Molecular mechanisms of iron metabolism and ferroptosis in cardiovascular diseases and intervention strategies targeting natural products (Review)

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Received July 27, 2025; Accepted April 30, 2026

DOI: 10.3892/mmr.2026.13931

Abstract. Obesity, hypertension and high cholesterol diets are factors that contribute to the development of cardiovascular diseases (CVDs), posing risks to both physical and mental health. The occurrence and progression of CVDs are associated with multiple cell death pathways, such as ferroptosis and autophagy. Ferroptosis, a relatively recently identified form of regulated cell death, is an iron-dependent process of lipid peroxidation that can accumulate to lethal levels, resulting in oxidative damage to cell membranes. The mechanism of ferroptosis involves glutathione (GSH) depletion, iron overload and excessive production of reactive oxygen species (ROS). Iron homeostasis plays a crucial role in maintaining cardiac function and is closely related to the occurrence and progression of CVDs. Studies of various CVD models have found that the major metabolic pathways regulating ferroptosis include iron metabolism, GSH metabolism and lipid metabolism. Modulating these metabolic pathways can regulate the occurrence and execution of ferroptosis in cardiac myocytes, potentially improving CVDs. Targeting the metabolic pathways of ferroptosis may become a new therapeutic direction for CVDs. Therefore, the present review summarized the relationship between ferroptosis and various CVDs, including myocardial diseases, heart failure, atherosclerosis, myocardial ischemia, reperfusion injury, hypertension and aortic dissection, to offer new insights into CVD treatment. In addition, it summarized the inhibitors targeting ferroptosis in CVDs, such as iron chelators (deferoxamine and deferiprone), ROS inhibitors, lipid peroxidation inhibitors and antioxidants (such as alpha-lipoic acid, selenium), which have been proven to be effective in basic experiments and clinical trials and can exert cardiovascular protection.

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Key words: ferroptosis, iron overload, lipid peroxidation, cardiovascular diseases, natural products

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1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide (1). With the aging population in China and the continuous prevalence of metabolic risk factors, the incidence of CVDs is increasing. According to the World Health Organization, ~17.9 million individuals succumb to CVDs globally in 2016, accounting for 44% of mortalities from chronic non-communicable diseases (2). Currently, there are ~330 million individuals in China who have a CVD (2). In 2016, the mortality rates for CVDs in rural and urban areas of China were 309.33 and 265.11 cases per 100,000 individuals, accounting for 45.50 and 43.16% of total mortalities in those areas, respectively (3). In recent years, total hospitalization costs for CVDs in China have been rising rapidly, with an annualized growth rate notably higher than that of gross domestic product, placing a heavy economic burden on the country (4). Therefore, the high incidence, high mortality and high hospitalization rates of CVDs impose a significant burden on socioeconomic development. Developing effective drugs to treat CVDs is urgently required. Understanding the potential mechanisms underlying the occurrence and progression of CVDs is of notable significance for the diagnosis,

prevention and treatment of these diseases (5). Studies have identified eight hallmark features of cardiovascular aging, including macrophage dysfunction, proteostasis loss, genomic instability, epigenetic changes, mitochondrial dysfunction, cellular senescence, neuroendocrine signaling imbalance and inflammation (6,7). These results indicate that the pathological mechanisms underlying CVDs involve programmed cell death, including ferroptosis and autophagy, in various cardiovascular cells (such as cardiomyocytes, endothelial cells and smooth muscle cells) and immune cells (including macrophages and neutrophils) (8-11). Research has found that ferroptosis plays a crucial role in CVDs.

Iron is an essential mineral element necessary for physiological functioning and is involved in processes such as energy metabolism, nutrient synthesis and nucleotide metabolism (12). Previous clinical studies have confirmed that the majority of patients with CVDs exhibit varying degrees of disturbances in iron and lipid metabolism, which contribute to disease progression (13). Programmed cell death is widespread in organisms and is critical for restoring cardiac tissue homeostasis after stress (14). Ferroptosis is a distinct iron-dependent form of regulated cell death driven by the accumulation of reactive oxygen species (ROS) and lipid peroxides. Morphologically, biochemically and genetically, it differs from other cell death processes such as apoptosis, necrosis and autophagy (15,16). The primary mechanism of ferroptosis centers on the iron-dependent buildup of ROS and lipid peroxides (17). When there is a disturbance in cellular iron metabolism, excessive iron ions generate large amounts of ROS through the Fenton reaction (18). The antioxidant system fails to promptly clear these ROS, leading to the attack on polyunsaturated fatty acids (PUFAs) in lipid membranes and the destruction of cellular membrane structures, ultimately culminating in ferroptosis (19). Accumulating evidence demonstrates that ferroptosis is strongly associated with the initiation and progression of a wide range of diseases, including cancer, neurodegenerative disorders, immune system diseases, gastrointestinal diseases, hepatic diseases and renal diseases (20-24). In recent years, iron metabolism, glutathione (GSH) metabolism and lipid metabolism have been identified as the primary metabolic pathways regulating ferroptosis in various CVD models. Modulating these key pathways can effectively control the occurrence and execution of ferroptosis in cardiomyocytes, thereby offering potential therapeutic benefits for CVDs. Consequently, targeting the metabolic regulation of ferroptosis is emerging as a promising strategy for treating CVDs. Therefore, investigating the role of ferroptosis in CVDs and reviewing recent advances in this area can reveal novel therapeutic targets. The present review summarized the relationships between iron signaling, related molecular pathways and ferroptosis in the context of CVDs. In addition, it discussed potential ferroptosis-targeted therapeutic strategies for CVDs, along with their limitations and future research directions. The timeline of ferroptosis research is illustrated in Fig. 1.

2. Overview of ferroptosis

Definition and characteristics of ferroptosis. Since 2003, researchers have identified that small molecules such as Erastin, Ras-selective lethal compound (RSL)3 and RSL5 can trigger a previously unrecognized form of cell death in tumor cells harboring mutated Ras genes (25,26). This type of cell death is morphologically, biochemically and genetically distinct from apoptosis, necrosis and autophagy and cannot be rescued by inhibitors of these classical pathways. However, it can be effectively blocked by iron chelators such as deferoxamine or antioxidants, including vitamin E, indicating a strong dependence on iron and ROS (27).

In 2012, Dixon *et al* (28) formally designated this iron-dependent regulated cell death as ferroptosis. Ferroptosis exhibits unique characteristics that distinguish it from other forms of cell death. Morphologically, it features mitochondrial shrinkage, disappearance of mitochondrial cristae, increased mitochondrial membrane density and rupture of the outer mitochondrial membrane, while nuclear morphology remains largely unchanged (28). Biochemically, it is marked by intracellular iron accumulation, excessive ROS production, inhibition of the cystine/glutamate antiporter System Xc^-, reduced cysteine uptake and GSH synthesis and diminished activity of GSH peroxidase (GPX)4 (29). At the genetic level, ferroptosis is governed by specific regulatory pathways and displays distinctive gene expression profiles and molecular mechanisms (29).

Key indicators of ferroptosis. Currently, researchers primarily detect changes in cell morphology, metabolism and molecular biology to study ferroptosis. Transmission electron microscopy provides direct observation of changes in the cell ultrastructure during ferroptosis, such as mitochondrial shrinkage, disappearance of mitochondrial cristae, increased mitochondrial membrane density and outer membrane rupture, while nuclear morphology remains largely unaffected (30).

Morphological features. Transmission electron microscopy currently provides the most intuitive means of observing changes in cell ultrastructure during ferroptosis. It reveals mitochondrial shrinkage, disappearance of mitochondrial cristae, increased mitochondrial membrane density and outer membrane rupture, while nuclear morphology remains unaffected (30).

Intracellular labile iron ion detection. The instability and high reactivity of Fe^{2+} can generate hydroxyl radicals through the Fenton reaction. Hydroxyl radicals can directly react with PUFAs in cell membranes and plasma membranes, leading to the formation of lipid ROS and causing ferroptosis. Changes in iron ion levels are key indicators of ferroptosis. Fluorescent probes such as FerroOrange, RhoNox-1 and FRET iron probe 1 can be used for rapid and efficient fluorescence imaging of intracellular Fe^{2+} in live cells (31-33).

GSH content detection. Depletion of GSH is one of the important inducers of ferroptosis in cells (34). GSH consists of two forms: Reduced GSH and oxidized GSH disulfide (GSSG). The principle of detection is that GSH reacts with dithiodinitrobenzoic acid to produce a yellow product with maximum absorption at a wavelength of 412 nm, which can be quantified by colorimetry to determine GSH levels (35).

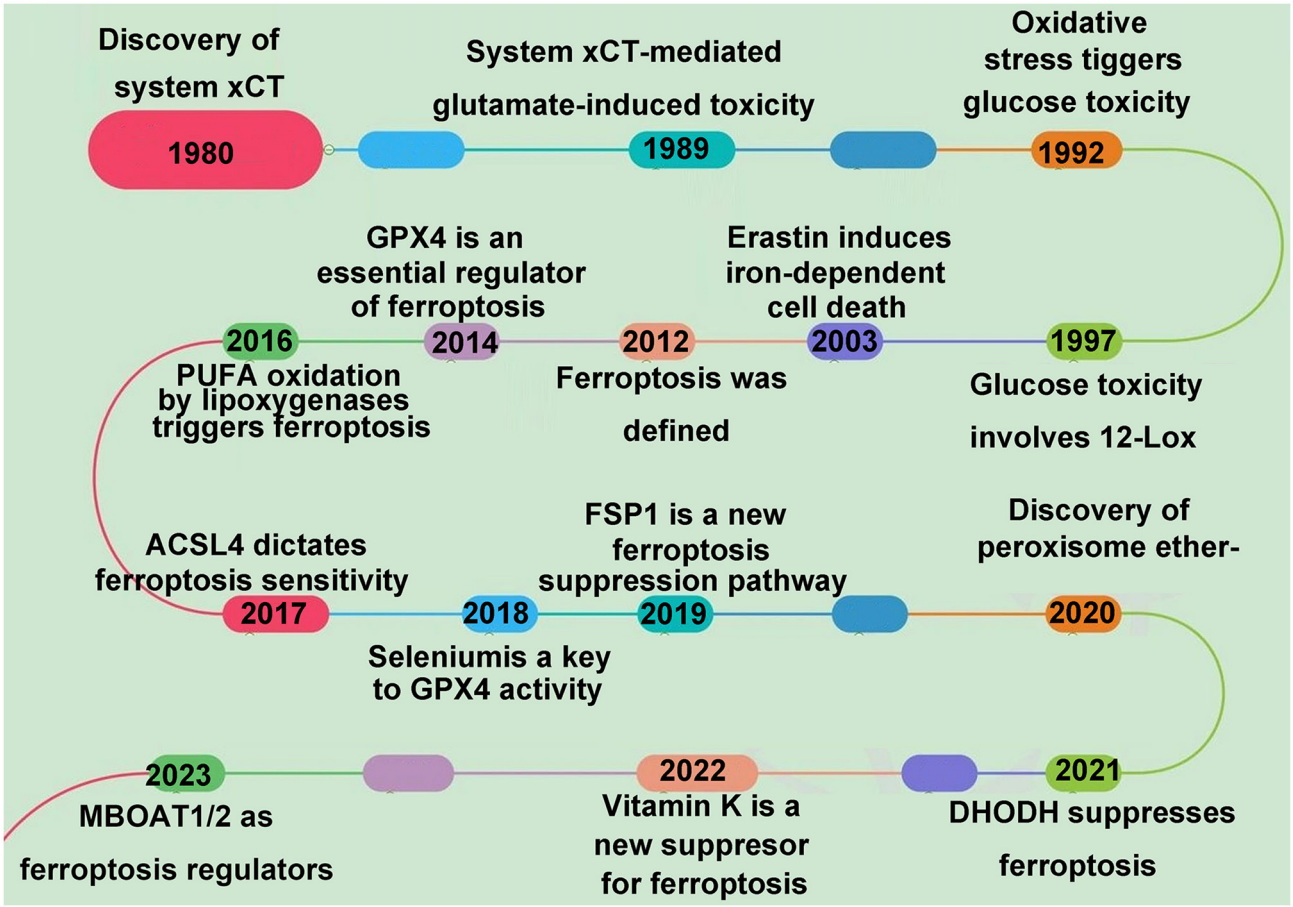

Figure 1. Key milestones timeline in ferroptosis research: from mechanism elucidation to cardiovascular disease intervention. This timeline outlines the core research advances in ferroptosis from 1980 to the present. The progression of these discoveries provides essential theoretical support for interventions in cardiovascular diseases. The foundational period (1980-1997) featured discoveries such as system xCT and 12-LOX, which revealed the role of oxidative stress and lipid metabolism in cell death. The mechanism establishment period (2003-2017) involved erastin-induced ferroptosis, the definition of the ferroptosis concept and identification of key regulators including GPX4 and ACSL4. This clarified ferroptosis as iron-dependent cell death driven by lipid peroxidation. The regulatory network expansion period (2018-2023) included the discovery of new inhibitory pathways such as FSP1, DHODH and vitamin K. These provided multi-level targets for natural compound interventions targeting ferroptosis. This timeline establishes an important foundation for the precise regulation of ferroptosis in cardiovascular diseases. GPX4, glutathione peroxidase 4; PUFA, polyunsaturated fatty acid; ACSL4, acyl-CoA synthetase long-chain family member 4; FSP1, ferroptosis suppressor protein 1; DHODH, dihydroorotate dehydrogenase; MBOAT, membrane bound O-acyltransferase domain containing.

ROS and lipid peroxidation. Iron-dependent accumulation of lipid-derived ROS occurs across all pathways associated with ferroptosis. Uncontrolled lipid peroxidation serves as a defining hallmark of this process. Consequently, ferroptosis is marked by elevated levels of lipid peroxides and ROS. The fluorescent probe 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA) is widely employed to measure intracellular ROS levels. Although inherently non-fluorescent, this compound readily crosses the cell membrane and undergoes hydrolysis by intracellular esterases to form DCFH. Subsequent oxidation of DCFH by ROS generates the fluorescent product DCF, whose intensity provides an indirect indicator of intracellular ROS concentration (36). Reagents such as C11-BODIPY581/591 (intracellular), Liperfluo (intracellular) and MitoPeDPP (mitochondrial) are also used to detect lipid peroxidation levels, reflecting the degree of lipid oxidation in ferroptosis (37-39).

Detection of key regulated genes and proteins in ferroptosis. During ferroptosis, changes occur in the gene and protein expression levels of key regulators, including glutathione peroxidase 4 (GPX4), solute carrier family 7 member 11 (SLC7A11) and transferrin receptor (TfR). Fluorescent quantitative PCR and western blotting can be used to detect changes in the gene transcription and translation levels of key proteins, providing a basis for the detection of cellular ferroptosis (40).

Mechanisms of ferroptosis. Ferroptosis occurs when cellular iron homeostasis is disrupted, lipid peroxides accumulate and the balance of amino acid antioxidants is disrupted. Mechanistically, cellular metabolism is central to ferroptosis, driving lipid peroxidation, generating lipid peroxides and modulating GPX4 activity. Iron further contributes to this process via its cellular uptake, storage and release, as well as through the actions of iron regulatory proteins that maintain intracellular iron balance.

From a regulatory standpoint, several biological processes, including oxidative-reductive reactions, iron homeostasis and cellular metabolism, shape ferroptosis by upregulating or downregulating specific molecules, thereby determining its onset and intensity. For example, nuclear factor erythroid

2-related factor 2 (NRF2) attenuates ferroptosis by inducing the expression of its downstream target genes. Conversely, the E-cadherin-NF2-Hippo-YAP signaling pathway modulates cellular sensitivity to ferroptosis by controlling cell density and intercellular contacts (16,20).

Disruption of iron metabolism. Iron metabolism maintains a balance in the body under normal physiological conditions. Intestinal absorption of dietary iron by enterocytes is crucial for maintaining overall iron levels in the body. The iron reductase primarily reduces non-heme iron in the diet in duodenal epithelial cells, transported across the intestinal cell membrane by divalent metal transporter 1 (DMT1), where it enters the bloodstream to form an iron-transferrin complex (Fe-Tf) when bound to transferrin (Tf) (41,42). The Fe-Tf complex binds to TfR1 on target cell membranes to form the TfR1-Fe-Tf complex, which is endocytosed into the cell. Once iron is released, the complex is recycled to the cell surface for reuse (43). Intracellular iron is reduced to the ferrous state and enters the cytoplasm or organelles, such as mitochondria, to participate in processes such as heme synthesis and iron-sulfur cluster synthesis. Alternatively, it binds to the cytoplasmic iron storage protein (ferritin) within the cell. Excess iron is exported from the cell via transmembrane iron transport proteins (44,45). By contrast, heme iron from meat is directly degraded in intestinal epithelial cells by heme carrier protein and then released into the bloodstream via DMT1 (46). At the systemic level, iron homeostasis is primarily regulated by hepcidin, a hormone produced by liver cells that reduces cellular iron efflux, thereby affecting intestinal iron uptake and macrophage iron release (47-49). In addition to iron levels, inflammation, hypoxia and erythropoiesis regulate hepcidin expression (50). Abnormal metabolism of stored iron, leading to iron overload, occurs when any of these regulatory levels are disrupted. In terms of iron overload in circulation, blood system disorders such as hereditary hemochromatosis associated with major histocompatibility complex class I-like transmembrane protein (HFE) gene mutation (homozygosity for C282Y mutation), juvenile hemochromatosis caused by mutations in the hemochromatosis (hemojuvelin) or hepcidin genes and hemochromatosis caused by mutations in the TfR2 gene are often accompanied by increased serum ferritin levels and transferrin saturation (51). The occurrence of these diseases leads to a lack of hepcidin, resulting in excessive iron absorption from food by intestinal cells and subsequent iron overload. Additionally, hemochromatosis caused by mutations in the SLC40A1 iron transport protein gene results in normal hepcidin levels but decreased sensitivity to hepcidin in various tissues. These two types of hemochromatosis exhibit common phenotypes, including hyperferritinemia and substantial iron overload (52). Chronic diseases requiring repeated blood transfusions, such as severe β-thalassemia, myelodysplastic syndrome, milder forms of sickle cell disease and chronic kidney failure requiring repeated hemodialysis, can lead to chronic iron overload due to plasma transferrin saturation with iron (52,53).

In these cases, non-transferrin-bound iron appears in circulation and the presence of non-transferrin-bound iron in cells does not depend on TfR-mediated endocytosis. Therefore, large amounts of iron are distributed throughout the bloodstream, resulting in iron overload in various organs and toxicity. Compared to hemochromatosis, transfusion iron overload exhibits the highest level of non-transferrin-bound iron (54-56). Additionally, erythroid receptor signal transduction alterations or Tf gene mutations that lead to Tf deficiency can increase non-transferrin-bound iron levels and cause iron overload (57). In terms of cellular iron overload, limited iron export and excessive iron import can result in intracellular iron overload. Diseases characterized by limited iron export, such as iron transport protein disorders caused by mutations in the SLC40A1 and six-transmembrane epithelial antigen of the prostate 3 (STEAP3) genes, disrupt the 'iron export' function of cells and limit iron efflux while not markedly affecting iron import (58,59). Conversely, diseases characterized by excessive iron import, such as those caused by mutations in the SLC11A2 gene, accelerate nuclear iron input and result in visceral iron overload (60,61). Moreover, congenital hypochromic microcytic anemia, caused by mitochondrial deficiency affecting iron metabolism, as proposed by Brissot *et al* (62), is characterized by mitochondrial iron overload in mature red blood cells.

Accumulation of lipid peroxides. Lipid metabolism is a major determinant of cellular sensitivity to ferroptosis. Free PUFAs such as arachidonic acid (AA) and adrenic acid (AdA), once incorporated into membrane phospholipids, are readily oxidized by intracellular ROS, leading to the formation of lipid peroxides that initiate ferroptosis (63,64). A study has identified lysophosphatidylcholine acyltransferase 3 (LPCAT3) and acyl-CoA synthetase long-chain family member 4 (ACSL4) as key enzymes responsible for phosphatidylethanolamine (PE) biosynthesis and remodeling, as well as for the activation and incorporation of PUFAs into membrane phospholipids. The two enzymes function as critical drivers of ferroptosis (65).

The process of lipid peroxide accumulation mainly proceeds through ACSL4-mediated conversion of AA and AdA into acyl-CoA derivatives, followed by their esterification by LPCAT3 to generate arachidonic acid-containing phosphatidylethanolamine (PE-AA). Subsequent oxidation of PE-AA by arachidonate 15-lipoxygenase (ALOX15) produces lipid hydroperoxides, ultimately triggering ferroptosis (66). Conversely, depletion of LPCAT3 or ACSL4 impairs PUFA activation and incorporation into phospholipids, thereby inhibiting ferroptosis (67). Overall, the enzymes LPCAT3, ACSL4 and ALOX15, which orchestrate PUFA synthesis and incorporation, play essential roles in modulating cellular sensitivity to ferroptosis and in regulating its occurrence.

Imbalances in amino acid antioxidant systems. The cysteine/glutamate antiporter System Xc^- exists as a transmembrane heterodimer assembled from the light-chain subunit SLC7A11 and the heavy-chain subunit SLC3A2. It facilitates ATP-dependent antiport of extracellular cysteine in exchange for intracellular glutamate (68). GSH is present in reduced GSH and oxidized GSSG forms. The reduced form GSH acts as the main cofactor for GPX4, a pivotal regulator in ferroptosis. Antioxidant defense is disrupted when cysteine undergoes rapid reduction together with glutamate exchange, which promotes GSH biosynthesis and subsequent consumption by GPX4, thereby inhibiting ferroptosis (69). The core

mechanism of the imbalance in the antioxidant system is that cysteine, upon entering the cell through the light chain SLC7A11 and heavy chain solute carrier family 3 member 2, is rapidly reduced to cysteine and glutamate, which together synthesize GSH. GSH, when acted on by GPX4, can inhibit the activity of the light chain SLC7A11 transporter and catalyze the reduction reaction of lipid peroxides, leading to the inactivation of GPX4 and the accumulation of ROS, ultimately inducing ferroptosis (70). This indicates that the cysteine/glutamate antiporter primarily regulates ferroptosis by maintaining the balance between intracellular and extracellular cysteine and glutamate and by regulating reduced GSH levels.

Other mechanisms. Ferroptosis suppressor protein 1 (FSP1) is a more recently identified GPX4-independent ferroptosis suppressor. Bersuker *et al* (71) and Doll *et al* (72) independently demonstrated that FSP1 functions as a potent anti-ferroptotic factor capable of inhibiting ferroptosis induced by GPX4 deficiency. FSP1, through its oxidoreductase activity, utilizes nicotinamide adenine dinucleotide phosphate (NADPH) to reduce CoQ10 to CoQ10H2, thereby inhibiting lipid peroxidation and suppressing ferroptosis (71,72). Thus, the NADPH/FSP1/CoQ10 pathway cooperates with the System Xc^-/GSSG/GPX4 axis to synergistically suppress lipid peroxidation and ferroptosis. Voltage-dependent anion channels situated on the outer mitochondrial membrane exert a significant regulatory influence on ferroptosis (73). Yagoda *et al* (26) demonstrated that the ferroptosis inducer Erastin directly targets voltage-dependent anion channels, resulting in mitochondrial metabolic and oxidative dysfunction, increased ROS production and eventual induction of cellular ferroptosis. In addition, ferroptosis can be modulated by transsulfuration pathways. Under conditions of oxidative stress, methionine is converted to cysteine via this route and subsequently incorporated into GSH, thereby supporting antioxidant activity (74). Other studies have shown that P62/Keap1/NRF2 (75), GCH1/BH4/phospholipids (76) and glutamine metabolism pathways effectively control intracellular iron and ROS levels, thereby playing important regulatory roles in ferroptosis (77).

Ferritinophagy. Ferritinophagy represents a selective autophagic process that controls cellular iron metabolism. Ferritin, which functions as the principal intracellular iron storage protein, is selectively recruited to autophagosomes by the cargo receptor nuclear receptor coactivator 4 (NCOA4) and subsequently degraded through the autophagosome-lysosome fusion pathway, thereby liberating free iron ions (78). Mancias *et al* (79) analyzed all the proteins present in autophagosomes, including cargo receptors, through quantitative proteomics and found a close association between NCOA4 and ferritin, leading to the identification and coining of ferritinophagy.

Ferritinophagy regulation is governed primarily by the abundance of NCOA4, whose own levels are tightly controlled by intracellular iron concentrations. The precise involvement of the ubiquitin-proteasome pathway in this regulatory axis remains to be clarified.

Under physiological conditions, elevated intracellular iron promotes the iron-dependent interaction between NCOA4 and the E3 ubiquitin ligase HERC2, thereby marking NCOA4 for degradation via the ubiquitin-proteasome pathway. Consequently, NCOA4 levels decline, thereby attenuating ferritinophagy. By contrast, when iron levels are low, both NCOA4 abundance and ferritinophagy activity increase, thereby restoring available iron stores (80).

Purified-protein experiments have further demonstrated that high iron concentrations directly impair the binding of NCOA4 to ferritin, providing an additional means of suppressing ferritinophagy (81). However, in lipopolysaccharide (LPS)-induced sepsis, ferritinophagy is strongly upregulated and drives ferroptosis. Under these conditions, pharmacological inhibition of the ubiquitin-proteasome pathway does not alter ferritin levels (82), indicating that LPS-triggered ferritin degradation likely proceeds independently of the ubiquitin-proteasome system.

However, whether increased ferritin expression under stress conditions compensates for the consumption induced by ferritinophagy remains unknown and the specific mechanism warrants further investigation. Under pathological conditions, changes in ferritinophagy levels may manifest as upregulation, suppression. In pancreatic ductal adenocarcinoma, the E3 ubiquitin ligase tripartite motif-containing protein 11 inhibits ferritinophagy (83), while the antifungal drug ciclopirox promotes ferritinophagy (84). Ferritinophagy levels remain unchanged in HeLa cells following treatment with erastin (85). The changes in ferritinophagy levels under pathological conditions remain undetermined and the effects of drug interventions on ferritinophagy require further investigation. Regarding the relationship between ferritinophagy and ferroptosis, they are closely associated, with the majority of studies suggesting that ferritinophagy is an important regulator of ferroptosis. Upregulation of ferritinophagy promotes the occurrence of ferroptosis, while downregulation of ferritinophagy suppresses ferroptosis. Hou *et al* (85) found that knocking out or downregulating autophagy-related proteins 5 and 7 inhibited erastin-induced ferroptosis, leading to decreased free iron levels, reduced lipid peroxidation and increased GSH levels.

Silencing the NCOA4 gene also inhibits ferritin degradation and ferroptosis, resulting in reduced free iron levels, reduced oxidative stress and increased GSH levels. Conversely, NCOA4 overexpression promotes ferritin degradation and ferroptosis. Extracellular vesicles from endothelial cells can counteract glucocorticoid-induced osteoporosis by inhibiting ferritinophagy, thereby suppressing ferroptosis in osteoblasts (86). However, in a study by Gryzik *et al* (64) using NCOA4 gene expression regulation technology and various ferroptosis inducers across multiple cell lines, although most experimental results supported the regulatory role of ferritinophagy in ferroptosis, the level of ferroptosis induced by Ras-selective lethal compound 3 in HeLa cells was independent of ferritinophagy levels. Therefore, in the majority of cases, ferritinophagy plays a regulatory role in ferroptosis, but in specific tissues, cell types and pathological conditions, the relationship between ferritinophagy and ferroptosis remains unclear.

The role of ferroptosis in ferritinophagy is not clear and ferritinophagy levels mediated by NCOA4 can vary under the action of different ferroptosis inducers. Increased NCOA4 expression has been observed in stellate cells following

sorafenib treatment, while no difference in NCOA4 expression before and after treatment with erastin has been observed in pancreatic cancer cells (85). In addition, it has been found that treatment of hepatic stellate cells with artemisinin results in decreased levels of NCOA4 and ferritinophagy (87), suggesting that ferroptosis may lack a specific mechanism for regulating ferritinophagy. Whether the complexity of changes in ferritinophagy levels observed after treatment with ferroptosis inducers is attributable to specific cells, pathological conditions, or compounds remains to be determined.

NCOA4-mediated ferritinophagy serves as a crucial regulator of cellular and systemic iron metabolism and is vital for maintaining iron homeostasis (88). NCOA4 knockout leads to hematopoietic disorders and microcytic hypochromic anemia due to impaired iron availability (80,89). This occurs due to defective ferritinophagy, which prevents the degradation of ferritin and the subsequent release of stored iron. As a result, the body exhausts serum iron reserves to meet physiological needs, ultimately causing decreased circulating iron levels and iron-deficiency microcytic hypochromic anemia (80,89). These observations highlight that NCOA4-mediated ferritinophagy is indispensable for proper iron metabolism and dysregulation of this process can lead to iron imbalance and disease pathogenesis.

Mitochondrial involvement in ferroptosis. Mitochondria, as the powerhouse and metabolic center of cells, play a crucial role in ferroptosis, such as the regulation of cysteine deficiency-induced ferroptosis (90). Compared with other regulated cell-death modalities, ferroptosis is defined by a distinct ultrastructural phenotype, most notably a pronounced cytoplasmic ballooning in which cells appear rounded, translucent and depleted of electron-dense cytoplasmic material (91). During ferroptosis, mitochondria undergo contraction, increased membrane density, exhibit a reduction in cristae density and the dissipation of the membrane potential, indicating functional abnormalities (92). Mitochondria serve as integration sites for intra- and extracellular signals, determining cell fate (93,94). Changes in mitochondrial morphology during ferroptosis can be distinguished from those in other forms of cell death, but their specific roles remain contested. Calcium ion homeostasis is closely associated with mitochondria in ferroptosis. Calcium-regulating proteins on the mitochondrial membrane, such as the permeability transition pore, can modulate mitochondrial permeability transition (95). During ferroptosis, alterations in the mitochondrial membrane can lead to the release of intracellular calcium ions and the generation of ROS, ultimately triggering apoptosis. The release of calcium ions further activates a series of signaling pathways, leading to cell death (96). Therefore, mitochondria play a key role in ferroptosis by regulating calcium ion homeostasis and their impairment can induce cell death (16). Mitochondria contain 20-50% of the total cellular iron, with iron-containing proteins as essential cofactors for enzymatic redox reactions (97). During ferroptosis, an imbalance in mitochondrial iron metabolism may lead to iron overload or iron deficiency, subsequently causing cellular damage and death. In addition, mitochondrial iron metabolism may influence the production and clearance of ROS, further exacerbating ferroptosis (97) (Fig. 2).

3. Ferroptosis and CVDs

Nevertheless, the combination of unhealthy dietary habits, lifestyle choices and a rapidly aging global population has led to a steady annual increase in both the incidence and mortality of CVDs. This trend is especially pronounced in developing countries, where CVDs have become the leading cause of death (1). CVDs encompass a wide range of conditions, primarily myocardial infarction, reperfusion injury, atherosclerosis (AS), hypertension, myocardial hypertrophy, heart failure, diabetic cardiomyopathy (DCM) and doxorubicin-induced cardiomyopathy (DIC) (98).

Cardiomyocytes represent the primary cell type in mammalian cardiac tissue and account for ~75% of the total heart mass. Their functional integrity substantially influences overall cardiac performance, while cardiomyocyte death plays critical physiological roles in regulating cardiac development, aging and homeostasis (99).

Several types of cell death occur in cardiomyocytes, including apoptosis, necrosis, necroptosis, autophagy, pyroptosis and ferroptosis (100). These processes are governed by intricate signaling networks. Apoptosis is typically marked by cell shrinkage, cytoplasmic condensation, loss of mitochondrial membrane potential, changes in membrane permeability and the formation of intact apoptotic bodies. By contrast, necrosis represents an accidental and uncontrolled form of cell death that generally arises from severe physical or chemical injury (101).

Necroptosis is a genetically programmed form of necrosis in which the death receptor TNFR1 acts as a central mediator (102). Autophagy serves as a cytoprotective pathway that sequesters and delivers damaged or superfluous cellular components to lysosomes for degradation, thereby supporting metabolic homeostasis (103). Pyroptosis is an inflammatory, regulated cell death modality that is primarily activated as a defensive response against invading pathogens, including viruses, bacteria and fungi (104). Unlike these pathways, ferroptosis is morphologically and mechanistically distinct. Growing evidence underscores its significant contribution to the development and progression of CVDs.

Ferroptosis and cardiomyopathy

Ferroptosis and DIC. Doxorubicin is an anthracycline antitumor drug widely used to treat various malignancies, including acute leukemia, lymphoma and sarcoma. However, due to its strong cardiotoxicity, it can promote the development of a cumulative and progressive cardiomyopathy, known as DIC (105). In a mouse model of DIC, the Doxorubicin-Fe^{2+} complex in cardiac mitochondria can markedly downregulate GPX4 expression, while acrolein and malondialdehyde (MDA) levels are markedly increased, leading to lipid peroxidation and ultimately resulting in ferroptosis in cardiomyocytes. This results in cardiac atrophy, impaired cardiac contractile function and cardiac fibrosis, among other cardiac injuries (106). The pathological changes include cardiomyocyte swelling, loss of striations, blurred cell boundaries, eosinophilic cytoplasm and focal myolysis. Masson's trichrome staining reveals diffuse or focal interstitial collagen deposition, accompanied by numerous inflammatory cells infiltrating around the damaged cardiomyocytes. Prussian blue staining

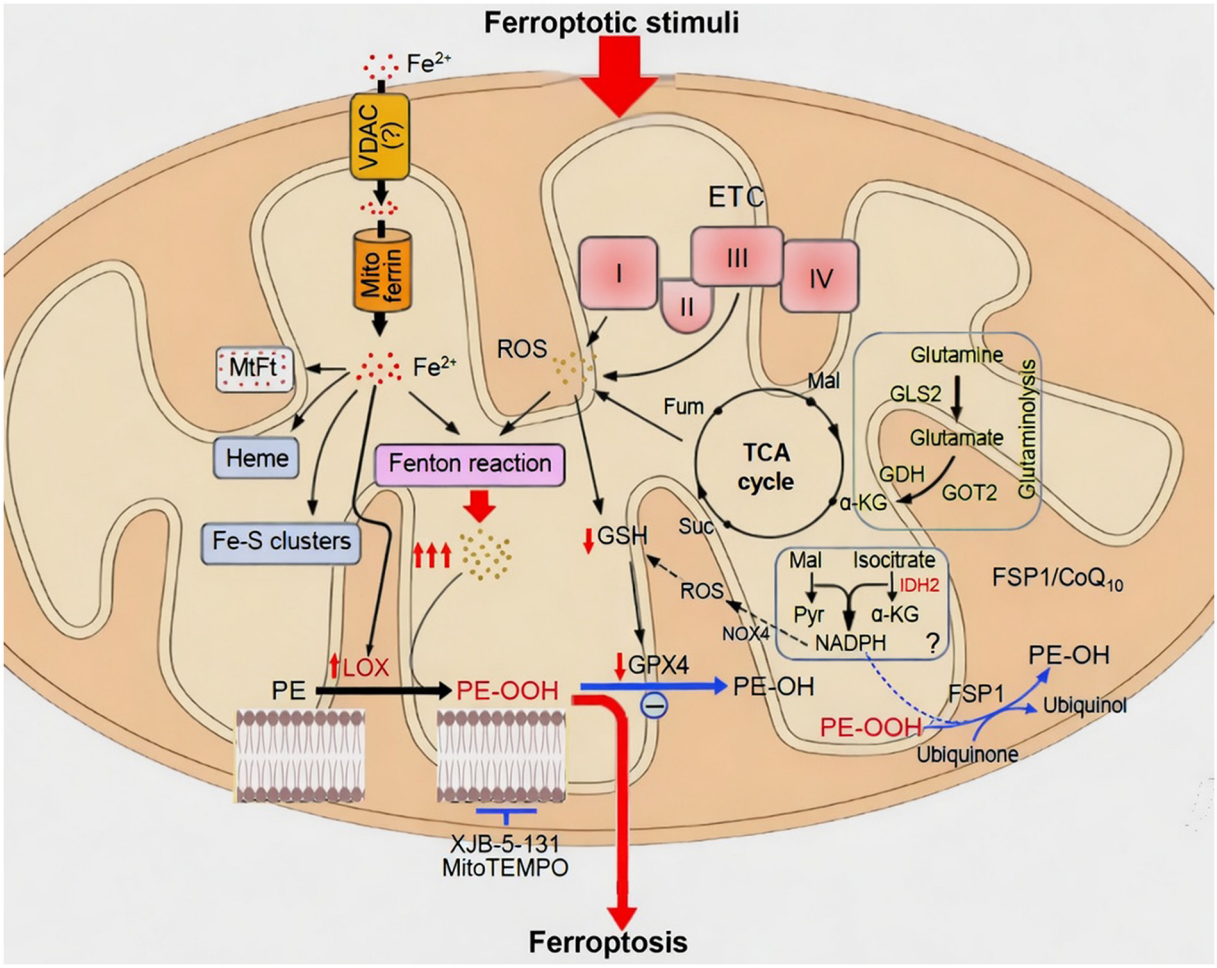

Figure 2. Core role of mitochondria in ferroptosis: intervention targets in cardiovascular diseases. Mitochondria are a key organelle in ferroptosis. In cardiovascular diseases, they drive ferroptosis through the following mechanisms: Iron overload (Mitoferrin/VDAC transport of Fe^{2+} and heme/Fe-S cluster iron release), ROS generation (TCA/ETC) and the Fenton reaction that exacerbates oxidative stress. LOX catalyzes PE to generate PE-OOH. The GPX4/FSP1 pathway provides antioxidant defense. Mitochondria-targeted antioxidants (such as XJB-5-131 and MitoTEMPO) can inhibit lipid peroxidation, providing new directions for the treatment of cardiovascular diseases. VDAC, voltage-dependent anion channel; ROS, reactive oxygen species; TCA, tricarboxylic acid cycle; ETC, electron transport chain; LOX, lipoxygenase; PE, phosphatidylethanolamine; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; XJB-5-131, a mitochondria-targeted ROS and electron scavenger, MitoTEMPO, a mitochondrially targeted antioxidant; MtFt, mitochondrial ferritin; NADPH, Nicotinamide adenine dinucleotide phosphate, reduced.

demonstrates prominent iron deposition in the cytoplasm of ferroptotic cardiomyocytes. This iron deposition represents a characteristic histological marker of ferroptosis and its extent is positively associated with the severity of myocardial injury.

Furthermore, doxorubicin activates Nrf2, which upregulates heme oxygenase-1 (HO-1). This promotes heme degradation and the release of substantial quantities of free iron, ultimately triggering ferroptosis and resulting in cardiac injury (71). Subsequent studies have demonstrated that GPX4 overexpression or targeted chelation of mitochondrial Fe^{2+} with iron chelators can effectively reverse doxorubicin-induced iron overload, lipid peroxidation and ferroptosis in mouse cardiomyocytes. Moreover, the ferroptosis inhibitor Fer-1 alleviates doxorubicin-associated cardiotoxicity by attenuating iron overload in cardiomyocytes, thereby suppressing ferroptosis and protecting against both myocardial injury and ultrastructural alterations in cardiomyocyte mitochondria (107). Consequently, modulating ferroptosis regulation may represent a promising new therapeutic approach for the treatment of DIC.

Ferroptosis and iron overload cardiomyopathy (IOC). IOC features progressive electromechanical dysfunction of the heart and constitutes a leading cause of death in patients with hemochromatosis. It initially manifests as diastolic dysfunction and arrhythmias, which can progress to systolic dysfunction and end-stage heart failure in the absence of timely intervention (108). Iron overload can disrupt mitochondrial function in cardiomyocytes, interfere with mitochondrial dynamics and alter mitochondrial morphology, ultimately inducing ferroptosis in cardiomyocytes and causing cardiac injury (109). Furthermore, with the help of iron ions, lysyl oxidase directly oxidizes PUFAs to form lipid peroxides, leading to lipid peroxidation and ferroptosis (110). The current standard treatment for IOC includes venesection and iron chelation therapy. In the early stages of the disease, patients with hypertension who have cardiomyopathy and refractory arrhythmias can undergo aggressive venesection to mobilize iron from storage organs for hemoglobin production, thereby achieving iron depletion and improving cardiac function. Commonly used iron chelators include deferoxamine and

deferiprone. Deferoxamine forms stable complexes with Fe^{3+} released during the decomposition and metabolism of aging red blood cells, which are subsequently excreted in urine, thereby achieving iron removal. Compared with monotherapy with deferoxamine, subcutaneous deferoxamine combined with oral deferiprone lowers myocardial iron load in patients with mild-to-moderate cardiac iron burden due to beta-thalassemia major and improves ejection fraction and endothelial function (111). It is worth noting that when using iron chelators, monitoring iron levels is also necessary to ensure the iron concentration remains within a safe range.

Ferroptosis and septic cardiomyopathy. Septic cardiomyopathy represents one of the most serious complications of sepsis. It is characterized by varying degrees of myocardial dysfunction, typically presenting as reduced myocardial contractility, peripheral vasodilation, decreased left ventricular ejection fraction and reversible biventricular dilatation (112).

Mitochondrial alterations observed in LPS-induced myocardial injury closely resemble the mitochondrial features associated with ferroptosis in cardiomyocytes. Ferritinophagy-mediated ferroptosis further aggravates myocardial damage during sepsis. Consequently, ferroptosis appears to be intimately involved in the progression of LPS-induced septic cardiomyopathy. Dexmedetomidine, a selective α2-adrenergic receptor agonist, attenuates sepsis-induced HO-1 overexpression and lowers serum iron levels while upregulating GPX4 expression. These actions effectively suppress ferroptosis and mitigate sepsis-associated myocardial injury (113).

With respect to ferritinophagy, studies indicate that ferritinophagy-mediated ferroptosis plays a key role in sepsis-induced cardiac injury (114). In addition, both iron chelators and ferroptosis inhibitors markedly reduce ferroptosis in cardiomyocytes by scavenging intracellular ROS.

Ferroptosis and DCM. DCM is a distinct cardiac condition that develops independently of conventional cardiovascular risk factors such as coronary artery disease, significant valve disease and hypertension. It is primarily driven by hyperglycemia and insulin resistance. The primary characteristics include left ventricular hypertrophy, diastolic dysfunction and interstitial vascular fibrosis. Oxidative stress and impaired antioxidant systems under high glucose conditions are the basis for the development of DCM (115). An imbalanced antioxidant system leads to excessive ROS production, which can cause ferroptosis, apoptosis, inflammation and fibrosis in myocardial cells. Diabetes-induced autophagy defects suppress Nrf2-mediated protective mechanisms, thereby heightening cellular susceptibility to ferroptosis and aggravating the progression of DCM (116). Nrf2, together with its target genes exert antioxidant, anti-inflammatory, anti-apoptotic, anti-ferritin and anti-fibrotic effects that safeguard pancreatic β-cells from high-glucose-induced oxidative damage in the context of DCM (117). Pancreatic β-cells in the human body are susceptible to ferroptosis induced by erastin or RSL3 and this damage can be reversed by Fer-1 (118).

Regarding ferritinophagy, a study has shown that the (pro)renin receptor may affect the pathological progression of DCM in mice by promoting cardiomyocyte ferroptosis via the NCOA4-mediated ferritinophagy pathway (119). Furthermore, α-linolenic acid alleviates DCM by activating the AMPK-STAT3 pathway, thereby inhibiting ferritinophagy and strengthening the SLC7A11-GPX4 antioxidant axis (114).

Endoplasmic reticulum (ER) stress constitutes a cellular response to ER dysfunction and can be triggered by ROS. Ferroptosis contributes to ischemia-reperfusion (I/R) injury in DCM via this ER stress pathway. Inhibition of ferroptosis can effectively attenuate myocardial I/R injury in DCM, thereby providing a potential therapeutic target for DCM (120).

Ferroptosis and Friedreich's Ataxia (FRDA). FRDA is a rare inherited neurodegenerative disorder caused by a deficiency of frataxin, a key mitochondrial matrix protein. The condition is characterized by progressive sensory and motor deficits, neurodegeneration, iron accumulation in brain cells and hypertrophic cardiomyopathy, which ultimately results in premature death (121). Frataxin is a highly conserved essential protein that plays a critical role in iron-sulfur cluster biogenesis. Its deficiency leads to dysregulation of iron metabolism and mitochondrial dysfunction (122). Iron overload combined with elevated oxidative stress constitutes a distinctive pathological feature of FRDA. Increased production of lipid peroxides and their byproducts, such as MDA, has been observed in the plasma of FRDA patients and serves as an important indicator of ferroptosis. Moreover, reduced GSH levels and decreased GPX activity, particularly GPX4, strongly link ferroptosis to the pathogenesis of FRDA (123). EPI-743 and SFN are established Nrf2 activators. Treatment with EPI-743 effectively prevents ferroptosis in fibroblasts derived from FRDA patients with mitochondrial disease. In both *in vitro* and *in vivo* FRDA models, SFN enhances mitochondrial function and biogenesis (124). The two agents promote the nuclear translocation of Nrf2, thereby alleviating oxidative imbalance and inhibiting ferroptosis. Therefore, Nrf2 activators represent promising therapeutic strategies for preventing ferroptosis-related damage in neurodegenerative diseases.

Frataxin, as a key mitochondrial protein, has been confirmed to play a regulatory role in myocardial ferroptosis. A relevant study identified potential E3 ubiquitin ligases that interact with frataxin in cardiac tissue using LC-MS/MS technology and employed adeno-associated virus to achieve cardiac-specific overexpression of frataxin. The study demonstrated that frataxin can directly reduce myocardial sensitivity to ferroptosis by regulating iron homeostasis, providing direct experimental evidence for its cardioprotective effects (125). Building upon these findings, intervention research using the ferroptosis inhibitor Fer-1 further confirms the central role of ferroptosis in myocardial injury. This inhibitor specifically targets mitochondrial iron-sulfur clusters and aconitase, markedly ameliorating heart failure in Sirtuin 3 (Sirt3) cardiomyocyte-knockout mice and identifying potential pharmacological targets for the intervention of frataxin-related cardiomyopathies (126). In terms of disease association, decreased frataxin expression is the core pathogenic mechanism of FRDA and ferroptosis is a key pathological link in its progression. Research has shown that activation of the Nrf2 pathway can effectively block ferroptosis in FRDA, further refining the causal chain 'decreased frataxin expression → iron homeostasis imbalance → ferroptosis activation →

myocardial and multi-organ damage' (127). Notably, cardiomyopathy (for example, hypertrophic cardiomyopathy) is the most prominent organ manifestation of FRDA. The aforementioned basic research provides important theoretical support for the design of Phase II clinical trials in FRDA targeting ferroptosis and restoring frataxin function, thereby providing an effective bridge between basic mechanistic understanding and clinical translation (128).

In summary, cardiomyopathy constitutes a severe cardiac disorder capable of precipitating life-threatening complications, such as arrhythmias, thrombosis, heart failure and sudden death. Ferroptosis represents a newly identified iron-dependent mode of regulated cell death driven by lipid peroxidation. Accumulating evidence underscores the pivotal contribution of ferroptosis to the initiation and advancement of various cardiomyopathies. Excessive iron buildup within cardiomyocytes emerges as a central driver in cardiomyopathy pathogenesis. This iron overload disrupts iron homeostasis, promotes lipid peroxidation and activates ferroptosis, ultimately leading to cardiomyocyte demise and compromised cardiac performance. Investigators are actively investigating pharmacological agents and other strategies to modulate iron metabolism and diminish intracellular iron levels, thereby attenuating ferroptosis risk and enhancing clinical symptoms and long-term prognosis in cardiomyopathy. Nonetheless, the bulk of existing research remains confined to preclinical models, highlighting the necessity for expanded clinical trials to delineate underlying mechanisms and validate the therapeutic effectiveness of these interventions. Moreover, the specific regulatory mechanisms of ferroptosis and its crosstalk with other forms of cell death, such as apoptosis, necrosis and pyroptosis, still require further investigation. The exploration of these potential mechanisms will undoubtedly provide new biomarkers and prospective targets for the prevention and treatment of CVDs, offering more precise and effective strategies for the prevention and treatment of cardiomyopathy.

Ferroptosis and abdominal aortic aneurysm (AAA). The pathogenesis of AAA is complex and primarily involves oxidative stress, inflammation, vascular smooth muscle cell loss, extracellular matrix degradation and vascular calcification (129). A study has reported markedly elevated iron content in the aortic wall of patients with AAA, accompanied by significant upregulation of TfR1 and intracellular iron transport proteins (130). Iron overload promotes oxidative stress and inflammatory responses that accelerate AAA progression, whereas restricting iron intake has been shown to alleviate overload and delay disease development. These observations highlight the central importance of iron homeostasis in AAA pathophysiology and suggest that ferroptosis may play a substantial role in its initiation and progression.

Ferroptosis has also been implicated in the pathogenesis of AS and aortic dissection (131,132). Its underlying molecular mechanisms share notable similarities with those driving AAA formation. Clinical observations reveal that circulating levels of iron, transferrin and hemoglobin differ markedly between patients with AAA and healthy individuals, with these parameters correlating with aortic diameter. In addition, iron deposition along with altered expression of transferrin, TfR and ferritin has been documented in the arterial walls of patients with AAA, indicating profound dysregulation of iron metabolism (133).

In an angiotensin II (Ang II)-induced AAA mouse model, Sawada *et al* (134) demonstrated that iron restriction markedly reduced iron deposition in the arterial wall, attenuated oxidative stress and inflammation and markedly lowered AAA incidence. Consistent with these findings, elevated tissue iron levels have been proposed as a contributing factor in the development of aortic aneurysm (135). Taken together, abnormal iron metabolism in the arterial wall may promote ferroptosis and actively participate in the occurrence and progression of AAA. Overall, accumulating evidence strongly supports the involvement of ferroptosis in the development and progression of AAA.

Ferroptosis and oxidative stress. Oxidative stress refers to the excessive production of ROS, leading to cellular and tissue damage. The level of ROS within cells is related to both the ROS generation system and the antioxidant defense system. NADPH oxidase (NOX) is the major source of ROS in cells. Chen *et al* (136) found that knockout of the NOX4 gene reduced cell damage, improved cardiac function and markedly inhibited ferroptosis in cardiac myocytes. NOX4 is also closely associated with the formation of AAA. It has been found that NOX4 is elevated in human and murine AAA tissues and is related to the expansion of AAA (137). A study has shown that in AAA models with NOX4 knockout, the elastic layer of the vessel wall is intact and aneurysms are reduced (138). Therefore, NOX4 may be involved in AAA development through its induction of ferroptosis, although the specific mechanism requires further research.

GPX4, a component of the antioxidant system, is a key molecule in the mechanism of ferroptosis. It can effectively reduce phospholipid chlorohydrins in biomembranes and its activity is related to the synthesis of GSH and the function of the system XC- (68). When system XC-is inhibited, GSH levels decrease, GPX4 activity decreases and it becomes difficult to eliminate the excess lipid peroxides within cells, leading to ferroptosis (139). Wiernicki *et al* (140) found reduced expression of GPX4 in AAA and considered GPX4 to be a key gene in ferroptosis in AAA. Studies have also observed changes in iron deposition and altered expression of transferrin, TfR and ferritin in the arterial wall of patients with AAA, suggesting disrupted iron metabolism. Wiernicki *et al* (140) found that resolvin D1 (RvD1) attenuated elastase-induced AAA formation and aortic inflammation in C57BL/6 mice. Further research showed that RvD1 could regulate the signal of formyl peptide receptor 2 (FPR2) in macrophages. The RvD1/FPR2 signaling pathway effectively inhibited the signaling pathways associated with triggered ferroptosis and activated the antioxidant pathway through NOX, thereby preventing the release of pro-inflammatory mediators, relieving aortic inflammation and inhibiting tissue remodeling (140). These studies suggest that ferroptosis may contribute to AAA development by promoting aortic inflammation.

Ferroptosis and inflammation. Ferroptosis is associated with inflammation. The release of certain cytokines from cells undergoing ferroptosis will promote inflammatory reactions. Inhibition of ferroptosis has been shown to markedly

reduce nonalcoholic steatohepatitis, neuroinflammation and metabolic inflammation (141-144). IL-6 is an inflammatory cytokine that also plays an important role in ferroptosis. It has been found that ferroptosis in cardiac myocytes of hypertensive mice is associated with upregulation of the IL-6/STAT3 signaling pathway (145). IL-6 not only promotes iron uptake but also inhibits iron transport protein function by upregulating hepcidin levels, thereby preventing iron export from cells and leading to iron accumulation and cell death (146). Inflammatory reactions are closely associated with AAA formation and there is significant inflammatory cell infiltration within the aneurysm wall (147). Elevated expression of IL-6 and its related signaling pathways in AAA promotes local inflammation and high levels of IL-6 are a characteristic feature of AAA lesions (148). Therefore, the aforementioned studies suggest that IL-6-mediated ferroptosis may contribute to the occurrence and progression of AAA. Filiberto *et al* (149) found that RvD1 attenuated elastase-treated AAA formation and aortic inflammation in C57BL/6 mice. They further demonstrated that the RvD1/FPR2 signaling pathway could modulate macrophages and interact with ferroptosis-related signaling pathways, thereby preventing the release of pro-inflammatory mediators and alleviating aortic inflammation and tissue remodeling (149). These studies suggest that ferroptosis, through its involvement in aortic inflammation, may contribute to the occurrence and development of AAA.

Ferroptosis and vascular smooth muscle cell (VSMC) dysfunction and loss. VSMCs reside predominantly in the medial layer of the abdominal aorta, where they are essential for preserving vascular tone, modulating blood pressure and controlling blood flow (150). Impaired VSMC function is recognized as a central pathological hallmark of AAA and is closely linked to aneurysmal expansion and rupture (151). In patients with AAA, the contractile capacity of smooth muscle cells is markedly diminished, accompanied by downregulation of key differentiation markers, including smooth muscle α-actin and smooth muscle myosin heavy chain. These changes reflect a phenotypic shift from a mature contractile state to a dedifferentiated synthetic phenotype, which actively drives aneurysmal growth (152).

Ferroptosis is closely linked to this phenotypic transition of VSMCs. Ji *et al* (153) showed that ferroptosis directly initiates VSMC dedifferentiation; conversely, its inhibition restores mitochondrial balance by attenuating excessive mitochondrial ROS production and hyperpolarization, thereby preventing the contractile-to-synthetic phenotypic switch. In complementary work, Zhang *et al* (154) reported that the ferroptosis inducer RSL3 (a GPX4 inhibitor) aggravated neointimal hyperplasia in a carotid artery ligation model and accelerated VSMC phenotypic switching. Administration of the ferroptosis inhibitor Fer-1 reversed these effects. Supporting *in vitro* data further demonstrated that RSL3 promoted the transition of VSMCs from a contractile to a synthetic phenotype, evidenced by decreased expression of contractile markers (smooth muscle myosin heavy chain and calponin) and elevated levels of the synthetic marker osteopontin (154).

Hypertension is one of the risk factors for AAA. Jin *et al* (155) found that the downregulation of GPX4 expression at the site of the aorta in hypertensive patients was associated with the increased occurrence of a novel VSMC phenotype, which refers to a subpopulation of VSMCs differentiated toward an inflammatory and endothelial function-inhibited phenotype. In *in vitro* experiments on VSMCs, high hydrostatic pressure (HHP) increased iron accumulation, lipid peroxidation and the expression of ferroptosis-related genes compared with normal pressure (100 mmHg). The study found that HHP, by reducing GSH levels in VSMCs and promoting cystathionine γ-lyase/H2S generation, induced ferroptosis in VSMCs (155). Sampilvanjil *et al* (156) treated VSMCs with cigarette smoke extract (CSE) and found that CSE promoted GSH depletion and lipid peroxidation in VSMCs, leading to ferroptosis. Thus, in AAA, ferroptosis may not only lead to the loss of the contractile phenotype of VSMCs, thereby affecting the structural stability of the vessel wall, but also directly cause VSMC death, weakening the media layer and promoting AAA progression.

Ferroptosis and vascular calcification. Vascular calcification is often associated with disrupted iron homeostasis, indicating a potential role of ferroptosis in vascular calcification (157). Palm acid (PA), a saturated free fatty acid associated with dyslipidemia, is closely related to cellular lipotoxicity and autophagy. Ma *et al* (158) found that PA treatment of VSMCs *in vitro* induced ferroptosis and increased calcium deposition in VSMCs. The study showed that PA promoted the expression and secretion of periostin (POSTN) and upregulation of POSTN inhibited system Xc-through inhibiting p53, resulting in GSH depletion and ferroptosis, ultimately promoting vascular calcification (158). Chen *et al* (159) discovered that PA activated the cyclic GMP.AMP synthase and stimulator of interferon genes signaling pathways, inducing ferritinophagy in VSMCs, which promoted ferroptosis. Furthermore, Ye *et al* (160) treated VSMCs with ferroptosis inducers erastin and Fer-1 and found that erastin promoted VSMC calcification through GSH depletion. Fer-1 attenuated this process in a dose-dependent manner. In *in vivo* experiments, Fer-1 reduced aortic calcification in vitamin D3-overloaded mice. Studies in patients with AAA have found that the severity of abdominal aortic calcification is more significant in patients with ruptured AAA compared with those undergoing elective surgery. Analysis of the AAA arterial wall revealed distinct levels of calcification in different locations, suggesting a clear association between vascular calcification and AAA development (161,162). Given the relationship between ferroptosis and vascular calcification, ferroptosis may play a role in the occurrence and development of AAA by influencing vascular calcification. However, more research is needed to provide experimental evidence to support this relationship.

In summary, ferroptosis appears to play a substantial role in the pathogenesis of AAA. The present review examined the potential mechanistic connections between ferroptosis and AAA development through the lenses of oxidative stress, inflammation, VSMC loss and vascular calcification, thereby offering fresh perspectives for future investigations into ferroptosis in AAA. Nevertheless, direct experimental evidence establishing a causal relationship between ferroptosis and AAA remains limited, particularly regarding whether targeted inhibition of ferroptosis can effectively prevent aneurysm formation. Moreover, the precise contribution of ferroptosis,

whether acting directly or indirectly, to the initiation and progression of AAA still requires further clarification. Future studies should therefore prioritize elucidating the specific molecular pathways through which ferroptosis contributes to AAA, thereby laying the foundation for novel preventive and therapeutic strategies. It is anticipated that continued exploration of this emerging form of regulated cell death will yield valuable insights and innovative approaches to the clinical management of aortic aneurysms.

Role of ferroptosis in hypertension and possible mechanisms

Ferroptosis induced by iron metabolism disorder and hypertension. Iron serves as an essential trace element in the human body, with intracellular iron homeostasis maintained through a dynamic equilibrium among its uptake, export and utilization. Consequently, precise control of iron transport, metabolism and storage is required (163). Circulating iron circulates predominantly as Fe^{3+} bound to transferrin. This Fe^{3+} is internalized into cells via TFR1 and delivered to endosomes, where it is reduced to Fe^{2+} by STEAP3. DMT1 subsequently releases Fe^{2+} from endosomes into the cytoplasmic labile iron pool (163). Surplus Fe^{2+} is exported from the cell by the membrane transporter ferroportin (FPN). However, intracellular Fe^{2+} overload activates the Fenton reaction, resulting in elevated ROS production that drives lipid peroxidation and cell death (164). Therefore, elevated intracellular iron levels increase the susceptibility to ferroptosis.

Iron overload is closely associated with hypertension. A cross-sectional study from Korea reported a positive association between serum ferritin levels and hypertension prevalence (165). Additionally, a large-scale longitudinal study conducted in a Chinese population revealed a positive association between hemoglobin and transferrin levels and the risk of developing hypertension (166), underscoring the critical role of iron homeostasis in the initiation and progression of this condition. Population-based investigations have further shown that mutations at the H63D locus of HFE and in the iron-regulatory protein hemojuvelin, both linked to iron overload, result in mild iron accumulation and elevate the risk of hypertension (167,168).

By contrast, restricting dietary iron intake has been demonstrated to attenuate vascular wall thickening, fibrosis and inflammatory responses in Dahl salt-sensitive hypertensive rats (169). Complementary experiments indicate that dietary iron limitation can prevent aldosterone/salt-induced hypertension and renal fibrosis in mice through the suppression of oxidative stress (170). Moreover, brain tissue from hypertensive rats exhibits elevated iron content, heightened lipid peroxidation and altered expression of ferroptosis-related markers compared with that from normotensive controls. However, these findings do not establish a direct causal link between ferroptosis and hypertension; it remains uncertain whether ferroptosis drives hypertension and subsequent brain injury or whether hypertension itself induces ferroptosis and worsens cerebral damage. The precise mechanisms by which hypertension promotes brain iron overload and the specific pathways through which ferroptosis contributes to hypertension-related brain injury also warrant further elucidation. Collectively, these observations suggest that iron overload arising from disrupted iron homeostasis may promote cellular damage and contribute to ferroptosis in hypertension, although the underlying mechanisms warrant further investigation.

Ferroptosis induced by abnormal amino acid metabolism and hypertension. A study has shown that depletion of GSH, deficiency of cysteine and inactivation of GPX4 can all induce ferroptosis (171). GPX4 primarily utilizes GSH to convert the peroxide bond of lipid peroxides into hydroxyl groups, inhibiting lipid peroxidation mediated by lipoxygenases (LOX) and preventing ferroptosis (172). Supplementing cells with the GPX4 inhibitor RSL3 promotes extensive lipid peroxidation and ROS production, thereby inducing ferroptosis. Jin *et al* (155) found that GPX4 expression in the aortic media was markedly lower in patients with hypertension compared with normal individuals. Treatment of VSMCs with HHP (200 mmHg) resulted in downregulation of cystathionine γ-lyase/H2S levels, further reducing GSH production and inhibiting GPX4 expression, leading to ferroptosis.

Cysteine plays a critical role in GSH synthesis. Extracellular cystine is imported into the cytoplasm and reduced to cysteine via the cystine/glutamate antiporter System Xc^- (composed of SLC7A11 and SLC3A2), while intracellular glutamate is simultaneously exported to the extracellular space.

Zhang *et al* (173) demonstrated that inhibition of SLC7A11 aggravated Ang II-induced cardiac hypertrophy in mice and elevated ferroptosis-related markers, including prostaglandin-endoperoxide synthase 2 (PTGS2), MDA and ROS levels. By contrast, overexpression of SLC7A11 reversed these pathological changes. These findings indicate that SLC7A11 attenuates hypertensive cardiac hypertrophy by suppressing ferroptosis and may therefore represent a promising therapeutic target for this condition. Collectively, the available evidence highlights the importance of GSH depletion and GPX4 inactivation in driving ferroptosis during hypertension. Downregulation of GPX4 facilitates lipid peroxidation, thereby promoting ferroptosis and accelerating the progression of hypertension.

GPX4 is a selenoprotein whose active site contains selenocysteine (174). Consequently, reduced selenium availability in serum or cytoplasm can compromise GPX4 activity, thereby promoting lipid peroxidation and triggering ferroptosis (175). Clinical observations indicate that serum selenium concentrations are markedly lower in patients with hypertension (176). In addition, a large 20-year population-based cohort study demonstrated that higher dietary selenium intake is associated with a decreased risk of developing hypertension (177). In a rat model of hypertension induced by adolescent alcohol exposure, selenium levels in both kidney and serum were markedly reduced; selenium supplementation restored GPX4 activity, lowered serum aldosterone and consequently reduced systolic blood pressure (178). These results imply that ferroptosis arising from selenium deficiency may contribute to the development of hypertension.

Lipid peroxidation is closely linked to ferroptosis in the context of hypertension. This process involves the reaction of ROS, reactive nitrogen species and reactive lipids with PUFAs in cell membranes, leading to the generation of lipid peroxides. As a critical step in ferroptosis, lipid peroxidation produces toxic by-products such as 4-hydroxy-2-nonenal (4-HNE) and

MDA, which compromise membrane integrity and ultimately drive ferroptotic cell death (179).

Currently, there is both basic and clinical evidence showing that lipid peroxidation can mediate hypertension. For example, the lipid peroxidation product MDA has been shown to be markedly enhanced in hypertension and is associated with endothelial damage (180). Several clinical studies have found higher levels of lipid peroxidation products in the plasma of hypertensive patients compared with healthy controls (181,182). These pieces of evidence suggest the existence of lipid peroxidation in hypertension. However, whether lipid peroxidation affects hypertension through the promotion of ferroptosis and to what extent ferroptosis is involved in this process are not yet clear and require further research.

A large body of evidence has established that ROS are central to the vascular remodeling and endothelial dysfunction observed in hypertension. Elevated ROS levels drive endothelial impairment, stimulate VSMC proliferation and remodeling and thereby increase peripheral vascular resistance and blood pressure (155). An increase in intracellular ROS is a defining biochemical hallmark of ferroptosis (183). An *in vitro* study has shown that exposure of VSMCs to HHP triggers ferroptosis, accompanied by a pronounced rise in ROS production (155). These findings support the involvement of ferroptosis in the pathophysiological processes underlying hypertension.

LOX enzymes catalyze enzymatic lipid peroxidation, thereby promoting ferroptosis. Shintoku *et al* (184) demonstrated that LOX directly induces enzymatic lipid peroxidation and facilitates ferroptotic cell death. Conversely, Shah *et al* (185) reported that pharmacological inhibition or genetic knockout of LOX effectively suppresses ferroptosis. Collectively, these data indicate that LOX participates in the regulatory network of ferroptosis. The isoforms 12-LOX and 15-LOX are particularly important, as they are major sources of ROS and contribute markedly to hypertension pathogenesis. In Ang II-treated mice, both 12-LOX and 15-LOX enhance VSMC contractility and elevate blood pressure (186,187). Furthermore, the dual 12/15-LOX inhibitor baicalein has been shown to markedly decrease MDA levels, attenuate cardiac hypertrophy and fibrosis and restore contractile function in Ang II-induced hypertensive mice (188).

These observations collectively implicate LOX in both ferroptosis and hypertension. Nevertheless, it remains unclear whether LOX directly triggers ferroptosis to influence hypertension or acts indirectly through other regulatory pathways and the precise mechanisms by which LOX modulates ferroptosis in the context of hypertensive vascular damage require further elucidation.

The ACSL4/cyclooxygenase-2 (COX-2) axis: Key biomarkers and regulatory mediators of ferroptosis in hypertension. ACSL4 activates PUFAs to form long-chain acyl-CoA, thereby participating in the process of lipid peroxidation (189). Müller *et al* (190) found that knocking out ACSL4 can protect cells from death induced by the ferroptosis inducer RSL3, indicating that ACSL4 is a reliable biomarker of ferroptosis. Moreover, ACSL4 overexpression reduces GPX4 activity, leading to increased lactate dehydrogenase release and decreased cell survival. However, compared with normal pressure (100 mmHg), HHP induces ferroptosis in VSMCs and upregulates ACSL4 expression while markedly downregulating GPX4 expression (155). This suggests that ACSL4 is involved in ferroptosis in VSMCs during the development of hypertension, but the underlying mechanism warrants further exploration. COX-2, encoded by PTGS2, is a biomarker for ferroptosis and its elevation is a reliable biological marker for ferroptosis (191). Increased COX-2 expression has been observed in the kidneys and thoracic aortas of hypertensive patients and animal models (192,193). Further research has found that HHP induces ferroptosis in VSMCs, accompanied by upregulation of COX-2 expression (155). In summary, COX-2 upregulation may serve as a reliable biomarker of ferroptosis in hypertension. Conversely, enhanced COX-2 activity may promote oxidative stress, thereby exacerbating the progression of hypertension. Exogenous monounsaturated fatty acids (MUFAs) can effectively inhibit ferroptosis and this protective effect is primarily mediated through ACSL3, which channels MUFAs into phospholipid synthesis and subsequently suppresses ROS accumulation in the plasma membrane (194). Lee *et al* (195) reported that high MUFA intake is protective against hypertension and markedly reduces the risk of developing the disease. Although MUFAs influence both ferroptosis and hypertension, it remains unclear whether their protective effects against hypertension are mediated by ferroptosis inhibition and, to what extent, ferroptosis contributes to this process.

Mitochondrial dysfunction-induced ferroptosis in hypertension. Hypertension is closely associated with mitochondrial dysfunction, which contributes to the pathophysiology of the disease through impaired energy metabolism, increased mitochondrial ROS and mitochondrial DNA mutations. Mitochondrial dysfunction amplifies oxidative stress, exacerbates endothelial dysfunction and vascular remodeling and thereby promotes the development of hypertension (196-199). Elevated mitochondrial ROS (mtROS) leading to endothelial dysfunction is one of the key mechanisms underlying hypertension (200). Pharmacological agents such as MitoTEMPO, which specifically target mtROS, have been shown to lower blood pressure effectively (201). Emerging evidence indicates that mitochondrial dysfunction can mediate ferroptosis (202-204). For example, deletion of the deacetylase Sirt3 impairs the mitochondrial capacity to scavenge mtROS and promotes ferroptosis (205). Further studies have demonstrated that Sirt3 deficiency in hypertensive patients leads to mitochondrial dysfunction, thereby aggravating endothelial impairment, vascular wall thickening, vascular inflammation and end-organ damage (206), suggesting that Sirt3 loss may promote the progression of hypertension by inducing ferroptosis. In addition, hypertension is strongly associated with damage and loss of cardiolipin, a unique phospholipid localized exclusively within the mitochondrial inner membrane and essential for cristae formation. Studies have shown a marked reduction in cardiac cardiolipin content in a porcine model of renovascular hypertension (206). Niu *et al* (207) found that restoring mitochondrial cardiolipin levels protects mitochondrial function and suppresses ferroptosis. Regarding ferritinophagy, a study found that mechanical stretch accelerates endothelial cell injury by inducing ER-mediated ferritinophagy (208). These findings collectively suggest

that enhancing mitochondrial cardiolipin may lower blood pressure by preserving mitochondrial integrity and inhibiting ferroptosis.

Ferroptosis-related regulatory factors and hypertension. NRF2 is a key regulatory factor of cellular antioxidant responses. NRF2 mediates the transcriptional regulation of various target genes and plays a critical role as a target nuclear receptor in the oxidative stress regulation of hypertension (209). Farooqui *et al* (210) found that inhibiting NRF2 can increase oxidative stress and inflammation, further exacerbating hypertension in mice. By contrast, activating NRF2 can suppress the progression of hypertension in hypertensive mice after 12-14 days of Ang II infusion (211). Research has found that deacetylase Sirt3 enhances NR2 expression, alleviates renal ferroptosis and lipid peroxidation in hypertensive mice and further mitigates renal fibrosis, injury and dysfunction, while inhibiting NRF2 markedly enhances Ang II-mediated renal tubular cell ROS generation, lipid peroxidation and ferroptosis, while inhibiting GPX4 expression (212). These findings suggest that NRF2 may modulate hypertension by inhibiting ferroptosis in renal tubular cells. However, further research is needed to determine how NRF2 activation inhibits ferroptosis to protect against hypertension.

Coenzyme Q10 (CoQ10) is a mitochondrial coenzyme involved in the electron transport chain, reducing ROS production. It also possesses antioxidant, free-radical-scavenging and vasodilatory properties. The reduced form of CoQ10 is an effective lipophilic antioxidant that inhibits lipid peroxidation by scavenging lipid peroxide radicals, thereby protecting against ferroptosis (72). Furthermore, CoQ10 can directly act on endothelial cells, stimulating vasodilation and reducing blood pressure (213). In addition, oral administration of CoQ10 can reduce hypertension induced by high salt intake in rats by reducing the activity of reduced NADPH oxidase in the paraventricular nucleus of the hypothalamus (214). These studies suggest that CoQ10 may inhibit ferroptosis by reducing mitochondrial lipid peroxidation in endothelial cells, thereby alleviating hypertension. However, further research is needed to investigate how CoQ10 regulates the inhibition of endothelial cell lipid peroxidation and the upstream and downstream targets involved in ferroptosis, providing a novel strategy for the treatment of hypertension.

Potential value of ferroptosis in the treatment of hypertension. Fer-1, a member of the ferrostatin family, effectively attenuates ferroptosis by inhibiting lipid peroxidation (215). A study showed that Fer-1 reversed HHP-induced ferroptosis in VSMCs (155). Moreover, Fer-1 administration markedly ameliorated sunitinib-induced hypertension and endothelial cell ferroptosis in mice (216). These findings indicate that Fer-1 may alleviate hypertension by suppressing ferroptosis in VSMCs and endothelial cells. However, further in-depth investigations are still required to fully evaluate the safety and clinical efficacy of Fer-1 in the treatment of hypertension.

Elabela is a newly discovered 32-amino acid peptide hormone that plays critical roles in multiple physiological processes, including cardiovascular regulation, angiogenesis and fluid homeostasis (217). In hypertensive mice, Elabela markedly inhibited Ang II-induced iron accumulation and lipid peroxidation. Additional studies demonstrated that Elabela attenuates ferroptosis, adverse cardiac remodeling, fibrosis and heart dysfunction in heart microvascular endothelial cells through regulation of the IL-6/sTAT3/GPX4 signaling pathway. These results suggest that Elabela holds therapeutic potential against hypertension and hypertension-related cardiac diseases via inhibition of the ferroptosis pathway (218).

The elevation of lipid peroxide radicals is associated with ferroptosis. Certain drugs and hormones approved by the US Food and Drug Administration have been found to have anti-ferroptosis properties (218), including carvedilol. Carvedilol is a classic antihypertensive drug that primarily reduces blood pressure by blocking β-adrenergic receptors and dilating blood vessels (219). In addition to its antihypertensive effects, carvedilol has been shown to act as an antioxidant, inhibiting ferroptosis by scavenging lipid peroxide radicals and chelating iron ions (220). However, further research is needed to determine whether carvedilol can treat hypertension by inhibiting the ferroptosis pathway. Statin drugs also have anti-ferroptosis properties. Ning *et al* (220) found that atorvastatin can inhibit iron-autophagy-induced ferroptosis and improve heart dysfunction, thereby protecting the heart. It has been suggested that atorvastatin may improve arsenic-induced hypertension by improving blood lipids, enhancing aortic nitric oxide signaling and restoring vascular oxidative-redox homeostasis (221), indicating that statin drugs may inhibit ferroptosis to improve hypertension. Other compounds also have the potential to suppress ferroptosis for the treatment of hypertension.

For example, N-acetylcysteine (NAC), a sulfur-containing compound and a precursor of reduced GSH, has been shown to exert anti-ferroptotic effects by regulating GPX4 expression (222). NAC is also an antioxidant and has antihypertensive effects. Treatment with NAC has been found to protect against hypertension in male offspring of spontaneously hypertensive rats (SHR), suggesting that NAC may have potential clinical applications in regulating ferroptosis to treat hypertension (223). Increasing evidence suggests that active ingredients in traditional Chinese medicine (TCM) also participate in ferroptosis through multiple pathways. Puerarin, an isoflavonoid derived from *Pueraria lobata*, has been extensively used to treat CVDs. It has also demonstrated notable antioxidant and anti-ferroptotic activities across various disease models by attenuating iron overload and lipid peroxidation (224,225). Moreover, puerarin has been shown to effectively reduce blood pressure in both high-salt-induced hypertensive mice and SHR (226,227). Although direct evidence demonstrating that puerarin alleviates hypertension via inhibition of ferroptosis remains limited, it may represent a promising therapeutic strategy for hypertension prevention. Despite the accumulating evidence linking antioxidants to hypertension and ferroptosis, additional research is still required to clearly elucidate the relationships among them.

Mechanisms of ferroptosis in myocardial infarction and I/R injury. I/R injury is a major contributor to the high recurrence rate and long-term mortality observed in myocardial infarction. The identification of effective therapeutic agents to alleviate I/R injury and the elucidation of their mechanisms remain prominent research hotspots in cardiovascular medicine.

Li *et al* (228) demonstrated that circRNA1615 regulates low-density lipoprotein (LDL) receptor-related protein 6 (LRP6) expression, thereby preventing LRP6-mediated ferroptosis-related autophagy in cardiomyocytes and modulating the pathological process of myocardial infarction. Song *et al* (229) developed an acute myocardial infarction model and revealed that extracellular vesicles from human umbilical cord blood-derived mesenchymal stem cells suppress DMT1 expression via miR-23a-3p, ultimately inhibiting ferroptosis in cardiomyocytes and facilitating myocardial repair. Zhou *et al* (230) demonstrated that miR-190a-5p directly targets glutaminase 2 (GLS2) in H9C2 cells, a key enzyme in the glutamine decomposition pathway. Upregulation of miR-190a-5p inhibits GLS2 expression, negatively regulating ferroptosis (230). Egr-1/miR-15a-5p/GPX4/ferroptosis has been identified as a novel signaling pathway involved in the progression of acute myocardial infarction (231). Knocking down miR-15a-5p reduces the death rate of hypoxia-treated cardiomyocytes, while overexpression of miR-15a-5p exacerbates ferroptosis and aggravates hypoxic injury in cardiomyocytes. Xu *et al* (232) demonstrated that paeonol alleviated myocardial infarction-induced ferroptosis by activating the AKT/Nrf2/HO-1 signaling pathway, providing a potential therapeutic target for myocardial infarction. Proteomic analysis in a mouse model of myocardial infarction revealed reduced GPX4 protein levels, leading to ferroptosis in cardiomyocytes. The decreased expression was observed at the transcriptional level, leading to the accumulation of lipid ROS and subsequent ferroptosis in cardiomyocytes (233). Inhibiting GPX4 transcription provides a new approach to protect cardiomyocytes from the effects of ferroptosis.

In the context of myocardial I/R, Baba *et al* (234) showed that, in isolated and cultured murine cardiomyocytes subjected to mTOR overexpression or knockout, mTOR suppressed ferroptosis by modulating ROS and iron homeostasis. Ma *et al* (235) showed that USP22 attenuates ferroptosis in myocardial I/R injury by suppressing the SIRT1/p53/SLC7A11 pathway, which, in turn, reduces ferroptosis in endothelial cells and promotes myocardial repair. Lillo-Moya *et al* (236) engineered polydopamine nanoparticles (PDA NPs) as a novel ferroptosis inhibitor that decreases Fe^{2+} accumulation and restores mitochondrial function in H9C2 cells. In a mouse I/R model, PDA NPs markedly reduced Fe^{2+} deposition, lipid peroxidation and myocardial injury (236). Sun *et al* (237) reported that lncRNA AABR07025387.1 was strongly upregulated in myocardial tissue during I/R injury and in hypoxia/reoxygenation-treated cardiomyocytes. AABR07025387.1 negatively regulated miR-205 expression, thereby enhancing ACSL4-mediated ferroptosis (237). Hwang *et al* (238) demonstrated that intravenous administration of echinochrome A before myocardial I/R markedly reduced ROS levels in cardiomyocytes by upregulating Nrf2 and downstream gene expression, maintaining intracellular GSH levels and upregulating GPX4 expression, thus inhibiting ferroptosis induced by Erastin and RSL3 in rat cardiomyocytes (238). Sun *et al* (239) reported that miR-135b-3p promoted myocardial I/R injury by downregulating GPX4 expression, suggesting a novel direction for the treatment of myocardial I/R injury. Chen *et al* (136) demonstrated that Toll-like receptor 4 (TLR4) and NOX4 are upregulated in myocardial tissues of heart failure mice. Gene knockout of TLR4 and NOX4 reduced autophagy and ferroptosis in cells and improved heart function (136). Liu *et al* (240) reported that puerarin blocked iron overload and lipid peroxidation in H9C2 cells and rat models of heart failure induced by isoproterenol treatment. Fang *et al* (241) established a knockout animal model of cardiac iron-ferritin heavy chain and found reduced expression of SLC7A11 in cardiomyocytes. Overexpression of SLC7A11 increased GSH expression and prevented ferroptosis in the heart, indicating the important role of ferritin in preventing ferroptosis and heart failure (241). Regarding ferritinophagy, a study has found that cardiomyocyte ferritinophagy promotes and aggravates heart failure in the setting of myocardial infarction (242).

Ferroptosis in AS. AS is a common CVD and its pathogenesis remains incompletely elucidated. The primary histopathological changes in AS include endothelial cell injury, lipid deposition and peroxidation, proliferation of VSMCs and macrophage transformation. Ferroptosis is involved in these pathological changes (243,244). In the process of endothelial cell injury, oxidized (ox)-LDL can induce iron deposition and lipid peroxidation in endothelial cells of the aortic wall in mouse models of AS, leading to ferroptosis in endothelial cells (21). During lipid deposition and peroxidation, iron deposition in the arterial intima and plaques can increase the number of lipid droplets in AS mouse plaques and excess iron can accelerate lipid peroxidation through the Fenton reaction (245). Iron deposition can induce transformation to a VSMC phenotype, similar to macrophages and promote VSMC migration (246). A mouse model of human hemosiderosis was successfully established by crossing human hemochromatosis with ApoE4 mice, demonstrating for the first time that non-heme-binding serum-free iron markedly promoted the progression of AS (247). A low-iron diet or iron chelators effectively reversed AS progression and plaque instability in ApoE.FPNc3268 mice and anti-inflammatory treatment (dexamethasone) partially improved the aforementioned pathological changes (247). Analysis of autopsy results from human coronary arteries showed upregulation of the ferroptosis marker genes PTGS2 and ACSL4 in advanced atherosclerotic plaques, while GPX4 expression was markedly downregulated. The severity of AS was positively associated with the expression of PTGS2 and ACSL4 and negatively associated with the expression of GPX4 (248). Together, these studies indicated that ferroptosis is involved in the progression of AS and the formation of vulnerable plaques.

Endothelial cell ferroptosis in AS. Endothelial cell dysfunction plays a crucial role in the occurrence and progression of AS. Endothelial dysfunction can upregulate adhesion factor expression and increase the release of inflammatory chemokines, thereby recruiting circulating monocyte-derived macrophages to adhere to and infiltrate the subendothelial layer of blood vessels. These macrophages engulf ox-LDL to form foam cells, which release numerous inflammatory factors and damage-associated molecular patterns, such as high-mobility group box 1 and histones, thereby creating a local inflammatory microenvironment and a necrotic core, promoting the development and progression of AS (249). The ferroptosis inhibitor Fer-1 can reduce the plaque area and lipid

core induced by a high-fat diet in ApoE mice, inhibit iron accumulation and lipid peroxidation in plaques and inhibit the death of arterial endothelial cells (131). Fer-1 can also inhibit ox-LDL-induced death in murine aortic endothelial cells, reduce intracellular iron accumulation and lipid peroxidation, promote the expression of the cystine/glutamate transporter SLC7A11, GPX4 and endothelial nitric oxide synthase and inhibit the expression of endothelial cell adhesion factors (250). The primary active ingredient of the TCM Danshen is salvianolic acid IIA, which can inhibit ferroptosis induced by the ferroptosis inducers erastin or RSL3 in human coronary artery endothelial cells and this protective effect is abolished by an Nrf2 inhibitor (ML385) (251). In addition, precursor endothelial cells can transfer miR-199a-3p to murine aortic endothelial cells through extracellular vesicles, inhibiting the transcription and translation of downstream specificity protein 1, thereby inhibiting ferroptosis and AS (252). Regarding ferritinophagy, a study found that NCOA4-mediated ferritinophagy in endothelial cells is a key regulatory factor that exacerbates aortic endothelial inflammation and AS (253). These results suggest that ferroptosis contributes to endothelial cell dysfunction, promoting the progression of AS and increasing plaque vulnerability.

Macrophage ferroptosis in AS. Macrophage death is a prominent feature of advanced plaques and a major cause of necrotic core formation and plaque instability (254). Ferroptosis not only regulates macrophage death but also affects macrophage polarization. Macrophages (M0) can be polarized into pro-inflammatory M1 or anti-inflammatory M2 macrophages under LPS/IFN-γ stimulation or IL-4 intervention, respectively. M1 macrophages secrete large quantities of pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, exacerbating local inflammation and oxidative stress. M2 macrophages, conversely, promote tissue damage repair by secreting anti-inflammatory factors such as IL-10 and TGF-β (255). A study has shown that, under conditions of excess iron, ox-LDL and LPS/IFN-γ stimulation in the vascular microenvironment, the proportion of M1 macrophages increases markedly. Iron overload can induce M1 polarization of macrophages through ROS/p53 acetylation and M1 macrophages exhibit stronger resistance to ferroptosis induced by RSL3 compared with M2 macrophages. In addition, M1 macrophages have higher iron levels, while M2 macrophages need to decompose and utilize heme iron through HO-1. These results indicate a close relationship between macrophage ferroptosis and phenotype polarization. Macrophages also play an important role in body iron homeostasis. Iron in the body is primarily absorbed by duodenal cells or recycled from senescent red blood cells by macrophages in the reticuloendothelial system and is regulated by the iron hormone hepcidin, secreted by the liver (248). Inflammatory cytokines such as IL-6 can upregulate hepcidin transcription in the liver through Janus kinase signaling and the transcriptional activator 3 pathway, thereby inhibiting iron absorption mediated by FPN in intestinal epithelial cells, leading to decreased serum iron levels and intracellular iron overload in macrophages. Macrophage iron overload can increase the production of inflammatory cytokines such as IL-6, TNF-α and ROS, inhibit the transcriptional expression of liver X receptor α, which mediates ATP-binding cassette transporter A1, leading to reduced cholesterol efflux and lipid accumulation, thereby promoting foam cell formation and plaque instability (256). Ox-LDL stimulation can induce upregulation of Nrf2 expression, promote transcriptional expression of HO-1, release free Fe^{2+} via heme degradation and inhibit intracellular iron efflux, thereby further exacerbating macrophage iron retention. Therefore, macrophage iron overload and ox-LDL lipid deposition may synergistically promote the progression of AS.

VSMC ferroptosis in AS. Aortic dissection (AD) is a life-threatening condition with high mortality rates and it is closely associated with the loss and degeneration of VSMCs (257). It has been found that patients with AD have markedly increased iron content in the aorta, as well as increased expression of TfR, ferritin, HO-1 gene and the lipid peroxidation product 4-HNE and significant downregulation of the gene expression of SLC7A11, FSP1 and GPX4 (130). The ferroptosis inhibitor liproxstatin-1 can effectively reduce the formation and rupture of AD in mice induced by β-aminopropionitrile (258). Smoking is currently the most important risk factor for AD. A study found that CSE can induce transcriptional upregulation of the PTGS2 gene, lipid peroxidation and depletion of intracellular GSH, leading to ferroptosis in rat VSMCs. Fer-1, liproxstatin-1, or the iron chelator deferiprone can reverse these pathological changes (132). RNA METTL3 can promote ferroptosis in human aortic smooth muscle cells by inhibiting the m6A methylation transferase 1 and FSP1 protein translation (258). The histone methyltransferase inhibitor BRD4770 can inhibit ferroptosis induced by erastin or RSL3 in VSMCs and may become a potential target for treating AD (156).

Ferroptosis is also associated with VSMC phenotype transition. RSL3 can promote the transition of VSMCs from a contractile phenotype to a synthetic-secretory phenotype and increase neointimal hyperplasia in rat carotid artery ligation models. The ferroptosis inhibitor Fer-1 and the ROS scavenger NAC can reverse the phenotype transition in VSMCs (154). In addition, SLC7A11 is markedly upregulated in the lungs of rats with hypoxia-induced pulmonary arterial hypertension (PAH) and in the lung tissues of patients with PAH. Overexpression of SLC7A11 in pulmonary artery smooth muscle cells can inhibit ferroptosis and promote cell proliferation, leading to pulmonary vascular remodeling and the progression of PAH (259). Ferroptosis is also involved in VSMC osteogenic differentiation and vascular calcification. Erastin, a ferroptosis inducer, can induce GSH depletion in VSMCs and promote cell calcification. Conversely, supplementation of the GSH precursor NAC can inhibit VSMC calcification (160). Metformin, through Nrf2 signal activation, enhances the antioxidant capacity of VSMCs, inhibits the ferroptosis of VSMCs induced by palmitic acid and reduces arterial calcium deposition in rats with hyperlipidemia (158). Furthermore, high phosphate and high calcium conditions can increase ferroptosis in VSMCs and Fer-1 can inhibit the osteogenic-like differentiation of VSMCs induced by high phosphate and high calcium, thereby reducing aortic calcification in mice with vitamin D3 overdose. Fer-1 and the iron chelator deferiprone can also inhibit vascular calcification in rats with chronic renal failure (160). These studies indicate that ferroptosis is closely associated with the biological functions of VSMCs and

contributes to the progression of aneurysms, AD and vascular calcification diseases.

In summary, ferroptosis has been shown to be closely related to AS. Ferroptosis can lead to endothelial cell dysfunction, regulate macrophage death and polarization and participate in the transition of the VSMC phenotype. Macrophages also play a role in maintaining body iron homeostasis and iron overload and lipid accumulation can synergistically promote the progression of AS. Currently, research on the relationship between ferroptosis and AS is growing, but several scientific questions remain to be explored. Studying the role of ferroptosis in AS will provide novel diagnostic and therapeutic strategies and new drug-development targets to improve the prevention and prognosis of coronary heart disease.

Interaction between inflammation and ferroptosis promotes AS. Regarding the ferroptosis-pyroptosis interaction driven by inflammatory factors in AS, it has been found that pyroptosis amplifies ferroptosis. Activation of the NLRP3 inflammasome and caspase-1-mediated pyroptosis triggers the release of IL-1β and IL-18. These cytokines upregulate TFR1 and downregulate ferritin in macrophages, expanding the labile iron pool and promoting lipid peroxidation and ferroptosis (260,261). Concurrently, ROS accumulation induced by pyroptosis further exacerbates the Fenton reaction and ferroptosis (253). In addition, ferroptosis fuels pyroptosis: Ferroptotic cells release damage-associated molecular patterns and pro-inflammatory lipid mediators, which activate the NLRP3 inflammasome in macrophages, promote caspase-1 cleavage and GSDMD pore formation and thereby trigger further pyroptosis (10). This creates a positive feedback loop of 'inflammation-ferroptosis-pyroptosis'.

Based on current evidence, it is hypothesized that the dynamic evolution of the 'inflammation-ferroptosis-pyroptosis' interaction across different plaque stages.

In the early fatty streak stage, intimal lipid deposition and macrophage infiltration are minimal and inflammatory cytokine levels are low. At this stage, the interaction between ferroptosis and pyroptosis is relatively weak, with the two pathways operating largely independently. This primarily manifests as mild endothelial injury and macrophage foam cell formation.

In the progressive plaque stage, lipid deposition and macrophage infiltration increase, leading to significant upregulation of pro-inflammatory cytokines and sustained activation of the NLRP3 inflammasome. Consequently, the ferroptosis-pyroptosis interaction is notably enhanced. The resulting positive feedback loop drives persistent amplification of inflammation, promotes phenotypic switching of VSMCs and extracellular matrix degradation and accelerates plaque progression.

In the vulnerable plaque stage of advanced AS, plaques are characterized by a large necrotic core, a thin fibrous cap and extensive macrophage infiltration. Here, the interaction between ferroptosis and pyroptosis reaches its peak: Extensive macrophage ferroptosis and pyroptosis drive expansion of the necrotic core, while the release of inflammatory cytokines and matrix metalloproteinases degrades the fibrous cap, ultimately resulting in plaque rupture, thrombosis and acute cardiovascular events.

Ferroptosis and heart failure. Heart failure is a clinical syndrome defined by decreased cardiac output at rest or during physical activity and/or elevated cardiac filling pressures arising from structural or functional cardiac abnormalities. It manifests with characteristic symptoms such as dyspnea, ankle swelling and fatigue, frequently accompanied by clinical signs including elevated jugular venous pressure, pulmonary crackles and peripheral edema (262). This syndrome results from multiple underlying etiologies and exhibits distinct pathophysiological mechanisms. Rather than an independent disease entity, heart failure represents the common end-stage outcome of diverse cardiac disorders, as nearly all CVDs ultimately progress toward this condition. In addition to the established roles of apoptosis, autophagy and necrosis in heart failure (263), the ferroptosis pathway contributes to disease progression by modulating critical pathophysiological features, including inflammation, cardiotoxicity, myocardial hypertrophy and fibrosis.

Inflammation has been recognized as a pathophysiological characteristic of heart failure (264). In heart failure, the production of various inflammatory mediators not only marks the activation of the inflammatory response but also directly affects the pathophysiological processes of heart failure by inducing ventricular contractile dysfunction, ventricular dilation, myocardial cell hypertrophy and apoptosis through various mechanisms. Ferroptosis is closely related to the inflammatory response and generates certain peroxides and inflammation factors associated with AA metabolism. Research has found increased expression of the PTGS2 gene, which encodes COX-2, in ferroptosis cells. COX-2 accelerates the metabolism of AA and both lipoxygenase and cyclooxygenase are the principal enzymatic tools involved in AA metabolism, decomposing it into leukotrienes, prostaglandins and certain peroxides (63). GPX4 regulates the Nuclear Factor-κB signaling pathway, inhibiting lipoxygenase, reducing ROS levels and alleviating the body's inflammatory response (142). However, the lack of GPX4 can induce an inflammatory response (265). Previous research has confirmed that the aforementioned inflammatory response and its associated inflammatory factors also participate in the occurrence and development of heart failure, demonstrating the close relationship between ferroptosis and heart failure (264). A study showed that Etv5 selectively couples GSH and pentose phosphate metabolism to regulate ferroptosis. Heart failure is the end stage of various CVDs and myocardial hypertrophy is an important node in its pathogenesis (266). Effectively inhibiting pathological myocardial hypertrophy plays an irreplaceable role in its prevention and treatment. Yin *et al* (267) found that mice with half the dosage of Beclin1 were resistant to cold-induced myocardial hypertrophy. Through *in vivo* and *in vitro* experiments, the researchers explored the specific mechanism and found that insufficient dosage of Beclin1 downregulates ferritin, upregulates SLC7A11 (a subunit of FL246) and activates GPX4, exacerbating iron accumulation and lipid peroxidation, promoting the occurrence of ferroptosis, aggravating myocardial hypertrophy and ultimately leading to heart failure.

A prospective study by Silvestre *et al* (268) concluded that there is a U-shaped relationship between ferritin levels and heart failure incidence, with a markedly higher incidence

when average ferritin exceeds 358 ng/ml. Widespread iron deposition in various tissue cells throughout the body promotes the formation of ROS, causing extensive tissue damage and endothelial dysfunction, thereby increasing the risk of adverse cardiovascular outcomes (269,270). Increased iron stores in the body damage the heart, leading to heart failure. β-thalassemia, through compensatory intestinal absorption of excess iron, leads to iron deposition in the myocardium, resulting in iron overload. The high concentration of iron ions induces apoptosis of myocardial cells. In addition, iron ions generated in the process of oxidative-reduction reactions produce a large number of oxygen free radicals, which have toxic effects on myocardial cells and affect myocardial contraction and/or relaxation function. Prolonged damage to myocardial cells ultimately leads to the development of heart failure and accelerates the progression of the disease (271). Liu *et al* (240) found that puerarin markedly blocks iron overload and lipid peroxidation in heart failure rats and H9C2 cells, protecting myocardial cells. This mechanism is associated with the modulation of the Nox4 signaling pathway. Furthermore, iron chelators are one of the main methods for treating iron overload. They promote the excretion of excess iron, but changes in iron metabolism should be monitored during their use to prevent excessive excretion that can lead to iron deficiency. Wang *et al* (272) found that the member of the MAP3K family, mixed lineage kinase 3, induces oxidative stress through the JNK/p53 signaling pathway, leading to ferroptosis and late-stage myocardial fibrosis in chronic heart failure. Inhibiting ferroptosis can prevent heart failure caused by iron overload and protect the heart from myocardial remodeling and the effects of heart failure induced by I/R. Iron also affects mitochondrial respiratory chain function. The accumulation of iron in mitochondria may be a key factor leading to mitochondrial lipid peroxidation-induced ferroptosis in the heart. Clearing mitochondrial lipid peroxidation can effectively inhibit doxorubicin-induced ferroptosis in cardiomyocytes (90,273).

ER stress and ferroptosis. The ER is an essential organelle for maintaining cellular homeostasis and is involved in protein synthesis, folding and processing (274). Under normal conditions, properly folded proteins are released from the ER. However, during stress conditions such as oxidative stress, inflammation and hypoxia, unfolded or misfolded proteins accumulate in the ER, disrupting protein processing and triggering the unfolded protein response (UPR) or ER stress (ERS) (275). To restore normal ER function, the UPR is initiated by unfolded proteins, activating the transmembrane proteins inositol requiring enzyme 1 (IRE1), protein kinase r-like endoplasmic reticulum kinase and activating transcription factor 6. This blocks protein translation, upregulates the expression of oxidative stress-related genes, enhances protein folding capacity within the ER, accelerates ER-related proteolysis and lysosomal degradation and clears misfolded proteins to restore cellular homeostasis. If the cell fails to recover, ER-associated protein degradation pathways are activated, leading to the activation of cellular autophagy and apoptosis pathways (276). In close proximity to the ER membrane, there is a stress-responsive kinase called Pak2, which is activated by ER stress in cardiomyocytes. Binder *et al* (277) found that when stressed or under pressure overload, Pak2-deficient mice exhibit defects in ER stress response, cardiac dysfunction and apoptosis. Conversely, by inducing the expression or transfer of related genes to activate Pak2 and inhibit protein phosphatase 2A activity, the IRE-1/XBP-1 signaling pathway is positively regulated, thereby promoting the unfolded protein response, enhancing ER function, restoring ER homeostasis, improving cardiac function, reducing cell apoptosis and protecting the heart. Thus, regulating Pak2 activity may serve as a novel therapeutic target for heart failure. A study suggests a synergistic effect between ferroptosis and ER stress. Cardiomyocyte damage is accompanied by increased levels of ferroptosis and ER stress and inhibiting ferroptosis or ER stress can alleviate cardiomyocyte damage (278).

In summary, ferroptosis markers display tissue- and cell-type-specific expression differences in the cardiovascular system. For example, in cardiomyocytes, baseline expression of GPX4, ACSL4 and TFR1 is high; in CVDs, the most prominent alterations are GPX4 downregulation and ACSL4 upregulation, which constitute the core markers of cardiomyocyte ferroptosis. In vascular endothelial cells, baseline expression of SLC7A11 and GPX4 is high; in AS and hypertension, SLC7A11 downregulation represents the earliest event in endothelial cell ferroptosis, accompanied by a decline in GSH levels. In VSMCs, baseline expression of ACSL4 and PTGS2 is high; in hypertension, AAA and AS, ACSL4 upregulation is a key driver of VSMC ferroptosis and phenotypic switching, while PTGS2 serves as a reliable biomarker. In macrophages, baseline expression of TFR1, ferritin heavy chain 1 and HO-1 is high; in atherosclerotic plaques, upregulation of TFR1 and HO-1 leads to iron overload and represents a characteristic marker of macrophage ferroptosis.

Future research should further elucidate the expression differences of these markers across various CVDs through single-cell multi-omics and spatial transcriptomics, while analyzing their tissue- and spatial location-specificity. Such efforts will provide essential guidance for selecting diagnostic biomarkers tailored to different CVDs.

4. Inhibitors of ferroptosis in CVDs

Targeting ferroptosis is becoming an important strategy for the prevention and treatment of CVDs. Various substances can block or inhibit ferroptosis, including iron chelators, ferrostatin 1, vitamin E, GSH, coenzyme Q10, curcumin and liproxstatin 1 (279-281). The known mechanisms of ferroptosis primarily involve iron metabolism, abnormal GSH dissolution and lipid membrane oxidation. Similarly, ferroptosis inhibitors primarily function through eliminating free radicals, inhibiting the enzymes that produce lipids or lipid peroxides, or reducing free iron levels (282). Based on this, ferroptosis inhibitors can be classified into three categories: Inhibitors of lipid peroxidation (antioxidants), agents targeting iron overload (iron chelators) and inhibitors of ROS formation. Here, the mechanism of action of various inhibitors is discussed based on this classification (Fig. 3) (245,282,283).

Antioxidants. Oxidative stress plays an essential role in mediating cellular ferroptosis. There are physiologically intrinsic antioxidative capabilities that prevent oxidative

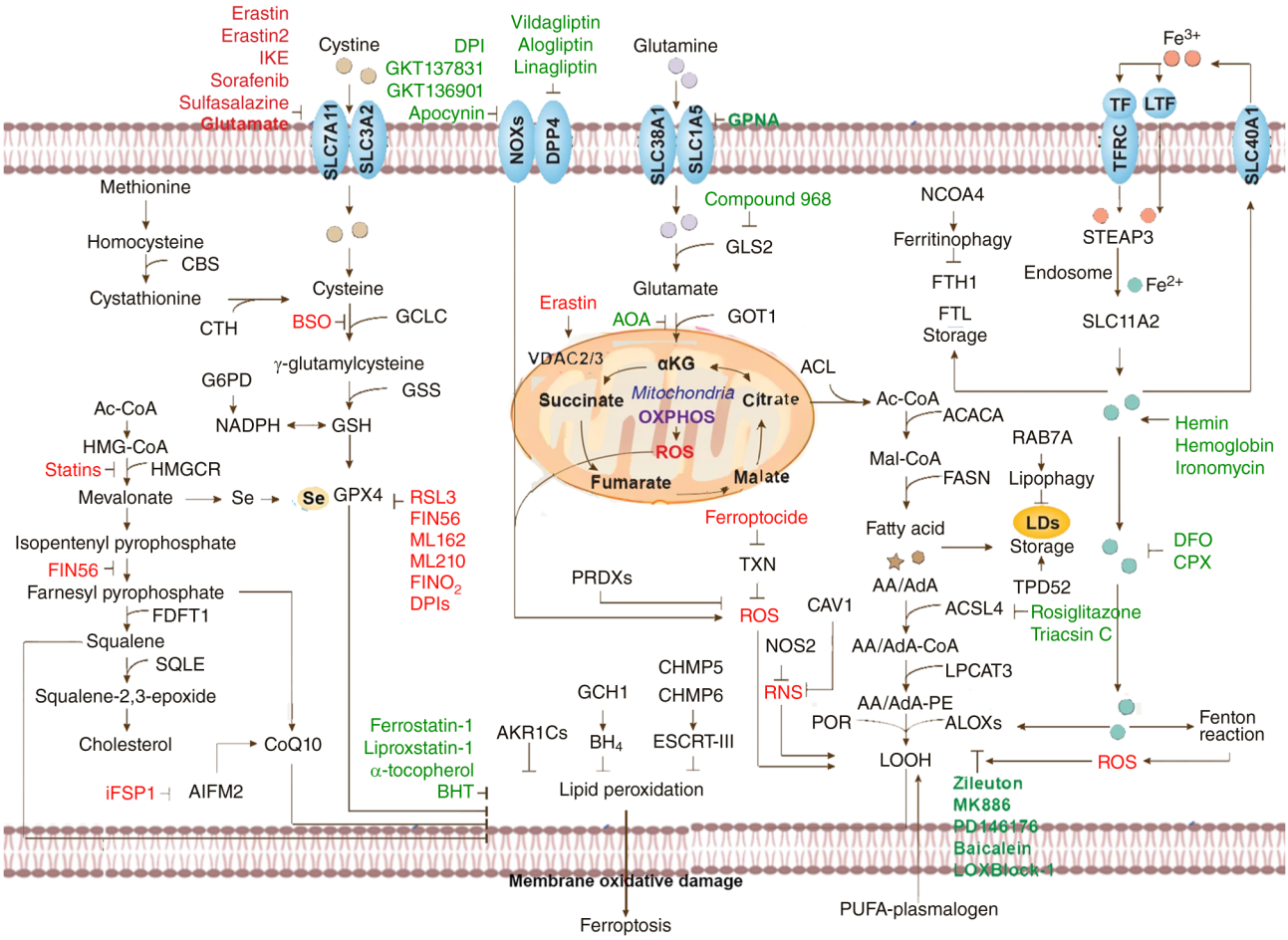

Figure 3. Systemic regulatory network of ferroptosis and panoramic overview of targeted intervention targets in cardiovascular diseases This figure provides a panoramic analysis of the multidimensional regulatory pathways of ferroptosis, covering core metabolic axes, organelle functions, iron homeostasis, lipid peroxidation cascade and key intervention targets. It offers a complete mechanistic framework for the development of ferroptosis-targeted intervention strategies in cardiovascular diseases. The core antioxidant defense axes consist of the System xC^- (SLC7A11/SLC3A2)-mediated cysteine uptake and GSH synthesis pathway that supports GPX4 activity and serves as the primary barrier against ferroptosis. The FSP1-CoQ10 and GCH1-BH4 pathways constitute GPX4-independent antioxidant defense lines. Iron metabolism regulation involves TfR/LTF-mediated iron uptake. NCOA4-dependent ferritinophagy releases free iron (Fe^{2+}), which drives oxidative stress through the Fenton reaction. Iron chelators (DFO, CPX) can specifically block this process. The core pathway of lipid peroxidation involves ACSL4/LPCAT3 catalyzing PUFA to generate peroxidation substrates. ALOXs and POR promote the accumulation of LOOH. LOX inhibitors such as Zileuton and Balsalazide can suppress this process. Mitochondria play a central driving role through OXPHOS that generates ROS, glutamine metabolism (GLS2, GOT1) that supplies energy for mitochondrial metabolism and VDAC2/3-mediated substance transport that regulates mitochondrial sensitivity to ferroptosis. Targeted intervention sites include ferroptosis inducers such as Erastin and RSL3, which act by inhibiting System xC^- and GPX4; inhibitors such as Ferrostatin-1 and vitamin E, which target the clearance of lipid peroxides and block core pathways; and clinically used drugs such as statins and DPP4 inhibitors, which indirectly intervene in ferroptosis by regulating metabolic pathways. These targets provide critical points for clinical translation in cardiovascular diseases. SLC, solute carrier family; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; GSH, glutathione; TfR, transferrin receptor; LTF, lactoferrin; DFO, deferoxamine; CPX, ciclopirox olamine; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; PUFA, polyunsaturated fatty acids; ALOXs, lipoxygenases; POR, ER-residing P450 oxidoreductase; LOOH, lipid peroxides; OXPHOS, oxidative phosphorylation; RSL3, RAS-selective lethal 3; DPP4, dipeptidyl peptidase 4.

damage. However, when these cellular antioxidant defense systems become dysregulated, oxidative damage occurs, leading to ferroptosis. Therefore, targeting cellular oxidative stress, specifically inhibiting lipid peroxidation, can serve as an approach to inhibit ferroptosis. Common antioxidants include ferrostatin 1, liproxstatin 1, vitamin E, trolox, statins, flavonoids and polyphenols found in TCM (92,284-286).

Statins. Statins are commonly used medications for the treatment of CVDs. High-intensity statin therapy at discharge in patients with myocardial infarction markedly reduces LDL-cholesterol levels by 50% and markedly decreases the rates of mortality and major cardiovascular events (287,288). The primary mechanism underlying statin therapy was previously hypothesized to involve the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which reduces cholesterol synthesis (289). However, statins can also improve endothelial function, inhibit systemic or local inflammation, enhance resistance to oxidative stress and inhibit adverse cardiac remodeling. Ning *et al* (220) demonstrated that atorvastatin calcium protected the heart against isoproterenol-induced injury by inhibiting the iron uptake-mediated ferroptosis pathway. Atorvastatin markedly increased GSH levels, the GSH/GSSG ratio and markedly decreased malondialdehyde levels in cardiac tissue. Atorvastatin also markedly inhibited cardiac remodeling, lipid peroxidation and iron accumulation, thereby improving cardiac function and preventing heart failure induced by isoproterenol (220,290). Therefore,

atorvastatin calcium may be used as a treatment for CVDs by inhibiting ferroptosis.

Iron chelators. Experimental evidence indicates that effective iron chelation therapy can postpone the onset of iron overload, mitigate the associated tissue damage and substantially enhance the prognosis of heart diseases, particularly in patients with primary or secondary iron overload complicated by heart failure. Iron chelators block iron-catalyzed redox reactions, thereby enabling efficient iron mobilization and excretion without redistribution. The most frequently used clinical agents include deferoxamine, deferiprone, deferasirox and dexrazoxane (291).

Beyond their established role in iron overload disorders, iron chelators also prevent iron from participating in the generation of ROS, thereby attenuating oxidative stress-related injury in conditions such as myocardial infarction, neurodegenerative diseases, inflammation and chemotherapy (292). Horackova *et al* (293) examined the effect of iron chelators during myocardial I/R and found that the lipophilic chelator salicylaldehyde isonicotinoyl hydrazone conferred rapid and potent cardioprotective effects against H_2O_2-induced oxidative stress, while deferoxamine similarly protected the heart from myocardial I/R damage *in vitro*. In addition, Ferrostatin 1 combined with the iron chelator dexrazoxane markedly reduced doxorubicin-induced cardiac injury and heart failure in a mouse model, providing the first direct demonstration that ferroptosis constituted a novel therapeutic target in heart disease. Consequently, ferroptosis inhibition through iron chelators has emerged as a promising strategy for the treatment of CVDs.

Inhibitors of ROS Formation. Ferroptosis is triggered by excessive iron accumulation, which causes a sharp rise in intracellular lipid ROS. The resulting ROS buildup promotes lipid peroxidation, ultimately leading to cell death. Therefore, suppressing ROS generation or accumulation can effectively mitigate oxidative stress and limit the formation of lipid peroxidation end-products. Common inhibitors of ROS include α-tocopherol analogs, acetylcysteine, SRS824, CA1, as well as various bioactive terpenoids derived from TCM (294).

A study has shown that tanshinone IIA, a lipophilic active component extracted from *Salvia miltiorrhiza*, exhibits multiple beneficial effects, including anti-inflammatory, antioxidant, endothelial protective and cardioprotective activities (295). Tanshinone IIA attenuates oxidative stress by decreasing ROS and MDA production while enhancing the activities of total superoxide dismutase and GPX. It also inhibits hepatocyte apoptosis and alleviates hepatic steatosis (296). In human coronary artery endothelial cells, tanshinone IIA markedly reduced the excessive accumulation of total ROS and lipid ROS induced by ferroptosis inducers and restored GSH levels (251). Furthermore, in a study on damaged hippocampal cells in mice, tanshinone IIA treatment increased cell viability and suppressed the overaccumulation of total ROS, lipid ROS, active iron and transferrin. Collectively, these findings suggest that inhibiting ferroptosis by reducing cellular and tissue ROS levels or blocking ROS generation offers a promising novel avenue for the prevention of CVDs (297).

In summary, understanding the mechanisms of action of these inhibitors and their interactions and correlations with different mechanisms may provide novel insights for research and prevention of clinical CVDs. Moreover, the development of highly specific targeted agents that can regulate iron metabolism, amino acids, ROS, lipids and other mechanisms may lead to a new approach for the treatment of CVD. Therefore, the next step will involve the simultaneous exploration and verification of research on antioxidants and iron chelators in animal models, in order to seek an appropriate and innovative targeted agent. Simultaneously, further research on the mechanisms and interactions of these agents, as well as the characteristics of their actions, will help develop a combination of Eastern and Western approaches with specific and higher selectivity for targeted ferroptosis inhibitors, providing novel directions for the treatment of CVDs.

Representative natural compounds. Natural compounds have been found to have therapeutic effects in CVDs (298). TCM is a treasure trove of natural compounds, containing various bioactive ingredients. Compound formulas and single herb extracts in TCM both demonstrate multi-target and multi-level actions. This section summarized the regulatory effects of related TCM on GPX4 in the treatment of CVDs, providing references for clinical medication.

Compound formulas. Tao Hong Si Wu Decoction, first mentioned in the book *Yi Zong Jin Jian* (299), nourishes and activates blood circulation, promotes new blood generation and is commonly used for blood deficiency and blood stasis conditions. Pharmacological studies have shown that these compounds have protective effects on endothelial cells, vasodilation, anti-inflammation, immune regulation and lipid-lowering effects (300). The combination of Shuangchen Decoction and Tao Hong Si Wu Decoction can increase the expression of SLC7A11 and upregulate the expression of GPX4, thereby exerting an anti-ferroptosis effect to improve AS damage (301). Lu Hong Fang, composed of deer antler, safflower, dogwood fruit and *Psoralea corylifolia*, has been shown to improve myocardial I/R injury. In rat serum, Lu Hong Fang has been shown to increase GSH levels (302); in rats with myocardial I/R injury, it reduced the infarct area, decreased oxidative stress, increased the expression of SLC7A11 and elevated GSH levels. By upregulating GPX4 activity, it inhibits oxidative stress and ferroptosis, providing protection against myocardial I/R injury (303). Tongxinluo Capsule is a commonly used patented Chinese medicine for the treatment of cardiovascular and CVDs (304). Composed of 12 vascular-active Chinese herbs, it has been found to inhibit endothelial inflammation and oxidative stress and protect endothelial cells and microvessels of the heart and brain (305). In a mouse model of chronic obstructive pulmonary disease combined with AS, Tongxinluo Capsule reduced the formation of atherosclerotic plaques, increased the expression of GPX4, elevated GSH levels and inhibited lipid peroxidation. Tongxinluo Capsule also exerted protective effects against atherosclerotic-related damage in vascular endothelial cells (306). Ge Gen Qin Lian Tang, a classic formula in the book *Shanghan Lun* (307). Research has found that administration of Ge Gen Qin Lian Tang in type 2 diabetic mice improved

left ventricular diastolic function. It achieved this effect by upregulating GPX4 expression, inhibiting lipid peroxidation and suppressing ferroptosis-induced cardiac damage (308). Shenmai Injection is a modified traditional Chinese medicine made from ginseng and *Ophiopogon japonicus*. It can alleviate myocardial I/R injury. In a rat model of myocardial I/R, Shenmai Injection markedly increased the expression of NRf2 protein, which in turn activated downstream GPX4 protein expression. This activation of GPX4 played a role in antioxidative stress, repairing damaged cell membranes, inhibiting lipid peroxidation and suppressing ferroptosis, thus protecting the myocardium (309).

Single herbs

Flavonoids. Flavonoids are among the most abundant compounds in TCM and exhibit strong antioxidant and anti-inflammatory properties that confer beneficial effects in CVDs. Puerarin, a major phytoestrogen, displays potent antioxidant activity (310). In mouse models of AS induced by aortic stenosis as well as in isoprenaline-treated H9C2 cells, puerarin upregulated GPX4 and FTH1 expression, suppressed lipid peroxidation and iron overload and effectively inhibited ferroptosis-induced cardiomyocyte death, thereby protecting the hearts of diabetic mice (240). *Ginkgo biloba* is often used as an antitussive and bronchodilator, exhibiting antioxidant, improved circulation and anti-inflammatory effects. *Ginkgo biloba* ethyl acetate extract inhibits ferroptosis and its primary active compound is bilobalide. In a human umbilical vein endothelial cell (HUVEC) ferroptosis model, bilobalide markedly reduced the excessive accumulation of total ROS and lipid ROS, restored GSH levels (311). Naringin, a compound found in grapefruit, has preventive effects on AS, hypertension and arrhythmias (312). A study has shown that naringin improved myocardial I/R injury by inhibiting ferroptosis. In a rat model of myocardial I/R injury, naringin markedly reduced myocardial infarct size and myocardial injury, decreased oxidative stress and ferrous iron levels, upregulated the expression of GPX4, SLC711 and NRf2 and inhibited lipid peroxidation and ferroptosis. This suggests that naringin exerts its protective effects against myocardial I/R injury by regulating GPX4 and related antioxidative systems (313). Baicalein, a flavone compound, exhibits anti-inflammatory, antioxidant and other pharmacological activities. In a rat heart I/R model, baicalein markedly upregulated the expression of NRf2, initiated downstream GPX4 expression, repaired damaged lipid membranes, inhibited lipid peroxidation and mitigated ferroptosis, thereby providing protection against myocardial I/R injury (314).

Triterpenoid saponins. Saikosaponin A, a triterpenoid saponin extracted from *Bupleurum falcatum* roots, exhibits multiple pharmacological activities, including anti-inflammatory and antioxidant effects. In H_2O_2-induced HUVECs, saikosaponin A suppressed ferroptosis through GPX4 activation and ACSL4 downregulation, resulting in decreased intracellular lipid peroxidation (315). Astragaloside IV, the primary bioactive constituent of *Astragalus*, demonstrated favorable therapeutic effects in CVDs (316). It protected against doxorubicin-induced myocardial injury by inhibiting ferroptosis. In doxorubicin-induced heart failure models, myocardial fibrosis and cardiac dysfunction develop alongside elevated inflammatory cytokines and ferroptosis activation. Astragaloside IV activated the NRf2 pathway, elevated GPX4 expression, attenuated oxidative stress and blocked ferroptosis, thereby exerting cardioprotective effects (317). Total saponins from *Dens draconis* exerted protective effects against myocardial I/R injury. The primary active component, saikosaponin A, upregulated GPX4 expression via the GR-NR3C1/p53/SLC7A11 axis in hypoxia/reoxygenation-treated AC16 cells, which facilitated the restoration of membrane integrity damaged by hypoxic stress (318).

Polyphenols. Resveratrol has been reported to alleviate oxidative stress, apoptosis, autophagy and ER stress, thereby exerting cardioprotective effects (319). It mitigates these same pathological processes and ultimately enhances cardiac function (320). In both hypoxia/reoxygenation-injured H9C2 cells and a rat I/R model (321), resveratrol markedly elevated GPX4 and FTH1 levels, lowered iron-dependent ROS accumulation, activated GPX4-dependent antioxidant defense, suppressed ferroptosis and ameliorated I/R injury.

Puerarin, one of the most abundant isoflavones, possesses strong antioxidant activity and exhibits estrogen-like effects in plants (322). Multiple clinical trials have confirmed its antioxidative, anti-lipid peroxidation and myocardial energy metabolism-enhancing actions. Based on these antioxidative properties, puerarin has been shown to improve heart failure. Animal studies further indicate that it can prevent cell death. Liu *et al* (240) demonstrated that puerarin inhibited lipid peroxidation and iron overload, thereby attenuating heart failure and protecting cardiomyocytes against isoprenaline-induced damage in H9C2 cells. Li *et al* (323) also showed that puerarin decreased ROS levels, suppressed apoptosis and increased cell survival in isoflurane-treated H9C2 cardiomyocytes. Zhang *et al* (324) found that puerarin downregulated TGF-β mRNA expression in a rat model of spontaneous hypertension, resulting in myocardial protection. In a separate myocardial infarction model, puerarin markedly blocked MCP-1 recruitment and activation in the infarcted heart while reducing TGF-β levels in myocardial tissue, which alleviates fibrosis and confers myocardial protection (325). Thus, puerarin can reduce ROS production, restore iron homeostasis and prevent iron overload, ultimately inhibiting ferroptosis.

Xanthones. Geniposide, the major active component of *Gardenia jasminoides*, has natural antioxidant and cardioprotective effects. Geniposide activates GPX4 and suppresses ACSL4, thereby reducing intracellular lipid peroxidation levels and inhibiting ferroptosis in erastin-treated HUVECs (326).

In summary, this section discussed the functions of natural compounds that target ferroptosis and their roles in CVDs. Among these compounds, flavonoids and triterpenoid saponins regulate ferroptosis through indirect effects on upstream molecules, such as Nrf2 and SLC7A11. However, research specifically targeting GPX4 is limited and the interactions between herbal compounds in formula prescriptions are not yet clear. Further studies are required to elucidate the structure-activity relationship of natural compounds and establish platforms for screening compounds that can regulate GPX4 activity. Developing natural small-molecule compounds that can regulate GPX4 activity, inhibit oxidative stress and

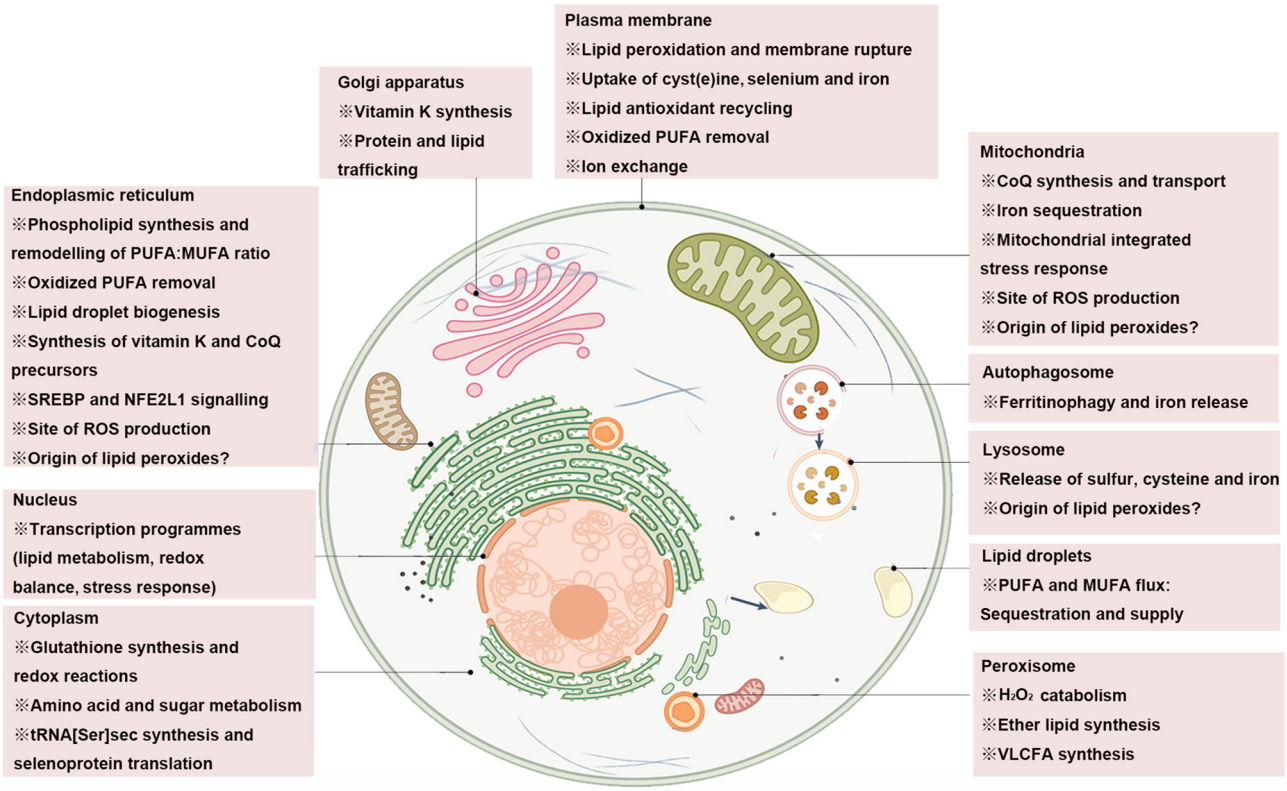

Figure 4. Overview of the intracellular organelles involved in ferroptosis. PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; CoQ, coenzyme Q; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein; NFE2L1, nuclear factor erythroid 2-like 1; H_2O_2, hydrogen peroxide; VLCFA, very long-chain fatty acids.

ferroptosis and mitigate oxidative damage-induced CVDs holds significant potential (Fig. 4).

Although the potential of natural compounds as ferroptosis inhibitors has been emphasized, the conclusions are largely based on data from *in vitro* and animal models. Substantial work is required to translate them clinically. In the present study, the pharmacokinetic analysis of select compounds were discussed. The key pharmacokinetic parameters of the major natural compounds mentioned in the manuscript are systematically reviewed, including oral bioavailability, half-life, metabolic pathways and tissue distribution and their clinical applicability and translational potential are evaluated. For example, among flavonoids, puerarin exhibits an oral bioavailability of 7-11%, a plasma half-life of 1.5-3 h and is primarily metabolized in the liver, with enrichment in myocardial tissue (327). Baicalin has an oral bioavailability of 20-30% and a half-life of 4-6 h, with favorable vascular tissue distribution (328).

Among triterpenoid saponins, astragaloside IV has an oral bioavailability of 2-5% and a half-life of 3-5 h, with accumulation in the heart and aorta (329). For polyphenols, resveratrol exhibits an oral bioavailability of <1%, but its metabolites exhibit high bioactivity, with a half-life of 8-14 h and favorable mitochondrial-targeting properties (330). Tanshinone IIA shows an oral bioavailability of 3-5% and a half-life of 2-4 h, with rapid distribution to myocardial tissue (328). In the iridoid glycosides category, geniposide has an oral bioavailability of 9.67% (rat data). Owing to its strong hydrophilicity and poor membrane permeability, its overall bioavailability is relatively low; its metabolite genipin has a half-life of 4-6 h (331). In the diterpenoid lactones category, ginkgolide B exhibits an elimination half-life of 9-11 h following oral administration in humans and 3.4 h after intravenous administration. It has a relatively long duration of action, reaching peak plasma concentration 3-4 h after oral administration; as a small lipophilic molecule, it is rapidly absorbed (332).

5. Conclusions and future prospects

Ferroptosis plays a critical role in the pathogenesis of cancer, kidney disease, neurological disorders and CVDs. As an iron-dependent form of regulated cell death driven by lipid peroxidation, ferroptosis is tightly controlled by iron metabolism, lipid metabolism and amino acid metabolism. In cardiomyocytes, excessive iron accumulation triggers oxidative stress and iron toxicity, ultimately inducing ferroptosis. In CVDs, abnormal expression of ferroptosis-related genes and excessive degradation of antioxidant proteins are major drivers of its activation.

The present review summarized recent advances in ferroptosis research and its involvement in key cardiovascular conditions, including myocardial infarction, heart failure and myocardial I/R injury, while highlighting potential therapeutic targets. It seeks to offer fresh insights into the underlying mechanisms and the important regulatory functions of ferroptosis in cardiovascular pathophysiology. However, current studies remain largely confined to cellular and animal models, underscoring the need for deeper

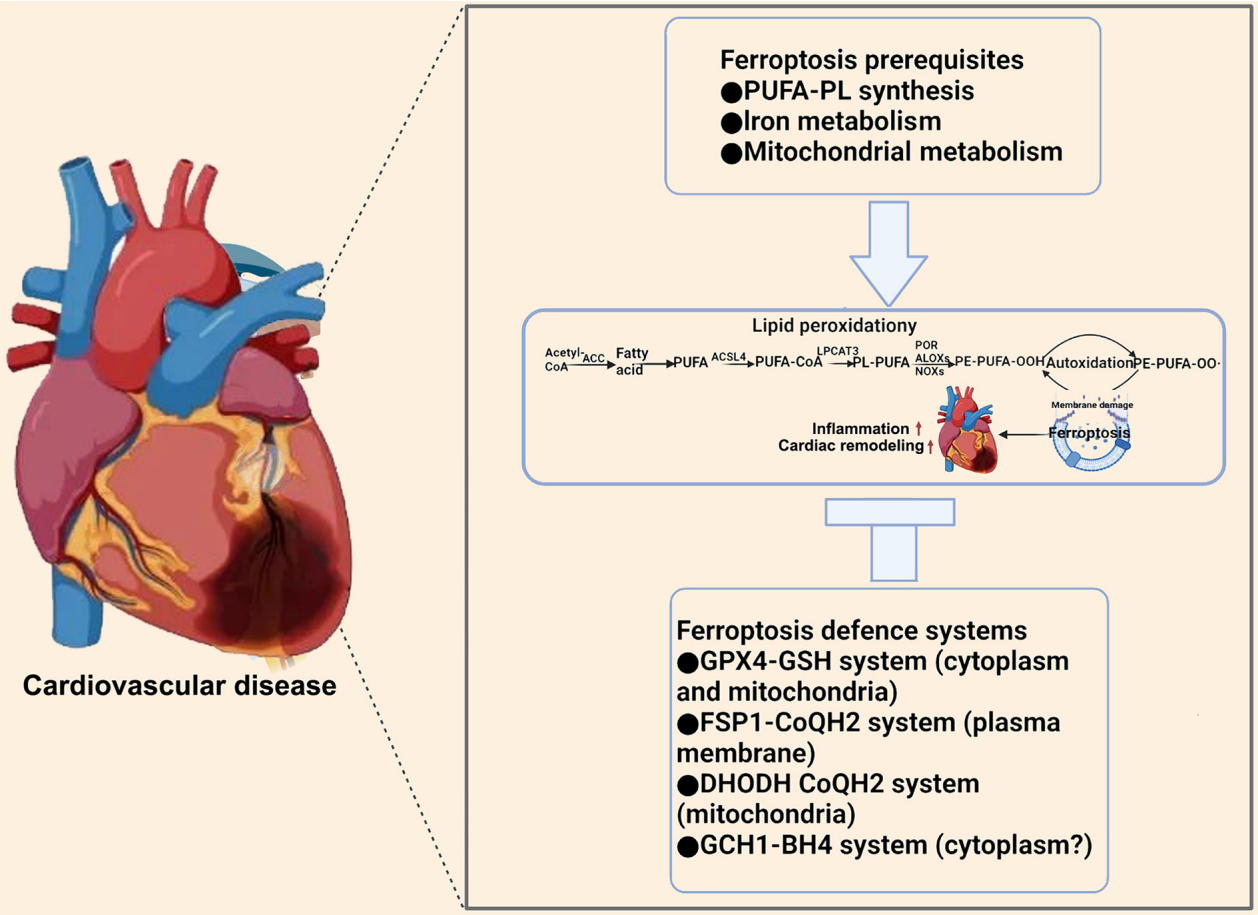

Figure 5. Driving-defense antagonistic mechanism of ferroptosis in cardiovascular diseases. Ferroptosis reflects the dynamic antagonism between the driving prerequisites of ferroptosis and the defense systems. In cardiovascular diseases, the driving prerequisites include the synthesis and peroxidation of PUFA-PL, iron metabolism and mitochondrial metabolism, which collectively provide substrates and catalytic conditions for lipid peroxidation. The defense systems primarily consist of the GPX4-GSH, FSP1-$CoQH_2$, DHODH-$CoQH_2$ and GCH1-BH4 systems, which maintain membrane homeostasis by clearing lipid peroxides. When the driving forces exceed the defense capacity, the accumulation of lethal lipid peroxides leads to membrane rupture and ferroptosis, subsequently triggering inflammation and cardiac remodeling, thereby promoting disease progression. PUFA, polyunsaturated fatty acid; PL, phospholipid; GPX4, glutathione peroxidase 4; GSH, glutathione; FSP1, ferroptosis suppressor protein 1; $CoQH_2$, reduced coenzyme Q (ubiquinol); DHODH, dihydroorotate dehydrogenase; GCH1, GTP cyclohydrolase 1; BH4, tetrahydrobiopterin.

investigations to enable clinical translation. In addition, reliable biomarkers and probes for monitoring ferroptosis progression are still lacking. Therefore, continued exploration of the molecular signaling pathways that govern ferroptosis regulation in CVDs is essential (Fig. 5).

Contributions and limitations of previous research in the field. Reviewing the research progress of ferroptosis regulation in CVDs, researchers have continuously delved into this topic and published numerous studies since the association between CVDs and ferroptosis was discovered. They have investigated various aspects, such as the roles of iron metabolism, lipid metabolism and amino acid metabolism in promoting or inhibiting ferroptosis. Ferroptosis has been found to play a role in the development of CVDs, as well as in the diagnosis and treatment of tumors, immune system disorders, neurological disorders and liver diseases. Particularly in the field of CVDs, utilizing the unique characteristics of novel carriers to inhibit ferroptosis has provided new possibilities. However, there are still some limitations in current research. First, there is no unified conclusion regarding the relationship between CVDs and ferroptosis and the upstream and downstream mechanisms of ferroptosis regulation in CVDs are not fully understood. Additionally, there are limited studies on ferroptosis in the context of inflammation and other related areas, which demonstrates the limitations of this therapeutic approach. Furthermore, most of the current research is based on animal models and *in vitro* experiments and translating this basic research into clinical outcomes requires further in-depth studies to solidify the foundation for comprehensive clinical applications. Finally, the regulation of ferroptosis by extracellular signals, such as proteins and lipid molecules carried by extracellular vesicles, has not been extensively studied. Exploring these areas could reveal deeper connections between ferroptosis and CVDs.

Unique features compared to previous works. In contrast to previous studies, the present review systematically elucidated the regulation of ferroptosis in various target cells (including endothelial cells, cardiomyocytes and immune cells) in CVDs. It presented a novel perspective on the relationship between

ferroptosis and CVDs and demonstrated the potential of inhibiting or promoting ferroptosis as a therapeutic strategy in various disease contexts.

Limitations and importance of the review. Although the present review sought to include all possible relevant studies, the current literature on the regulation of ferroptosis in CVDs remains limited. The mechanisms of ferroptosis regulation and its applications in various CVDs have not been comprehensively summarized and analyzed. Furthermore, due to limitations in the search strategy, some articles may have been inadvertently omitted, which may have restricted the breadth of the present review.

The present review focused on summarizing the regulation of ferroptosis and its important role in CVDs from different perspectives. It provided insights into potential mechanisms and the crucial regulatory function of ferroptosis in CVDs, aiming to arouse the attention of researchers and reveal the relationship between ferroptosis and CVDs more comprehensively. Additionally, it highlighted the potential value and application of using ferroptosis as a therapeutic target for oxidative stress-induced CVDs, thereby providing a basis for further improvement in disease treatment and drug development.

Acknowledgements

Not applicable.

Funding

The present review was supported by the National Natural Science Foundation of Hunan, China (grant no. 2022JJ30086), the Science and Technology Innovation Program of Changde City (grant no. 2024ZD198) and the Project of the First People's Hospital of Changde City (grant no. 2022ZZ04).

Availability of data and materials

Not applicable.

Authors' contributions

LG, TZ, JY and SX contributed to the writing of the manuscript. LL and YZ reviewed and revised the manuscript. JY was responsible for the collection of relevant literature and materials. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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