ current and SERCA-mediated Ca^{2+} uptake.[225] These disruptions elevate intracellular Ca^{2+}, prolong action potentials, slow conduction velocity, and promote triggered activity and reentry circuits. ROS also alter the expression of connexin 43 (Cx43), increasing electrical heterogeneity and anisotropy—key contributors to arrhythmia maintenance and sudden cardiac death.[226] Moreover, excessive ROS promote myocardial fibrosis, serving as a bridge between ferroptosis and arrhythmogenic substrate formation.[227] Mixed-lineage kinase 3 (MLK3), a member of the MAP3K family, exacerbates ferroptosis via JNK/p53 signaling and ROS-mediated oxidative stress, contributing to myocardial fibrosis and arrhythmia susceptibility.[52] Reducing ROS and iron overload suppresses ferroptosis and prevents atrial remodeling and AF progression,[228] supporting the hypothesis that ferroptosis actively participates in arrhythmogenesis. Long-chain acyl-CoA synthetase 4 (ACSL4) catalyzes PUFA incorporation into membrane phospholipids and promotes lipid peroxidation, making it a central driver of ferroptosis.[229] Yu et al showed that ethanol-induced atrial remodeling increases AF susceptibility, accompanied by upregulation of pro-ferroptotic proteins (PTGS2, ACSL4, p53) and downregulation of anti-ferroptotic molecules (GPX4, FTH1).[228] Importantly, these changes could be reversed by ferroptosis inhibitors but exacerbated by ferroptosis activators, reinforcing the role of ferroptosis in alcohol-associated arrhythmogenesis. Exogenous monounsaturated fatty acids (MUFAs) can competitively interfere with PUFA metabolism and effectively suppress ferroptosis, primarily through ACSL3 or stearoyl-CoA desaturase 1 (SCD1), rather than ACSL4.[230] Intriguingly, MUFA-rich diets are associated with lower arrhythmia incidence.[231] Mediterranean diets rich in oleic acid, a major MUFA found in olive oil, have been shown to reduce AF risk. Martínez-González et al followed 6705 participants without baseline AF for 4.7 years and found that regular olive oil consumption was linked to a significantly lower risk of incident AF.[232] Similarly, Chiuve et al reported that low MUFA intake was associated with higher risk of persistent or chronic AF over 19.2 years in a cohort of 33,665 women.[34] These findings suggest that MUFA-based interventions may offer protection against arrhythmias, although more research is needed to establish causality and molecular mechanisms.

Amino Acid Metabolism and Ferroptosis in Arrhythmias

The system Xc^-–GSH–GPX4 axis represents a canonical regulatory pathway in ferroptosis. GPX4, a selenoprotein, utilizes GSH to neutralize lipid hydroperoxides; loss of GPX4 activity leads to uncontrolled lipid ROS accumulation and ferroptotic death.[233] Patients with Sedaghatian-type spondyloepiphyseal dysplasia due to GPX4 deficiency exhibit arrhythmias, underscoring the physiological relevance of GPX4 in cardiac rhythm stability.[234] Bezna et al found that GPX variants in arrhythmic patients correlate with increased oxidative stress and arrhythmia onset.[235] Given that GPX4 is a selenoprotein, selenium deficiency may contribute to arrhythmogenesis. Ardahanli et al reported lower serum selenium levels in patients with newly diagnosed AF, suggesting that selenium supplementation might reduce arrhythmic episodes via GPX4 stabilization.[236] System Xc^-, composed of SLC7A11 and SLC3A2, mediates cystine import and glutamate export, playing a pivotal role in GSH biosynthesis and redox defense.[237] Suppression of system Xc^- impairs GSH synthesis, increases lipid ROS, and promotes ferroptosis. Liu et al demonstrated that rapid atrial pacing elevates MDA and total iron content in paced atrial tissues.[238] Exosomes derived from pacing-induced cardiac fibroblasts exacerbated ferroptosis in H9C2 cardiomyocytes, whereas treatment with the exosome inhibitor GW4869 attenuated fibrosis, inflammation, and ferroptotic markers (FTH1, SLC7A11, GPX4). Bioinformatic analysis revealed that miR-23a-3p is highly expressed in paced hearts and targets SLC7A11. This suggests that exosomal miRNA regulation of system Xc^- contributes to arrhythmia progression and that targeting exosome-mediated ferroptosis may prevent sustained AF development. These findings highlight the interplay between amino acid metabolism and ferroptosis in arrhythmia pathogenesis, emphasizing the need to maintain redox balance for proper cardiac rhythm.

Inflammatory Responses and Ferroptosis in Arrhythmias

Inflammation is a well-established contributor to arrhythmia development. Emerging evidence shows that inflammatory mediators, including cytokines and DAMPs, can trigger ferroptosis and thereby influence cardiac electrophysiological properties.[239] Notably, SARS-CoV-2 infection has been linked to cardiac rhythm disturbances. Han et al demonstrated that SARS-CoV-2 impairs human cardiac pacemaking and activates ferroptosis in hamster models.[239] Treatment with deferoxamine (DFO) and imatinib blocked viral entry and ferroptosis, offering protection against arrhythmia. In endotoxemia induced

by bacterial lipopolysaccharide (LPS), FPN downregulation increases intracellular iron availability, activates ferroptosis, and enhances AF susceptibility.[9] Further deletion of FPN exacerbates iron overload and oxidative stress, promoting arrhythmias. Conversely, ferroptosis inhibition reduces AF vulnerability, demonstrating a direct link between inflammation-driven ferroptosis and cardiac rhythm disturbances. These findings position ferroptosis as a mediator of arrhythmias in both infectious and sterile inflammatory contexts, providing new insights into virus-induced cardiac dysfunction and sepsis-related rhythm disorders.

Regulatory Factors of Ferroptosis in Arrhythmia Pathology

Nrf2, a master transcription factor in antioxidant defense, regulates multiple downstream genes including heme oxygenase-1 (HO-1), SLC7A11, GPX4, and glutathione reductase, thereby modulating ferroptosis through redox homeostasis, mitochondrial function, and iron metabolism.[240] Dong et al showed that Nrf2 suppression in H9C2 cardiomyocytes reduces antioxidant enzyme production, increases ROS, and markedly enhances arrhythmia incidence.[241] HO-1 serves as an endogenous antioxidant by generating carbon monoxide (CO), biliverdin, and Fe^{2+} upon heme degradation.[242] Activation of the Nrf2–HO-1 axis has been shown to play a crucial role in suppressing ferroptosis and improving cardiac outcomes.[243] Indeed, activation of this pathway reduces ventricular remodeling and arrhythmia severity in MI mouse models.[244] Li et al demonstrated that Linggui Zhugan Decoction, a traditional Chinese medicine, alleviates myocardial injury in rats with chronic arrhythmias via Nrf2–HO-1 signaling, reinforcing its therapeutic potential.[245] Coenzyme Q10 (CoQ10), an endogenous ferroptosis inhibitor, is abundantly expressed in energy-demanding organs such as the heart, liver, kidney, and pancreas. CoQ10 functions as a radical-trapping antioxidant in mitochondrial membranes, preventing lipid peroxidation and stabilizing electron transport chain function.[246] Administration of farnesyl pyrophosphate (a CoQ10 precursor) or idebenone (a water-soluble analog) inhibits ferroptosis, whereas CoQ10 depletion accelerates ferroptosis.[247] Wardhani et al found that CoQ10 supplementation reduces reperfusion-induced arrhythmias after coronary artery bypass surgery.[248] Similarly, Liu Cui et al reported that CoQ10 co-treatment in elderly hypertensive patients with arrhythmias improved rhythm control and safety profiles, possibly through endothelial protection and systemic redox modulation.[249] These findings indicate that CoQ10 may exert antiarrhythmic effects by inhibiting ferroptosis, though the exact molecular pathways remain to be elucidated. In summary, ferroptosis is increasingly recognized as a significant contributor to arrhythmia pathogenesis, linking iron overload, lipid peroxidation, redox imbalance, and inflammatory responses to cardiac rhythm disturbances. Experimental and clinical data support the notion that ferroptosis promotes arrhythmias through diverse mechanisms, including: (1) Disruption of ion channel function via iron-induced ROS; (2) Modulation of calcium handling and excitation–contraction coupling; (3) Induction of myocardial fibrosis and structural remodeling; (4) Alterations in connexin expression and electrical heterogeneity; (5) Interactions between inflammatory mediators and ferroptotic cascades. Regulatory nodes such as Nrf2–HO-1–GPX4, system Xc^{-}, calcium channels, and CoQ10 offer promising intervention points for future therapies aimed at limiting ferroptosis-induced arrhythmias. Despite accumulating evidence, several challenges remain. First, reliable biomarkers of ferroptosis in arrhythmic tissues are still lacking. Second, the precise molecular pathways connecting ferroptosis and arrhythmia are incompletely defined. Third, conflicting reports exist regarding the role of iron overload in different experimental models, necessitating deeper mechanistic exploration. To advance this field, future studies should integrate: (1) Multi-omics profiling to identify ferroptosis-specific signatures in arrhythmic myocardium; (2) High-resolution mapping of iron deposition and lipid peroxidation in patient-derived cardiac tissues; (3) Preclinical testing of novel ferroptosis inhibitors in models of arrhythmia and heart failure; (4) Clinical trials evaluating iron chelation, antioxidant therapy, and targeted redox modulation in arrhythmic syndromes. By addressing these gaps, we can harness ferroptosis as a novel therapeutic target and explore innovative strategies for arrhythmia prevention and management. As our understanding of ferroptosis expands, so too does the opportunity to develop precision interventions that preserve cardiac rhythm and improve patient outcomes.

Ferroptosis and Hypertension

Hypertension is a major global public health concern, representing one of the key risk factors for cardiovascular and cerebrovascular diseases such as atherosclerosis, heart failure, and myocardial infarction.[250,251] It is a systemic disease characterized by elevated arterial pressure, often accompanied by functional alterations in the vasculature, brain, kidney, and

heart. Its pathophysiology is primarily linked to increased vascular resistance, with hallmark features including endothelial dysfunction, enhanced vasoconstriction, and arterial remodelling.[250,251]

Iron Dyshomeostasis and Ferroptosis in Hypertension

Iron overload is closely associated with hypertension, and epidemiological studies have demonstrated a positive correlation between serum ferritin levels and hypertension prevalence, suggesting that iron homeostasis plays a crucial role in disease progression.[251,252] Population-based research has identified mutations in iron-regulatory proteins—such as the major histocompatibility complex class I-like transmembrane protein (HFE) at the H63D locus and the iron-overload-related gene hemojuvelin (HJV) —that result in mild iron overload and are associated with an increased risk of developing hypertension.

Conversely, dietary iron restriction in experimental models alleviates vascular wall thickening, fibrosis, and inflammation in Dahl salt-sensitive hypertensive rats,[253] and further studies show that limiting iron intake can prevent both hypertension and renal fibrosis in aldosterone/salt-induced mouse models by reducing oxidative stress.[254] These findings suggest that ferroptosis may be involved in hypertension through iron overload-induced cellular damage, although the underlying mechanisms remain to be fully elucidated.

Amino Acid Metabolism Dysregulation and Ferroptosis in Hypertension

Studies indicate that depletion of glutathione (GSH), cysteine deficiency, and inactivation of glutathione peroxidase 4 (GPX4) can all lead to ferroptosis.[255] GPX4 utilizes GSH to convert lipid hydroperoxides into non-reactive alcohols, thereby suppressing lipoxygenase (LOX)-mediated lipid peroxidation and inhibiting ferroptosis.[256] Administration of RSL3, a GPX4 inhibitor, promotes lipid ROS accumulation and enhances ferroptotic cell death. In the aortic media of hypertensive patients, GPX4 expression is significantly lower than in healthy controls. Exposure of vascular smooth muscle cells (VSMCs) to high hydrostatic pressure (200 mmHg) reduces cystathionine γ-lyase (CSE)/hydrogen sulfide (H_2S) levels, which further decreases GSH synthesis and GPX4 expression, ultimately triggering ferroptosis. High hydrostatic pressure or mechanical stretch can upregulate ACSL4 expression in VSMCs and cardiomyocytes. This increases the synthesis of easily peroxidized PUFA-PE, thereby driving lipid peroxidation and ferroptosis.[257]

The system Xc^-, composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), functions as a cystine/glutamate antiporter essential for GSH biosynthesis. Zhang et al found that SLC7A11 inhibition exacerbates angiotensin II (AngII)-induced cardiomyocyte hypertrophy and elevates ferroptosis markers such as PTGS2 (COX-2), malondialdehyde (MDA), and ROS levels. Overexpression of SLC7A11 reverses these effects, indicating that SLC7A11 suppresses ferroptosis and attenuates hypertension-associated cardiac hypertrophy, thus emerging as a potential therapeutic target.[258] These data collectively support a role for GSH deficiency and GPX4 inactivation in ferroptosis-driven hypertension. Downregulation of GPX4 accelerates lipid peroxidation and contributes to ferroptosis, which in turn worsens blood pressure regulation. As a selenoprotein, GPX4 contains selenocysteine within its active site,[259] and selenium deficiency in serum or cytoplasm has been shown to impair GPX4 function, promote lipid peroxidation, and induce ferroptosis.[260] Clinical observations reinforce this link: lower selenium levels are detected in hypertensive patients,[261] and a 20-year cohort study by Xie et al revealed that higher selenium intake correlates with reduced risk of hypertension.[262] In a rat model of alcohol-induced hypertension during adolescence, selenium supplementation increases GPX4 activity, lowers serum aldosterone levels, and reduces systolic blood pressure,[263] further supporting a role for selenium-dependent ferroptosis in hypertension development.

Lipid Peroxidation and Ferroptosis in Hypertension

Both basic and clinical evidence confirm that lipid peroxidation mediates hypertension. For example, elevated levels of malondialdehyde (MDA) —a major product of lipid peroxidation—have been observed in hypertensive individuals, along with signs of endothelial injury.[264,265] Multiple clinical studies report higher plasma lipid peroxidation levels in hypertensive patients compared to normotensive controls,[266,267] indicating widespread oxidative damage in this condition. Reactive oxygen species (ROS) play a central role in vascular remodelling and endothelial dysfunction in hypertension. Increased ROS promotes endothelial dysfunction, accelerates VSMC proliferation and vascular remodelling, leading to elevated peripheral resistance and sustained blood pressure elevation.[268,269] Elevated intracellular ROS is also a defining feature of ferroptosis.[270] Shintoku et al showed that lipoxygenases (LOXs) mediate enzymatic lipid

peroxidation and drive ferroptosis,[271] while Shah et al demonstrated that LOX inhibition or knockout prevents ferroptosis,[272] underscoring their regulatory roles in this process. In particular, 12-LOX and 15-LOX are key ROS-generating enzymes implicated in hypertension pathogenesis. Both isoforms enhance VSMC contractility and elevate blood pressure in AngII-infused mice.[273,274] Notably, the LOX inhibitor baicalein significantly reduces MDA levels, myocardial hypertrophy, and fibrosis in AngII-treated animals, improving systolic function.[275] These findings suggest that LOX-mediated lipid peroxidation may contribute to ferroptosis in hypertension; however, whether and how LOX directly triggers ferroptosis remains unclear. ACSL4, a long-chain acyl-CoA synthetase, activates polyunsaturated fatty acids (PUFAs) to form acyl-CoA derivatives, promoting lipid peroxidation and ferroptosis.[276] Müller et al reported that ACSL4 deletion protects human fibrosarcoma cells from RSL3-induced ferroptosis, identifying ACSL4 as a newly recognized reliable biomarker of ferroptosis.[277] Moreover, overexpression of ACSL4 impairs GPX4 activity, increases lactate dehydrogenase release, and reduces cell viability. In hypertension models, high hydrostatic pressure upregulates ACSL4 while suppressing GPX4, suggesting that ACSL4 participates in ferroptosis in hypertension-associated vascular pathology.[277] COX-2, encoded by PTGS2, serves as a marker of ferroptosis.[278,279] COX-2 expression is elevated in the kidneys and thoracic aortas of both hypertensive patients and animal models.[280,281] Further investigation reveals that high-pressure conditions in VSMCs induce ferroptosis alongside COX-2 upregulation, suggesting that COX-2 elevation may serve as a surrogate indicator of ferroptosis in hypertension. Conversely, COX-2 activation may amplify oxidative stress and accelerate disease progression. Exogenous monounsaturated fatty acids (MUFAs) effectively inhibit ferroptosis, primarily through acyl-CoA synthetase long-chain family member 3 (ACSL3) -mediated suppression of membrane ROS accumulation.[282] Lee et al reported that high MUFA intake confers protection against hypertension.[283] Although MUFAs influence both ferroptosis and hypertension, it remains to be determined whether the protective effect of MUFAs against hypertension occurs via ferroptosis inhibition and to what extent this mechanism is involved.

Mitochondrial Dysfunction and Ferroptosis in Hypertension

Mitochondrial dysfunction is increasingly recognized as a core component of hypertension pathophysiology, involving impaired energy metabolism, elevated mitochondrial ROS (mtROS) production, and mtDNA mutations that drive oxidative stress, endothelial dysfunction, and vascular remodelling.[284–286] mtROS-induced endothelial damage is a well-documented contributor to hypertension,[287] and mitochondria-targeted antioxidants such as MitoTEMPO have demonstrated efficacy in lowering blood pressure in preclinical models.[288] Emerging evidence indicates that mitochondrial dysfunction can mediate ferroptosis.[289–291] For instance, genetic ablation of Sirtuin 3 (SIRT3) —a key mitochondrial deacetylase—reduces mtROS clearance and promotes ferroptosis.[292] Studies show that SIRT3 deficiency in hypertensive patients leads to mitochondrial dysfunction, worsening endothelial impairment, vascular wall thickening, inflammation, and end-organ damage,[286] suggesting that SIRT3 loss-of-function may drive hypertension through ferroptosis. Additionally, cardiolipin—a phospholipid exclusively localized to mitochondrial membranes and essential for cristae formation—is markedly depleted in the hearts of pigs with renovascular hypertension.[293] Niu et al demonstrated that restoring cardiolipin content preserves mitochondrial integrity and suppresses ferroptosis,[294] indicating that enhancing mitochondrial cardiolipin may offer a novel strategy for blood pressure control through ferroptosis inhibition.

Regulatory Factors of Ferroptosis in Hypertension

Nrf2 (nuclear factor erythroid 2-related factor 2) is a master regulator of redox homeostasis and orchestrates the transcriptional regulation of multiple antioxidant genes. It acts as a nuclear receptor target in oxidative stress modulation and plays a key role in hypertension.[295] Farooqui et al showed that Nrf2 inhibition aggravates oxidative stress and inflammation, further worsening hypertension in mice.[296] In contrast, Nrf2 activation in AngII-infused mice (12–14 days post-treatment) mitigates disease progression.[297]

Recent studies show that deacetylase 7 ameliorates renal ferroptosis and lipid peroxidation in hypertensive mice by enhancing Nrf2 expression, thereby alleviating fibrosis and organ dysfunction.[298] Inhibition of Nrf2 significantly increases ROS generation, lipid peroxidation, and ferroptosis in renal tubular endothelial cells, while downregulating GPX4 expression. These findings suggest that Nrf2 modulates hypertension through suppression of ferroptosis in renal endothelium, though more mechanistic work is needed to define its antihypertensive potential. Coenzyme Q10 (CoQ10)

is a mitochondrial cofactor involved in the electron transport chain, ROS suppression, radical scavenging, and vasodilation. Its reduced form functions as a lipophilic antioxidant, effectively inhibiting lipid peroxidation and ferroptosis.[299] CoQ10 exerts direct vasodilatory effects on endothelial cells, contributing to blood pressure reduction.[300] Oral administration of CoQ10 alleviates high-salt-induced hypertension in rats by suppressing NADPH oxidase activity in the hypothalamic paraventricular nucleus,[301] suggesting that CoQ10 may protect against hypertension by reducing mitochondrial lipid peroxidation and ferroptosis in endothelial cells. However, upstream and downstream pathways linking CoQ10 to ferroptosis require further investigation to establish its therapeutic relevance.

Therapeutic Potential of Targeting Ferroptosis in Hypertension

Ferrostatin-1 (Fer-1), a selective ferroptosis inhibitor, reduces lipid peroxidation and suppresses ferroptotic death.[302] Recent studies demonstrate that Fer-1 reverses high-hydrostatic-pressure-induced ferroptosis in VSMCs and improves hypertension and endothelial ferroptosis in mice treated with lenvatinib,[303] highlighting its potential in managing hypertension through ferroptosis inhibition. However, extensive preclinical and clinical evaluations are required to validate its safety and translational feasibility. Elabela, a recently identified 32-amino acid hormone peptide, plays critical roles in cardiovascular function, angiogenesis, and fluid homeostasis. It potently suppresses iron accumulation and lipid peroxidation in AngII-induced hypertensive mice. Mechanistically, Elabela regulates the IL-6/STAT3/GPX4 pathway to inhibit microvascular ferroptosis, pathological remodelling, fibrosis, and cardiac dysfunction, suggesting its therapeutic potential in hypertension and related cardiovascular complications.[304] Elevated lipid peroxidation and free radicals are tightly linked to ferroptosis. Among FDA-approved drugs, several—including carvedilol —have shown anti-ferroptotic properties. Carvedilol, a β-blocker widely used in hypertension treatment, lowers blood pressure by blocking adrenergic receptors and dilating vessels.[305] Additionally, carvedilol exhibits antioxidant effects by scavenging lipid radicals and chelating Fe^{2+}, suggesting that it may suppress ferroptosis.[306] Whether carvedilol exerts antihypertensive effects specifically through ferroptosis inhibition remains to be explored.

Statins, known for their cholesterol-lowering and pleiotropic vascular benefits, also exhibit anti-ferroptotic activity. Atorvastatin inhibits ferritinophagy-mediated ferroptosis and improves cardiac function in murine models.[307] Furthermore, atorvastatin may alleviate arsenic-induced hypertension through lipid profile improvement, nitric oxide pathway restoration, and vascular redox rebalance,[308] implicating statins as dual-action agents in ferroptosis and hypertension management.

Other compounds with ferroptosis-inhibitory potential include N-acetylcysteine (NAC), a thiol-containing precursor of GSH that modulates GPX4 expression and exhibits antioxidant properties.[309] NAC treatment protects male offspring of spontaneously hypertensive rats (SHR) from developing hypertension,[310] indicating possible clinical applications in ferroptosis-targeted antihypertensive therapy. Puerarin, an isoflavone derived from Pueraria lobata root, is extensively used in cardiovascular and cerebrovascular disease treatment. It exerts antioxidant and anti-ferroptotic effects in various disease contexts by reducing iron overload and lipid peroxidation.[311,312] Experimental findings also show that puerarin lowers blood pressure in high-salt-induced hypertensive mice and SHR models.[313,314] While no direct evidence yet supports a role for puerarin in ferroptosis inhibition in hypertension, it presents a promising preventive strategy worth exploring. Despite accumulating evidence linking antioxidants to both ferroptosis and hypertension, further studies are required to clarify their interplay. The molecular mechanisms connecting ferroptosis to hypertension remain incompletely understood, and the identification of robust ferroptosis-specific biomarkers in hypertensive tissues is still lacking. Though ferroptosis has been observed in animal and cell culture models of hypertension, the precise contribution of ferroptosis to disease progression remains to be confirmed. Therefore, translation of these findings into clinical practice will require: (1) Multi-omics profiling to identify ferroptosis signatures in hypertensive patients; (2) High-resolution imaging of iron deposition and lipid oxidation in patient-derived tissues; (3) Preclinical testing of novel ferroptosis inhibitors in hypertension models; (4) Clinical trials evaluating iron chelators, antioxidants, and redox modulators in hypertensive syndromes.

Collectively, current evidence supports a significant role for ferroptosis in hypertension pathogenesis. With ongoing research, targeting ferroptosis may emerge as a viable and effective strategy for blood pressure control and cardiovascular protection in hypertensive individuals.

Ferroptosis in the Pathological Process of Aortic Dissection

Aortic dissection (AD) is a life-threatening condition characterized by intimal tear or intramural hemorrhage, leading to the separation of the aortic wall layers. It predominantly affects individuals aged 65–75 years, with an annual incidence rate of approximately 35 cases per 100,000 people in this demographic.[315] Established risk factors include hypertension, dyslipidemia, and inherited connective tissue disorders such as Marfan syndrome.[316] Recent studies have identified significant iron overload and lipid peroxidation in AD tissues, accompanied by widespread dysregulation of redox homeostasis-related gene expression. Key markers such as ferritin and terminal lipid peroxidation products like 4-hydroxynonenal (4-HNE) are markedly upregulated in the medial layer of dissected aortas.[317,318]

Furthermore, Tao et al found elevated protein expression of PTGS2 (COX-2) —a ferroptosis-promoting gene—and reduced expression of GPX4, a central anti-ferroptotic enzyme, particularly in endothelial cells from AD patients,[319] reinforcing the hypothesis that ferroptosis actively contributes to cellular degeneration in both endothelial and vascular smooth muscle cell compartments. The β-aminopropionitrile (β-APN) -induced mouse model of AD has been widely used to study disease mechanisms. β-APN causes medial degeneration, VSMC loss, and fragmentation of elastic fibers—hallmarks of AD pathology. In these models, iron death-related genes are significantly upregulated alongside increased lipid peroxidation, and these effects can be mitigated by specific ferroptosis inhibitors.[317,318] Mechanical stretch inhibits the CSE/H2S pathway in VSMCs, reducing GSH synthesis, downregulating GPX4 activity, and enhancing sensitivity to ferroptosis.[257] These findings suggest that ferroptosis is not merely a bystander effect but plays a direct role in structural degradation and disease progression in AD.

Iron Dyshomeostasis and Ferroptosis in Aortic Dissection

Cellular iron homeostasis is precisely maintained by a coordinated regulatory network of iron uptake, transport, storage, and export. When free iron accumulates excessively within the cell, it catalyzes hydrogen peroxide into highly reactive hydroxyl radicals through the Fenton reaction.[11,320] This initiates chain reactions of lipid peroxidation in polyunsaturated fatty acids, which constitute the core execution mechanism of ferroptosis. In this process, the endoplasmic reticulum acts as the central organelle for cellular lipid synthesis and remodeling. Its membrane-localized lysophosphatidylcholine acyltransferase 3 (LPCAT3) serves as a key regulator of lipid homeostasis: LPCAT3 specifically catalyzes the reacylation of phosphatidylcholine, enriching it with polyunsaturated fatty acids such as arachidonic acid and adrenic acid. These phospholipids provide the primary substrates for lipid peroxidation, directly amplifying the ferroptotic cascade. At the same time, disruption of endoplasmic reticulum lipid homeostasis further exacerbates endoplasmic reticulum stress, forming a vicious cycle with ferroptosis signaling that intensifies structural and functional damage to the vascular wall.

Clinical sample studies have confirmed that iron content in the serum and lesional aortic tissues of patients with aortic dissection (AD) is significantly higher than that in healthy control populations, with the iron load in dissected aortic tissue reaching twice the level of normal aortic tissue.[319] In AD lesion specimens, transferrin receptor 1 (TfR1), which is responsible for iron uptake, is significantly upregulated at both mRNA and protein levels. This is accompanied by elevated ferritin expression and significantly increased concentrations of total tissue iron and free divalent iron (Fe^{2+}), suggesting the presence of clear abnormal iron uptake and iron overload in the local lesion.[317,318]

However, epidemiological studies have presented seemingly contradictory conclusions: the incidence risk of Stanford type A and type B AD is negatively correlated with circulating iron concentrations, and peripheral blood transferrin levels, total iron-binding capacity, and transferrin saturation in AD patients are all significantly lower than in healthy individuals.[321,322] Animal experiments further confirmed that systemic iron deficiency induced by a low-iron diet combined with Ang can significantly exacerbate degenerative changes in the aortic media, promote phenotypic switching of vascular smooth muscle cells (VSMCs), mitochondrial fragmentation and functional damage, thereby accelerating the occurrence and development of AD.[321,322] Shi et al also found that iron deficiency can significantly aggravate endoplasmic reticulum stress, mitochondrial oxidative damage, and vascular cell apoptosis in AngII-treated mice, accompanied by downregulation of the key iron metabolism molecules TfR1 and the iron exporter FPN1.[323]

The aforementioned seemingly contradictory research findings collectively reveal the classic “iron paradox” phenomenon in the field of cardiovascular disease. Its core lies in the tissue-specific heterogeneity between systemic iron homeostasis and local vascular iron metabolism, as well as the dual pathological effects of bidirectional imbalance

between iron overload and iron deficiency. On the one hand, systemic iron deficiency can exacerbate degenerative changes in the aortic media by inducing endoplasmic reticulum stress, mitochondrial structural and functional damage, and phenotypic switching of VSMCs, thereby serving as an important susceptibility factor for the occurrence of AD. On the other hand, local iron overload in the aortic wall drives the lipid peroxidation cascade and ferroptosis through the Fenton reaction, directly compromising the structural integrity of the aortic wall and promoting the progression of AD. This differentiated pathological effect of systemic versus local iron metabolism has also been validated in other cardiovascular diseases: for example, systemic iron supplementation significantly improves cardiac function and clinical prognosis in patients with iron-deficient heart failure, while local vascular iron chelation intervention effectively inhibits vascular ferroptosis and remodeling processes. This distinction also provides a core direction for the precise prevention and treatment of AD—namely, the need to simultaneously maintain systemic iron homeostasis and regulate iron load at the lesional site, rather than relying on single iron supplementation or iron depletion therapy.

In addition, peripheral blood biomarkers based on iron homeostasis imbalance (serum iron, transferrin, ferritin, etc) have been integrated into AD diagnostic models such as the FLUTHE score. This model exhibits a sensitivity as high as 0.954 and a specificity of 0.905 in distinguishing AD from acute coronary syndrome, thereby providing a novel combination of biomarkers and a clinical tool for the early rapid differential diagnosis of AD.[324]

Heme Oxygenase-1 (HO-1) and Hypoxia-Inducible Factor-1α (HIF-1α) Signaling in AD Ferroptosis

HO-1, a key enzyme in heme degradation, is strongly induced under hypoxic and oxidative stress conditions.[325] As a master regulator of oxygen sensing, HIF-1α —the active subunit of HIF-1—plays a central role in modulating HO-1 expression.[326] In human AD tissues, both HO-1 and HIF-1α are significantly upregulated. The HIF-1α/HO-1 axis promotes massive heme breakdown, releasing free iron into the aortic wall, which subsequently fuels the Fenton reaction, generating ROS and driving lipid peroxidation and ferroptosis.[327] Shi et al further demonstrated that cystine deprivation or IKE-induced ferroptosis in human aortic smooth muscle cells (HASMCs) leads to decreased histone acetyltransferase P300, which activates the HIF-1α/HO-1 pathway and promotes ferroptosis.[328] This study reaffirms the pivotal role of HIF-1α/HO-1 signaling in AD-associated ferroptosis. Despite its pro-ferroptotic potential, HO-1 may also exert protective effects by neutralizing heme toxicity and reducing inflammation.[329] Liao et al proposed that downregulation of HO-1 could serve as a marker of ferroptosis in AD,[330] conflicting with earlier reports suggesting its activation promotes iron-dependent cell death. This discrepancy may arise from differences in experimental models and induction methods, highlighting the complexity of HO-1 function in ferroptosis regulation.

Lipid Peroxidation Induces Ferroptosis in Aortic Dissection

In addition to iron metabolic dysregulation, lipid peroxidation is another fundamental element contributing to ferroptosis in aortic dissection. Polyunsaturated fatty acids (PUFAs) and phosphatidylethanolamine (PE) are two major substrates for lipid peroxidation, among which phosphatidylethanolamine contains arachidonic acid or its derivative adrenic acid. Research has shown that the oxidation of both PUFAs and phosphatidylethanolamine transmits ferroptotic signals. Arachidonic acid can first be converted into arachidonoyl-CoA via acyl-CoA synthetase long-chain family member 4 (ACSL4), which further transforms into phosphatidylethanolamine-arachidonic acid, ultimately being oxidized into lipid peroxidation substrates.[331,332] Under conditions of high hydrostatic pressure or angiotensin II (Ang II) stimulation, ACSL4 expression in vascular smooth muscle cells (VSMCs) is significantly upregulated, which represents a key contributor to VSMC ferroptosis; inhibition of ACSL4 reduces the accumulation of intracellular lipid peroxidation substrates, thereby suppressing ferroptosis.[257,333] The Xc^- system and glutathione peroxidase 4 (GPX4) are core inhibitory factors in the regulation of lipid peroxidation during ferroptosis in aortic dissection. The Xc^- system functions as a glutamate/cystine antiporter, composed of a heterodimer formed by the light chain subunit SLC7A11 and the heavy chain subunit SLC3A2. Among these, SLC7A11 mediates the transport activity of the Xc^- system, while SLC3A2 primarily maintains the protein stability of SLC7A11.[334] The Xc^- system transports extracellular cystine into the cytoplasm for glutathione (GSH) synthesis, which serves as a crucial antioxidant protecting cells from oxidative stress-induced damage. In human aortic smooth muscle cells (HASMCs) stimulated with cystine deprivation, IKE, or GPX4 inhibitor RSL3, both SLC7A11 and SLC3A2 protein levels were significantly downregulated, leading to

suppression of the Xc^- system and impaired GSH synthesis. GSH deficiency directly inhibits GPX4 activity and results in excessive accumulation of phospholipid hydroperoxides, ultimately triggering ferroptosis and disruption of aortic homeostasis.[317,318] In addition to the Xc^- system and GPX4, other molecules such as ferroptosis suppressor protein 1 (FSP1), GTP cyclohydrolase 1 (GCH1), and dihydroorotate dehydrogenase (DHODH) have also been identified as important effectors involved in phospholipid hydroperoxide clearance and suppression of lipid peroxidation in aortic dissection.[328,335]

Other Factors Contributing to Ferroptosis in Aortic Dissection

In exploring ferroptosis-related genes in aortic dissection, Pan et al[336] identified DAZAP1 and GABARAPL2 as core ferroptosis-associated genes in Stanford type A aortic dissection based on high-throughput sequencing data from patients. DAZAP1, a widely expressed RNA-binding protein, plays an important role in post-transcriptional modification. GABARAPL2 was identified due to its involvement in protein trafficking and membrane fusion. Further immune infiltration analysis revealed that DAZAP1 expression showed a positive correlation with monocyte abundance, whereas GABARAPL2 expression exhibited a negative correlation with monocytes. Both genes may serve as potential diagnostic biomarkers for Stanford type A aortic dissection. Zou et al[337] constructed a protein-protein interaction network and identified six key ferroptosis-related genes—CA9, HMOX1, IL-6, CDKN1A, HIF1A, and MYC—from differentially expressed ferroptosis-associated genes between Stanford type A aortic dissection and normal aortic tissues. These six genes were all upregulated in Stanford type A aortic dissection.

Smoking-Induced Ferroptosis in Aortic Dissection

Smoking is a well-established risk factor for aortic dissection.[338] Studies have found that cigarette smoke extract (CSE) stimulation causes reduced viability and death of rat vascular smooth muscle cells, effects that can be completely inhibited by specific ferroptosis inhibitors or iron chelators. CSE exposure also induces elevated lipid peroxidation levels and triggers key features of ferroptosis, including inflammation and depletion of the endogenous antioxidant glutathione.[339] Zou et al[337] screened four ferroptosis-related genes—CA9, IL-6, CDKN1A, and HIF1A —in aortic dissection using bioinformatics approaches, and validated their close association with CSE-induced ferroptosis in HASMCs at the cellular level.

Mitochondria are one of the primary sites of cellular biooxidation, and mitochondrial morphological changes during ferroptosis are characterized by increased membrane density, reduced volume, and fragmentation or loss of mitochondrial cristae.[340] Transmission electron microscopy revealed extensive mitochondrial loss in vascular smooth muscle cells treated with CSE, with only a few residual mitochondrial fragments remaining. However, vascular smooth muscle cells pretreated with ferroptosis inhibitors showed resistance to CSE-induced damage, with relatively preserved mitochondrial structures.[339] Nicotine, a core component of CSE, has been shown to induce ferroptosis in human umbilical vein endothelial cells (HUVECs) in a dose-dependent manner, simultaneously suppressing GPX4 expression. Notably, the ferroptosis inhibitor Ferrostatin-1 can block nicotine-induced ferroptosis in HUVECs.[319]

Epigenetic Abnormalities in Ferroptosis During Aortic Dissection

Epigenetic mechanisms, including non-coding RNAs, RNA methylation, and protein methylation, are increasingly recognized as critical contributors to ferroptosis in aortic dissection.[341] MicroRNAs (miRNAs), endogenous non-coding single-stranded small RNA molecules, regulate ferroptosis by inducing mRNA cleavage or translational repression of target genes, playing pivotal roles in cardiovascular diseases such as aortic dissection.[342,343] High-throughput screening identified miR-1909-5p as capable of directly binding to the core anti-ferroptosis gene GPX4, thereby negatively regulating GPX4 expression at both transcriptional and translational levels. Overexpression of miR-1909-5p exacerbates nicotine-induced ferroptosis in HUVECs. Conversely, miR-1909-5p knockdown or supplementation with exogenous recombinant GPX4 protein partially reverses the pro-ferroptotic effects of nicotine, suggesting that miR-1909-5p plays a significant role in nicotine-induced ferroptosis of endothelial cells in certain smokers with aortic dissection.[319] Long non-coding RNAs (lncRNAs), which do not encode proteins, play essential regulatory roles in key physiological and pathological processes such as transcription, translation, post-transcriptional modifications, and RNA/protein stability, and are critically involved in the regulation of ferroptosis in cardiovascular diseases like aortic dissection.[343] Among

them, NORAD is a highly conserved lncRNA that inhibits ferroptosis through modulation of GPX4, exerting protective effects against aortic dissection.[330] The RNA methyltransferase METTL3 mediates m6A methylation of NORAD in an YTHDF2-dependent manner, indicating that NORAD could serve as a potential therapeutic target for aortic dissection.[330] Moreover, studies have found that METTL3 itself is significantly upregulated in the aortas of patients with aortic dissection, and its protein levels show a negative correlation with those of the ferroptosis-inhibiting proteins SLC7A11 and FSP1 in human aortas. Overexpression of METTL3 in HASMCs suppresses SLC7A11 and FSP1 expression, promoting ferroptosis sensitivity. In contrast, METTL3 knockdown enhances SLC7A11 and FSP1 expression and increases ferroptosis resistance in HASMCs.[317] Protein methylation is another common form of post-translational modification, particularly histone methylation. Emerging evidence suggests that histone methylation contributes to the pathogenesis of ferroptosis in aortic dissection.[344] Histone methylation sites H3K9me1, H3K9me2, and H3K9me3 were found to be upregulated in HASMCs treated with ferroptosis inducers such as cystine deprivation, IKE, or RSL3, indicating that H3K9 methylation is a key epigenetic mechanism regulating ferroptosis in the aortic wall.[318] Additionally, H3K4 methylation has also been implicated in ferroptosis associated with aortic dissection. Levels of H3K4me1 and H3K4me2 were reduced in mice with β-aminopropionitrile-induced aortic dissection, which further led to massive deposition of ferrous ions and intense Fenton reactions, ultimately resulting in ferroptosis.[335]

Immune Cell Dysfunction and Ferroptosis in Aortic Dissection

There is a close relationship between ferroptosis and immune dysfunction in aortic dissection.[345] T lymphocytes are essential components of the immune response system. Naive T cells differentiate into effector memory T cells upon antigen exposure, migrate to target organs, and reside there, playing a crucial role in orchestrating immune responses.[346] Li et al[347] investigated the activation and functional diversity of CD4+ T cells during differentiation and their impact on ferroptosis in aortic dissection. They found that the proportion of CD36-expressing CD4+ T cells was significantly upregulated in patients with aortic dissection. CD36 promotes ferroptosis in CD4+ T cells by facilitating fatty acid uptake, leading to T cell dysfunction, mitochondrial loss, and impaired differentiation, which are associated with poor postoperative outcomes in patients with aortic dissection. In addition to T lymphocytes, other types of immune cells such as macrophages are also closely linked to the progression of ferroptosis.[348] Ferroptosis in macrophages has been reported in the context of atherosclerosis and aneurysms,[349,350] although its potential role in aortic dissection remains to be fully elucidated.

Intervention Strategies Targeting Ferroptosis in Aortic Dissection

Ferrostatin-1 is the first-generation ferroptosis inhibitor, which was first reported in 2012 for its anti-ferroptotic effects.[351] Building upon this foundation, Zilka et al further elucidated the antioxidant mechanism of Ferrostatin-1 through structure–activity relationship studies of chemical compounds. They found that the N-cyclohexyl group in Ferrostatin-1 functions as a lipophilic anchor within biomembranes and serves as a critical structural basis for its reductive and antioxidant properties, making it essential for effective inhibition of ferroptosis.[351] Relevant studies have shown that Ferrostatin-1 can maintain cell viability in human aortic smooth muscle cells (HASMCs) under cystine deprivation, IKE, or RSL3 stimulation, while also downregulating HO-1 levels, suppressing lipid peroxidation, and preventing ferroptosis.[318] In addition, Ferrostatin-1 has been demonstrated to significantly inhibit ferroptosis in rat thoracic aorta smooth muscle cell line A7r5 and vascular smooth muscle cells induced by cigarette smoke extract (CSE), thereby preventing massive loss of aortic smooth muscle cells in CSE-treated mice.[339] However, due to its instability during plasma metabolism, the actual therapeutic efficacy of Ferrostatin-1 in vivo may be weaker than what is observed in vitro.[352]

Liproxstatin-1 is another specific inhibitor of ferroptosis, originally identified from tamoxifen-induced Gpx4 −/− mouse embryonic fibroblasts.[353] Zilka et al confirmed that Liproxstatin-1, similar to Ferrostatin-1, possesses strong radical-trapping antioxidant activity, with the quinoxaline ring being the key functional group responsible for scavenging peroxyl radicals.[354] Liproxstatin-1 has been shown to inhibit the development and rupture of aortic dissection in β-aminopropionitrile (BAPN)-induced mouse models, while simultaneously downregulating ferroptosis markers such as transferrin receptor and HO-1, demonstrating its potent inhibitory effect on ferroptosis in vivo.[317] Moreover, HIF-1α plays an important role as a driver of ferroptosis in aortic dissection, with its overexpression closely associated with oxidative stress in the microenvironment of dissected aortas. Shi et al discovered that BAY87-2243, a selective HIF-1α inhibitor, could significantly reduce HIF-1α

expression, suppress ferroptosis in HASMCs triggered by cystine deprivation and IKE, enhance cell viability, and decrease lipid peroxidation. Further in vivo validation is required to confirm these findings.[328] Given the potential role of histone methylation in aortic dissection, domestic researchers have found that BRD4770, a specific inhibitor targeting histone methylation sites H3K9me1/2/3, can significantly suppress ferroptosis in HASMCs, with therapeutic effects comparable to those of Ferrostatin-1. BRD4770 can also delay the onset and progression of BAPN-induced aortic dissection in mice by inhibiting ferroptosis, lipid peroxidation, and inflammation.[318] Notably, the protein levels of histone methylation sites H3K4me1 and H3K4me2 were found to be reduced in mouse aortic dissection tissues. Researchers screened out SP2509, a specific pharmacological agent targeting H3K4me1 and H3K4me2, capable of inducing demethylation of H3K4 in a flavin adenine dinucleotide (FAD)-dependent manner.[355] SP2509 can upregulate the protein levels of H3K4me1 and H3K4me2 in aortic dissection tissues and reduce intracellular ferrous iron levels by modulating iron transport mechanisms, thereby preventing ferroptosis in HASMCs.[335]

It is worth noting that although many small-molecule compounds exhibit promising anti-ferroptotic effects in vitro, their rapid degradation and low therapeutic efficiency in vivo may limit clinical translation. To address this limitation, some researchers have proposed a three-dimensional printed hydrogel system capable of sustained release of mesenchymal stem cell-derived exosomes, offering a novel drug delivery approach for treating aortic dissection by preventing aortic degeneration and ferroptosis.[356] These interdisciplinary studies based on nanomaterials provide new perspectives for targeted intervention strategies against ferroptosis in aortic dissection. In summary, current research has established the crucial role of ferroptosis in aortic dissection, and further clarification of its molecular mechanisms may offer novel precision intervention targets for this disease. Future research directions include the following: (1) Identification of Novel and Specific Biomarkers and Therapeutic Targets: Most of the currently identified ferroptosis-related targets in aortic dissection have previously been reported in other cardiovascular diseases or cancers. Future studies should employ multi-omics approaches and high-throughput screening technologies to identify and validate novel biomarkers and specific therapeutic targets for ferroptosis in aortic dissection. This will help establish a more precise understanding of the unique molecular signatures involved in aortic dissection-associated ferroptosis. (2) Clarifying the Causal Relationship Between Ferroptosis and Aortic Dissection: Aortic dissection results from the progressive accumulation of aortic degeneration. Therefore, to confirm ferroptosis as a driving factor in aortic dissection, it is essential to demonstrate the presence of iron overload and lipid peroxidation prior to the onset of dissection. Due to current limitations in animal models and clinical samples, most existing studies co-administer ferroptosis inhibitors and disease-inducing agents, leaving the causal link between ferroptosis and aortic dissection unproven. Future investigations should focus on dissecting the temporal dynamics of ferroptosis induction across different stages of aortic dissection modeling. Additionally, variations in modeling methods—such as the use of BAPN or Ang II—and differences in mouse strains, age, and sex should be systematically evaluated for their impact on ferroptosis in aortic dissection. As genome-wide association studies (GWAS) expand globally, methods such as Mendelian randomization could also be employed to verify the causal relationship between ferroptosis and aortic dissection. (3) Development of Stable and Efficient Delivery Systems for Ferroptosis Inhibitors: Drugs such as Ferrostatin-1 suffer from poor metabolic stability in vivo, whereas nucleic acid-based therapeutics like miRNAs and lncRNAs face challenges related to low delivery efficiency, poor stability, and susceptibility to nuclease degradation.[357] Nanomedicine has shown considerable promise in mitigating oxidative stress and enabling precise delivery of small molecules or nucleic acids in aortic diseases, including aortic dissection.[356,358,359] Thus, combining nanotechnology with ferroptosis-targeted therapies may facilitate deeper mechanistic insights and accelerate the translation of novel therapeutic strategies for aortic dissection. (4) Development of Specific Diagnostic Tools Based on Ferroptosis: Developing highly specific diagnostic tools and rapid detection kits targeting key components of the ferroptotic microenvironment, particularly iron ions, represents a promising avenue for future research.[360] Such tools could enable early diagnosis and monitoring of ferroptosis-related changes in patients at risk for aortic dissection. In summary, a deeper understanding of the key regulatory nodes of ferroptosis already identified in aortic dissection, combined with targeted basic and clinical investigations, will further elucidate the pathogenesis of this life-threatening condition. These efforts will not only contribute to the discovery of novel biomarkers and therapeutic interventions but also pave the way for the development of precision medicine strategies aimed at the prevention and treatment of aortic dissection.

Mechanisms of Ferroptosis Inhibitors and Inducers in Cardiovascular Diseases

Ferroptosis is a form of regulated necrosis driven by iron-dependent lipid peroxidation and redox imbalance, playing a pivotal role in the pathogenesis of various cardiovascular diseases (CVDs).[361] Therefore, understanding and targeting ferroptosis with pharmacological modulators—either inhibitors or inducers—has emerged as a promising strategy for therapeutic intervention.

Ferroptosis Inhibitors and Their Roles in Cardiac Pathology

Given its involvement in myocardial injury, heart failure, ischemia–reperfusion (I/R) damage, and chemotherapy-induced cardiotoxicity, ferroptosis has become a central focus in cardiac disease research. Current ferroptosis inhibitors act through multiple mechanisms, including iron chelation, ROS scavenging, and inhibition of lipid peroxidation, and can be broadly classified into three categories: antioxidants, iron chelators, and ACSL4 inhibitors.

Antioxidants

Lipophilic radical-trapping antioxidants inhibit ferroptosis by directly blocking the propagation of lipid peroxidation chain reactions.[361] For example, ferrostatin-1 (Fer-1) reduces mortality in doxorubicin (DOX)-induced cardiotoxicity models, significantly lowers the expression of hypertrophic markers at both mRNA and protein levels, and restores mitochondrial gene expression impaired by DOX.[362] Recent studies have identified that vitamin K, under the catalysis of ferroptosis suppressor protein 1 (FSP1), is converted into hydroquinone, a lipophilic antioxidant capable of preventing lipid ROS accumulation and suppressing ferroptosis.[363] These findings suggest that hydroquinone derivatives may hold promise in CVD therapy; however, further investigation—including clinical trials—is required to validate their efficacy and safety profile.

Iron Chelators

Iron chelators such as deferoxamine (DFO), dexrazoxane, and deferiprone reduce intracellular Fe^{2+} levels and inhibit Fenton reaction-driven ROS generation and lipoxygenase (LOX) activation, thereby suppressing lipid peroxidation and ferroptosis.[364]

Among these, dexrazoxane is currently the only FDA-approved agent for preventing DOX-induced cardiotoxicity in cancer patients.[362] Histological assessments indicate that dexrazoxane and Fer-1 exhibit comparable protective effects against DOX-induced cardiac injury.[362] Recent evidence suggests that deferiprone outperforms DFO and deferasirox in acute hemorrhagic myocardial infarction models, accelerating hematoma clearance, reducing inflammation, and attenuating chronic adverse remodelling post-injury.[365] Moreover, DFO protects against diabetic cardiomyopathy (DCM) by preserving cardiomyocyte viability and suppressing elevated ferroptosis markers, demonstrating its broad utility in metabolic heart disease.[122] These data support the potential use of iron chelation as a preventive strategy in acute hemorrhagic myocardial infarction.

ACSL4 Inhibitors

Thiazolidinediones (TZDs)—including rosiglitazone, pioglitazone, and troglitazone —are classical agonists of PPARγ but have recently been shown to inhibit acyl-CoA synthetase long-chain family member 4 (ACSL4), thereby suppressing ferroptosis and lipid peroxidation.[122] Rosiglitazone has been demonstrated to reduce COX-2 and LDH expression, inhibiting ferroptosis and alleviating I/R injury in experimental models.[366] However, this study was conducted using an intestinal I/R model, highlighting the need to evaluate rosiglitazone's efficacy specifically in myocardial I/R settings to overcome current limitations in cardiac applications. In atherosclerosis, rosiglitazone suppresses fatty acid conversion to diacylglycerol and triacylglycerol in smooth muscle cells and macrophages, thereby limiting lipid peroxidation and plaque progression.[367] Despite these benefits, TZDs lack specificity for ACSL4 and exert pleiotropic effects beyond ferroptosis inhibition. Thus, future efforts should prioritize the development of selective ACSL4-targeted therapies to better define their cardioprotective roles. Collectively, existing data demonstrate that dexrazoxane and Fer-1 significantly improve survival in DOX-treated mice,[362] while rosiglitazone exhibits anti-ferroptotic activity in multiple experimental models.[366] These findings highlight the therapeutic potential of ferroptosis inhibition in CVD; however, large-scale clinical validation is necessary to assess translational feasibility and safety.

Ferroptosis Inducers and Their Roles in Cardiac Disease

Although ferroptosis is often viewed as a pathological mechanism, certain inducers are being explored for their potential in promoting targeted cell death in specific disease contexts. Based on their molecular targets, ferroptosis inducers can be categorized into four main classes: (1) Those targeting system Xc^-; (2) Those impairing GSH synthesis; (3) Those inhibiting GPX4; (4) Those increasing iron availability and ROS production. Erastin, a classic ferroptosis inducer, binds to voltage-dependent anion channel 2 (VDAC2) and promotes lipid ROS production.[368] It also induces GSH depletion via system Xc^- inhibition, enhances VSMC calcification, and exacerbates cardiac injury in models of DOX-induced cardiomyopathy and I/R injury.[369–371] Similarly, RAS-selective lethal compound 5 (RSL5) interacts with VDAC3 to trigger ferroptosis.[368] Another GPX4 inhibitor, RAS-selective lethal compound 3 (RSL3), accelerates VSMC calcification and worsens I/R injury when mediated by frataxin,[372] indicating that GPX4 inhibition plays a direct role in cardiac pathology. The enzyme glutamate–cysteine ligase (GCL) is essential for GSH biosynthesis. Its inhibition by buthionine sulfoximine (BSO) leads to robust induction of ferroptosis.[373] BSO treatment results in cardiac remodelling, including cardiomyocyte hypertrophy, interstitial fibrosis, reduced contractility, and disrupted ejection fraction,[374] reinforcing the importance of maintaining GSH homeostasis for myocardial function. These findings illustrate that although ferroptosis inducers were originally developed for oncologic applications, they can also drive cardiac injury under certain conditions. Their use in cardiovascular research provides valuable mechanistic insights into how ferroptosis contributes to disease progression, emphasizing the need for tightly regulated therapeutic strategies.

Prospects: Multidimensional Regulation of Ferroptosis and Iron Homeostasis in Cardiovascular Diseases and Clinical Translation

Ferroptosis, a newly identified form of regulated cell death discovered in recent years, is characterized by aberrant iron accumulation, excessive production of lipid reactive oxygen species (ROS), and disruption of the antioxidant defense system. In the cardiovascular field, ferroptosis has been increasingly implicated in multiple pathological processes, including myocardial ischemia-reperfusion injury (MIRI), doxorubicin-induced cardiotoxicity, dilated cardiomyopathy (DCM), atherosclerosis, and cardiac fibrosis. These findings provide novel insights into the pathogenesis of cardiovascular diseases and lay the foundation for developing therapeutic strategies targeting ferroptosis as a core intervention node.

Diversity and Complexity of Ferroptosis Regulatory Networks in Cardiovascular Pathology

The regulatory network of ferroptosis exhibits high complexity and multi-dimensional characteristics. Its core regulatory axes encompass three major modules: the antioxidant defense system centered on system Xc^-/GSH/GPX4, the lipid remodeling and peroxidation metabolism mediated by the ACSL4/LPCAT3 axis, and the iron homeostasis regulated by the TfR1/FPN1/ferritin axis. In addition, this network is deeply interconnected with multiple cellular biological pathways, including autophagy, epigenetic modifications, endoplasmic reticulum stress, and mitochondrial metabolism.

In the cardiovascular system, the ferroptosis regulatory network displays significant tissue specificity, cellular heterogeneity, and spatiotemporal dynamics. The pathological microenvironments of different cardiovascular diseases can differentially activate upstream triggering signals of ferroptosis, whereas distinct cell subpopulations—such as cardiomyocytes, vascular endothelial cells, vascular smooth muscle cells, and macrophages—exhibit marked differences in their sensitivity to ferroptosis, core triggering pathways, and regulatory patterns. These differences indicate that ferroptosis-targeted interventions must adopt precise cell- and disease-specific strategies rather than generalized inhibitory approaches.

A System of Stratum-Specific Biomarkers for Ferroptosis in Cardiovascular Diseases

For ferroptosis to be truly applied in clinical targeted therapy, precise detection and differential diagnosis are the key prerequisites. Currently, laboratory identification of ferroptosis still primarily relies on non-specific oxidative stress indicators such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), and total ROS. These markers are difficult to distinguish from cellular damage or death caused by other forms of oxidative stress, which has become the greatest bottleneck for clinical translation.

To address this problem, the present chapter systematically constructs a three-layer specific biomarker system for ferroptosis in the field of cardiovascular disease. It also clarifies the detection value, specificity, and clinical applicability of various types of markers and proposes joint detection strategies.

The core specific lipid biomarker is oxidized phosphatidylethanolamine (PE-OOH), particularly the oxidized PE derived from long-chain polyunsaturated fatty acids containing arachidonic acid (AA) and adrenic acid (AdA). This is the specific substrate and core marker in the execution phase of ferroptosis. Unlike ordinary lipid peroxidation products, AA/AdA-PE-OOH is the specific catalytic substrate of GPX4, and its elevated levels can directly reflect the activation of the core pathway of ferroptosis. It exhibits high specificity in distinguishing ferroptosis from apoptosis, pyroptosis, and other non-specific oxidative stress injuries, making it the current gold standard marker for identifying ferroptosis.

Pathway-specific protein biomarkers include the specific cleavage fragment of GPX4, the ferritin heavy chain/light chain ratio (FTH1/FTL1), and the specific splice variant of SLC7A11. Among them, the GPX4 cleavage fragment directly reflects the inactivation of the core antioxidant defense system in ferroptosis; the FTH1/FTL1 ratio enables precise tracking of intracellular iron availability and iron homeostasis imbalance, offering greater specificity than measuring total ferritin; the SLC7A11-specific splice variant reflects functional abnormalities in the system Xc^- pathway. The combined use of these three allows comprehensive assessment of the activation status of the core regulatory pathways of ferroptosis.

Clinically accessible circulating biomarkers include non-transferrin-bound iron (NTBI), 4-HNE-protein adducts, and miR-1909-5p. These markers can be detected via peripheral blood and are easily obtainable in clinical practice. Among them, NTBI directly reflects the load of free iron with oxidative activity in circulation and has been confirmed in patient cohorts with aortic dissection, heart failure, and acute myocardial infarction to be significantly associated with disease severity; 4-HNE-protein adducts are more stable than free 4-HNE and can better reflect the accumulation level of lipid peroxidation in vivo; miR-1909-5p participates in ferroptosis by targeting and regulating GPX4, and its circulating levels are closely related to the prognosis of patients with myocardial ischemia-reperfusion injury and heart failure.

Based on the above layered biomarker system, a joint detection strategy of "core specific markers + circulating easy-to-detect markers" can be adopted clinically. This enables precise differentiation of ferroptosis, risk stratification, and efficacy monitoring, thereby laying a reliable diagnostic foundation for the clinical application of ferroptosis-targeted therapy.

The Threshold Effect Triggering Ferroptosis and the Core Regulatory Role of Mitochondria

The occurrence of ferroptosis is not the result of a simple linear accumulation of iron buildup and elevated lipid ROS levels. Rather, it exhibits a distinct "threshold" effect: irreversible lipid peroxidation chain reactions are triggered, ultimately leading to ferroptosis, only when intracellular free iron (ie, the labile iron pool, LIP) and lipid ROS levels simultaneously exceed the compensatory capacity of the cellular antioxidant defense system. In this process, free iron serves as the core catalyst driving the chain reaction through the Fenton reaction, while mitochondria, as the primary intracellular site for iron metabolism and ROS generation, act as the key hub regulating the ferroptosis threshold and execution process.

In terms of threshold control of free iron, the normal physiological concentration of the intracellular labile iron pool is generally maintained at 0.5–1.5 μmol/L. Once this concentration exceeds 2.5 μmol/L, the Fenton reaction is markedly activated, rapidly converting hydrogen peroxide into highly reactive hydroxyl radicals. This substantially lowers the energy barrier for lipid peroxidation and thereby initiates the chain reaction. Conversely, if GPX4 activity decreases by more than 80% or glutathione (GSH) is depleted by more than 70%, the cell essentially loses its capacity to clear lipid peroxides. Under these conditions, even if free iron and ROS remain at physiological levels, ferroptosis can still be induced. This threshold effect varies significantly among different cell types: cardiomyocytes, owing to their high mitochondrial content and elevated basal ROS generation, exhibit a markedly lower ferroptosis triggering threshold than other cells and display greater sensitivity to iron accumulation and lipid peroxidation.

Mitochondria play a dual core role in the regulation of ferroptosis. On one hand, they serve as important initiators and amplifiers of ferroptosis. Dysfunction of the mitochondrial tricarboxylic acid cycle and electron transport chain (ETC) constitutes a key upstream signal for ferroptosis. In particular, damage to ETC complexes I and III leads to the production of large amounts of superoxide anions in mitochondria, providing the initial ROS for lipid peroxidation. At the same

time, mitochondria are the primary site for intracellular iron-sulfur cluster synthesis and heme metabolism. Mitochondrial iron overload directly triggers the Fenton reaction internally, causing lipid peroxidation and membrane damage within the mitochondria themselves. This further amplifies endoplasmic reticulum stress and lipid synthesis disorders through mitochondria–endoplasmic reticulum contact sites, thereby lowering the ferroptosis triggering threshold even further.

On the other hand, mitochondria can also exert a negative regulatory effect on ferroptosis. Dihydroorotate dehydrogenase (DHODH), located on the mitochondrial membrane, synthesizes ubiquinone (CoQ) that cooperates with GPX4 to eliminate lipid peroxides within mitochondria, forming a mitochondria-specific defense system independent of the cytosolic GPX4 pathway. In cardiovascular diseases, pathological processes such as myocardial ischemia-reperfusion injury and doxorubicin-induced cardiotoxicity significantly lower the ferroptosis triggering threshold in cardiomyocytes by inducing mitochondrial iron overload, ETC dysfunction, and DHODH pathway inhibition, ultimately resulting in irreversible cellular damage.

Mechanisms of Differential Regulation of Ferroptosis in Core Cardiovascular Cell Types

In the cardiovascular system, different functional cells exhibit substantial differences in their patterns of iron metabolism, lipid composition characteristics, and antioxidant system expression levels. These inherent differences directly lead to marked cell-specificity in the triggering mechanisms, regulatory pathways, and pathological consequences of ferroptosis. This chapter systematically compares the differential regulatory features of ferroptosis among three key effector cell types in cardiovascular diseases: cardiomyocytes, vascular endothelial cells, and macrophages.

Cardiomyocytes are terminally differentiated cells with extremely high mitochondrial content (approximately 30–40% of cell volume) and very limited regenerative capacity. Ferroptosis in these cells results in irreversible cardiomyocyte loss and cardiac function impairment. Their ferroptosis is primarily driven by mitochondrial metabolic abnormalities and loss of GPX4 function, and they are particularly sensitive to ACSL4-mediated long-chain polyunsaturated fatty acid lipid remodeling and peroxidation. Iron homeostasis in cardiomyocytes is precisely regulated by TfR1 (iron uptake) and FPN1 (iron export). In pathological states, upregulation of TfR1 combined with downregulation of FPN1 rapidly induces intracellular iron overload. Cardiomyocyte ferroptosis constitutes the core injury mechanism in myocardial ischemia-reperfusion injury (MIRI), doxorubicin cardiotoxicity, dilated cardiomyopathy (DCM), and myocardial fibrosis.

Vascular endothelial cells serve as the principal component of the vascular barrier. Ferroptosis in endothelial cells represents the initiating event in atherosclerosis, aortic dissection, and hypertensive vascular remodeling. The core triggering factors include inhibition of system Xc^- function, abnormal hemodynamic shear stress, and mechanical stretch injury. Endothelial cells are highly sensitive to pro-atherogenic stimuli such as oxidized low-density lipoprotein (ox-LDL) and cigarette smoke extract. Once ferroptosis occurs, it directly compromises the integrity of the vascular endothelial barrier, resulting in endothelial dysfunction, lipid infiltration, and recruitment of inflammatory cells, thereby initiating and accelerating the progression of vascular lesions. Unlike cardiomyocytes, ferroptosis regulation in endothelial cells depends more heavily on the SLC7A11/GSH pathway rather than the mitochondrial metabolic pathway.

Macrophages act as the central effector cells in the progression and instability of atherosclerotic plaques. Their ferroptosis is mainly driven by intracellular iron overload resulting from hemoglobin phagocytosis and heme catabolism, and is subject to bidirectional regulation by the HO-1/HIF-1α axis. Macrophages display distinct polarization subtype differences: pro-inflammatory M1 macrophages exhibit higher intracellular iron loading due to elevated expression of iron uptake molecules and reduced expression of the iron exporter FPN1, rendering them significantly more sensitive to ferroptosis than anti-inflammatory M2 macrophages. Macrophage ferroptosis leads to foam cell necrosis within plaques, expansion of the lipid core, and massive release of inflammatory mediators, serving as a critical mechanism that promotes atherosclerotic plaque progression and vulnerability to rupture.

Based on these cell-specific differences, targeted interventions for ferroptosis necessitate cell-specific delivery strategies and target selection. For instance, strategies directed at cardiomyocytes should prioritize mitochondrial iron metabolism and the GPX4 pathway; interventions targeting vascular endothelial cells should focus on preserving system Xc^- function; and those aimed at macrophages should emphasize regulation of intracellular iron homeostasis and the HO-1 pathway. Such approaches enable precise therapeutic intervention while minimizing non-specific side effects.

Progress in the Clinical Translation of Ferroptosis-Targeted Therapy

Based on the central driving role of ferroptosis in cardiovascular diseases, the research and clinical translation of ferroptosis-targeted therapeutic agents have emerged as a major research hotspot in the cardiovascular field. Currently, systematic progress has been achieved at three levels: repurposing of approved drugs, development of novel ferroptosis inhibitors, and exploration of clinical trials.

In the area of repurposing approved drugs, drug repurposing serves as the core pathway for ferroptosis-targeted therapies to rapidly advance into clinical application. Several clinically approved drugs have been shown to exert cardiovascular protective effects by regulating ferroptosis, and all of them possess well-documented clinical safety data.

For example, iron chelators such as deferasirox and deferiprone can inhibit ferroptosis by chelating intracellular free iron. Among them, dexrazoxane has already been used to prevent anthracycline-induced cardiotoxicity, with its primary mechanism being the chelation of free iron, suppression of mitochondrial iron overload, and inhibition of ferroptosis. Deferasirox has demonstrated significant cardiovascular protective effects in preclinical studies of myocardial ischemia-reperfusion injury (MIRI), heart failure, and atherosclerosis, and has now entered the stage of small-sample clinical exploration.

SGLT2 inhibitors such as dapagliflozin and empagliflozin, which have been approved for the treatment of heart failure, exert part of their cardiovascular protective effects through the inhibition of ferroptosis. Specifically, these agents can upregulate the expression of SLC7A11 and GPX4, restore cellular antioxidant capacity, and simultaneously inhibit ACSL4-mediated lipid peroxidation, thereby attenuating ferroptosis in cardiomyocytes and endothelial cells.

Statins such as atorvastatin and rosuvastatin, in addition to their classical lipid-lowering effects, can also inhibit ferroptosis in macrophages and vascular smooth muscle cells by suppressing ACSL4 expression, reducing the generation of lipid peroxidation substrates, and upregulating FPN1 to promote iron export, thereby delaying the progression of atherosclerosis.

In addition, PPARγ agonists such as pioglitazone and rosiglitazone can upregulate the expression of GPX4 and FSP1 by activating the PPARγ pathway, thereby enhancing cellular defense against ferroptosis. These agents have shown clear myocardial protective effects in preclinical models of MIRI and diabetic cardiomyopathy.

In the translational research of novel ferroptosis inhibitors, the first-generation specific inhibitors Ferrostatin-1 (Fer-1) and Liproxstatin-1 (Lip-1) can potently scavenge lipid free radicals and block lipid peroxidation chain reactions, demonstrating excellent protective effects in multiple animal models of cardiovascular diseases. However, they still face several critical bottlenecks in clinical translation: Fer-1 is rapidly metabolized in plasma, resulting in a short half-life and low bioavailability; although Lip-1 exhibits better metabolic stability, it suffers from poor tissue penetration and lack of cell-specific targeting.

To address these bottlenecks, current research mainly focuses on three directions: first, prodrug design, through chemical modification of Fer-1 and Lip-1 to synthesize precursor drugs with markedly improved plasma stability that release the active component via enzymatic hydrolysis after entering the body, thereby substantially enhancing bioavailability; second, nanocarrier delivery systems, utilizing liposomes, polymeric nanoparticles, or cell-membrane biomimetic carriers to achieve long-term circulation and, through modification with cardiomyocyte-targeting peptides or endothelial cell-targeting ligands, to realize specific delivery to cardiovascular tissues and reduce systemic off-target effects; third, tissue-specific targeting modifications, through chemical engineering of the inhibitor molecules to enable precise localization to specific sites such as cardiomyocyte mitochondria or vascular endothelial cell membranes, thereby increasing local drug concentration and enhancing therapeutic efficacy.

Core Obstacles and Countermeasures for the Clinical Translation of Ferroptosis

Although ferroptosis-targeted therapy has achieved significant progress in preclinical studies, it still faces multiple important obstacles before it can truly transition from the laboratory to clinical application. This chapter systematically analyzes these translational challenges and their corresponding solutions, with a focus on issues such as differences between animal models and humans as well as drug safety.

First-generation ferroptosis inhibitors (such as Fer-1 and Lip-1) exhibit problems of short plasma half-life, susceptibility to metabolism, and low bioavailability. Most animal experiments employ intraperitoneal injection or local

administration, whereas the clinically common oral or intravenous routes show markedly reduced efficacy, making it difficult to meet practical needs. The primary solutions involve using nanocarriers to achieve long-acting drug circulation and protection, chemical modification of prodrugs to improve plasma stability and half-life, and employing tissue-targeting modifications to concentrate the drug more on cardiovascular lesion sites, thereby reducing the systemic dosage.

Secondly, off-target effects and systemic safety risks arising from non-specific interventions cannot be overlooked. Ferroptosis regulatory molecules are widely expressed across multiple organs throughout the body; systemic administration may lead to liver function abnormalities, reproductive system damage, systemic iron deficiency, neurological side effects, and even potential tumorigenic risks. Key solutions to these problems include developing cardiovascular tissue-specific targeted delivery systems (such as cardiomyocyte-targeting peptides or endothelial-targeting ligands), adopting local administration methods (such as intracoronary administration or local lesion injection), developing subtype-specific inhibitors, and switching to short-term pulse dosing rather than long-term continuous administration to minimize systemic adverse reactions.

Third, the majority of current preclinical studies are based on rodent animal models, which exhibit clear differences from humans in iron metabolism patterns, lipoprotein composition, and the pathological progression of cardiovascular diseases. In addition, animal experiments commonly use preventive administration, whereas clinical cardiovascular diseases typically require therapeutic intervention after disease onset, resulting in substantial differences in timing. Solutions to bridge this gap include using non-human primates for validation, employing human iPSC-induced differentiated cardiomyocytes, endothelial cells, and cardiac organoid models for drug screening, and conducting multi-omics studies based on human clinical samples to verify the true relevance of the relevant targets in humans.

Finally, there is currently a lack of a clinical efficacy evaluation system based on ferroptosis-specific markers, which prevents accurate determination of the actual regulatory effects of drugs on the ferroptosis pathway and makes it difficult to establish the relationship between drug dosage, degree of inhibition, and clinical benefit. To address this issue, the ferroptosis layered biomarker system established previously can be utilized to formulate standardized clinical detection and efficacy evaluation protocols. Dynamic changes in ferroptosis markers can serve as key indicators in clinical trials, thereby providing a reliable basis for dose optimization and efficacy assessment.

Summary: Future Perspectives on Ferroptosis in Cardiovascular Diseases

As a novel form of programmed cell death, ferroptosis is reshaping our understanding of the pathophysiological mechanisms underlying cardiovascular diseases. It not only clarifies the mechanisms of cardiovascular cell injury that cannot be fully explained by traditional oxidative stress theories, but also establishes a new, targetable core node for the prevention and treatment of cardiovascular diseases. From the perspective of basic mechanistic research, the regulatory network of ferroptosis is not a single linear pathway but a complex network deeply interconnected with multiple pathways, including iron homeostasis, lipid metabolism, mitochondrial function, and endoplasmic reticulum stress. Moreover, it exhibits marked cell- and disease-specificity, providing a fresh perspective for understanding both the common and specific injury mechanisms across different cardiovascular diseases.

From the standpoint of clinical translational prospects, the rapid advances in structural biology, artificial intelligence-assisted drug design, gene editing technology, organoid models, and nanodelivery systems are progressively overcoming the translational bottlenecks of ferroptosis-targeted therapy. On the one hand, repurposing studies of already approved drugs offer a feasible route for the rapid clinical translation of ferroptosis-targeted treatments. The elucidation of ferroptosis regulatory mechanisms in widely used clinical agents such as SGLT2 inhibitors, statins, and iron chelators not only provides a novel theoretical explanation for their cardiovascular protective effects but also supplies evidence-based support for expanding their clinical indications. On the other hand, novel ferroptosis inhibitors featuring high specificity, high stability, and tissue-targeting properties are advancing rapidly, with multiple clinical trials progressing steadily; these agents hold promise for introducing entirely new classes of drugs for cardiovascular disease therapy.

Looking ahead, multidisciplinary research on ferroptosis is poised to emerge as a new frontier in cardiovascular therapeutics. Precision-targeted intervention strategies against ferroptosis can provide innovative approaches not only for myocardial protection, improvement of cardiac function, inhibition of vascular remodeling, and reversal of fibrosis, but also for achieving therapeutic breakthroughs in cardiovascular diseases—such as heart failure, ischemic heart disease,

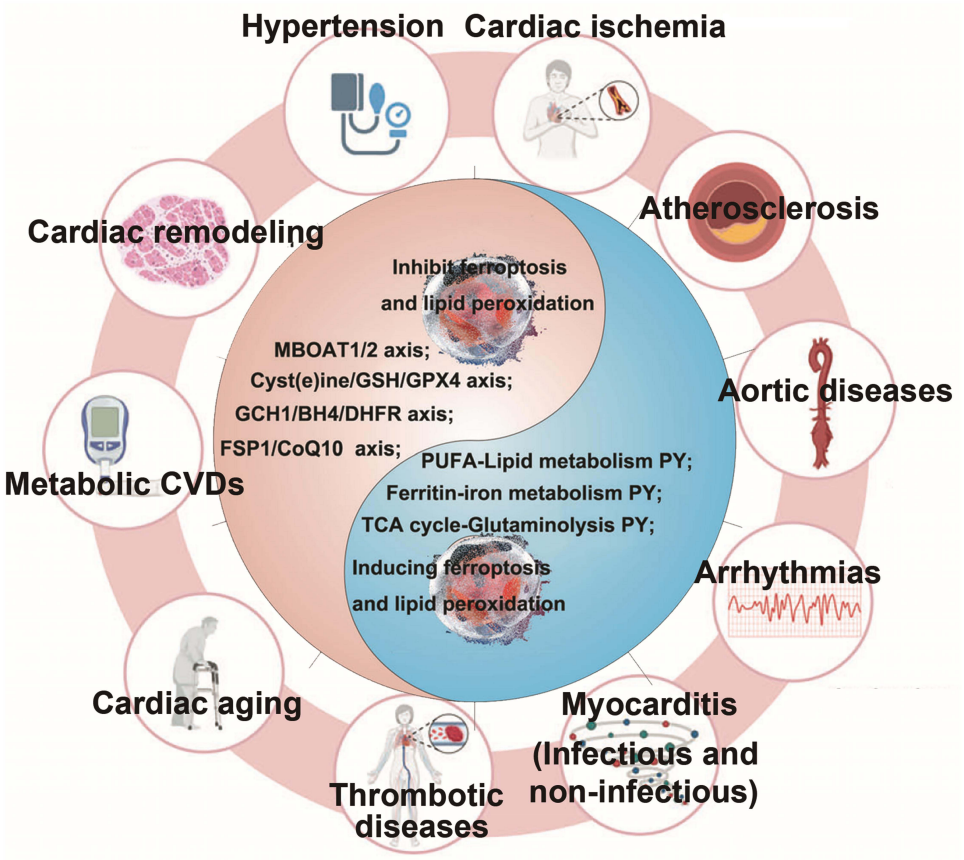

Figure 8 Schematic diagram of the bidirectional regulatory network of ferroptosis/lipid peroxidation and its role in cardiovascular disease [The Tai Chi Yin-Yang model is employed to illustrate the bidirectional regulation of ferroptosis and lipid peroxidation. Dynamic equilibrium between inhibitory pathways (cyst(e)ine/GSH/GPX4, FSP1/CoQ10, and others) and inductive pathways (PUFA-lipid metabolism, iron metabolism, and related pro-pathways) maintains cardiovascular homeostasis, whereas disruption of this balance drives the onset and progression of the full spectrum of cardiovascular diseases, including atherosclerosis, hypertension, and myocardial ischemia. This provides a panoramic theoretical framework for the prevention and treatment of cardiovascular diseases targeting the ferroptosis–iron homeostasis axis. The figure was created with BioRender.

chemotherapy-related cardiotoxicity, aortic dissection, and atherosclerosis—that currently lack effective curative options. To present an intuitive overview of the core regulatory network of ferroptosis, its multidimensional associations with various cardiovascular diseases, and the clinical translational pathways, we have constructed a panoramic schematic diagram of ferroptosis and cardiovascular diseases (Figure 8). This figure systematically integrates the three core regulatory modules of ferroptosis, key molecular pathways, cell-specific regulatory features, and targeted intervention strategies, thereby offering a visualized theoretical framework for subsequent basic research and clinical translation.

Through continued deepening of basic mechanistic studies on ferroptosis, resolution of the core bottlenecks in clinical translation, and establishment of a standardized system for clinical diagnosis and efficacy evaluation, ferroptosis-targeted therapeutic strategies are expected to achieve full translation from bench to bedside. This will represent a revolutionary paradigm for the precise prevention and treatment of cardiovascular diseases and usher in a new era of precision cardiology.

Data Sharing Statement

The data used to support the findings of this study are included within the article.

Ethical Approval and Informed Consent

This article is a review and does not involve any studies with human participants or animals performed by any of the authors. Therefore, ethical approval and informed consent were not required.

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Author Contributions

Tianqing Zhang, Sijie Xiao, Yanfu Xia, and Kun Chen are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, 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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Disclosure

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