Clinical Epigenetics

REVIEW

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Epigenetic regulation and post-translational modifications of ferroptosis-related factors in cardiovascular diseases

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Abstract

As an important element of the human body, iron participates in numerous physiological and biochemical reactions. In the past decade, ferroptosis (a form of iron-dependent regulated cell death) has been reported to contribute to the pathogenesis and progression of various diseases. The stability of iron in cardiomyocytes is crucial for the maintenance of normal physiological cardiac activity. Ferroptosis has been detected in many cardiovascular diseases (CVDs), including coronary heart disease, myocardial ischemia–reperfusion injury, heart failure, and chemotherapy-induced myocardial damage. In cardiomyocytes, epigenetic regulation and post-translational modifications regulate the expression of ferroptosis-related factors, maintain iron homeostasis, and participate in the progression of CVDs. Currently, there is no detailed mechanism to explain the relationship between epigenetic regulation and ferroptosis in CVDs. In this review, we provide an initial summary of the core mechanisms of ferroptosis in cardiomyocytes, with first focus on the epigenetic regulation and expression of ferroptosis-related factors in the context of common cardiovascular diseases. We anticipate that the new insights into the pathogenesis of CVDs provided here will inspire the development of clinical interventions to specifically target the active sites of these factors, reducing the harmfulness of ferroptosis to human health.

Keywords Cardiovascular diseases, Ferroptosis, Epigenetic regulation, Post-translation modification

Background

Ferroptosis is a form of iron-dependent regulated cell death characterized by lethal iron-catalyzed lipid damage. Morphologically, ferroptotic cells show typical necrotic changes, such as swelling and plasma membrane rupture, with biochemical changes including lethal levels of iron-dependent lipid peroxidation[1]. Ferroptosis plays an important pathophysiological role in the development of cardiovascular diseases (CVDs). Imbalanced iron homeostasis and excessive accumulation of reactive oxygen species (ROS) and ferrous iron (Fe^{2+}) can induce ferroptosis by increasing oxidative stress and damaging the cell membrane in cardiomyocytes. However, ferroptosis is precisely regulated at multiple levels, including post-translational modification (PTM) of proteins and epigenetic modification of the genome. Epigenetic regulation

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in cardiovascular disease is an emerging field. Epigenetic modifications, which include DNA methylation, histone modification, and non-coding RNA (ncRNA) regulation, are dynamic and reversible processes that regulate gene expression without altering the DNA sequence[2, 3]. PTMs introduce specific chemical modifications through covalent or enzymatic mechanisms to dynamically regulate the localization, activity, and molecular interactions of proteins. PTMs include phosphorylation, ubiquitination, acetylation, glycosylation, and many other types of modifications[4]. Epigenetic modifications and PTMs regulate the expression levels of ferroptosis-related genes and participate in the maintenance of iron homeostasis and the regulation of antioxidant pathway-related factors in cardiomyocytes, deepening our understanding of potential pathological processes in CVDs.

Past research has primarily focused on the role of non-coding RNA in the progression of ferroptosis-related cardiovascular diseases, and there is no detailed mechanism to explain the relationship between epigenetic regulation and ferroptosis in cardiovascular disease. Therefore, in this review, we provide an initial summary of the core mechanisms of ferroptosis in cardiomyocytes, with first focus on the epigenetic regulation and expression of ferroptosis-related factors in the context of common cardiovascular diseases.

By elucidating how these modifications in cardiomyocytes precisely interact with ferroptosis to cause the occurrence and progression of CVDs, we identify targets for the control of progression and clinical intervention of these common diseases.

Discovery of ferroptosis

Iron, a metal element essential for the human body, is involved in numerous physiological and biochemical processes, including the synthesis of hemoglobin and myoglobin, storage and transport of oxygen, mitochondrial respiration, DNA synthesis and repair, and iron-dependent catalytic reactions. However, excessive iron accumulation can be toxic.

Ferroptosis, derived from the Latin "ferrum" meaning "iron" and the Greek "ptosis" meaning "falling," is a novel form of cell death [5]. In 2012, Dixon and colleagues first reported ferroptosis as an iron-dependent, non-apoptotic form of cell death [6]. Its characteristics include changes in mitochondrial morphology, such as swelling, density alterations, and outer membrane rupture, as well as excessive production of lipid peroxides and inhibition of antioxidant pathways. These mechanisms disrupt the phospholipid bilayer structure of the cell membrane, changing its permeability and affecting its normal function, and ultimately lead to cell death [7].

Stable iron content in the myocardium is crucial for maintaining normal cardiac activity and function. Both primary and secondary iron overload can cause cardiac dysfunction through oxidative damage. Studies have shown that iron deficiency can lead to pathological illnesses, including impaired mitochondrial function in myocardial cells, leading to cardiac dysfunction. Indeed, excess or deficiency of iron is associated with various CVDs [8].

Iron metabolism and ferroptosis

Iron homeostasis

The metabolism of iron is a dynamic process that includes iron absorption, utilization, storage, and efflux. The iron metabolism pathways are an essential component of the regulatory mechanisms of ferroptosis, and genes associated with these pathways also serve as potential targets for modulating ferroptosis. Iron taken up into cells can form transferrin (TF)-bound iron (TBI) by binding to TF; however, when the TF binding sites are saturated, iron binds to serum albumin and citrate, forming non-TF-bound iron (NTBI). The pathways and regulatory mechanisms for the entry of TBI and NTBI into myocardial cells differ. Cardiomyocytes accumulate TBI via binding with its receptor, TF receptor protein 1 (TFR1), and accumulate NTBI through divalent metal transporter 1 (DMT1), calcium channels, and zinc transporter proteins [9]. The cellular uptake of iron is mediated by the binding of iron-bound TF (which contains two ferric iron [Fe^{3+}] molecules) to TFR1, triggering endocytosis under the acidification by vacuolar ATPase and leading to the reduction of Fe^{3+} to Fe^{2+} by the six-transmembrane epithelial antigen of prostate (STEAP) family of metalloreductases [9]. Fe^{2+} is then released into the cytoplasm via natural resistance-associated macrophage protein 2 (NRAMP2), while apo-TF and TFR1 are recycled back to the cell surface for reuse [10]. TFR1 and ferritin are key regulatory factors in the iron metabolism pathways. Down-regulation of TFR1 expression in cells is associated with the suppression of erastin-induced ferroptosis [11].

In the absence of TFR1, ZIP14 or SLC39A14 can act as iron transporters to bring iron into the cell [12]. In the cytoplasm, Fe^{2+} is oxidized to Fe^{3+} by ferritin, with iron-bound ferritin degraded for use in enzymatic reactions or stored for future use [13]. Ferritin, which comprises heavy chain (FTH1) and light chain (FTL) subunits, is a significant modulator of iron homeostasis, with FTH1 possessing ferroxidase activity to transform Fe^{2+} into Fe^{3+} [14]. Fe^{3+} forms ferritin–protein complexes, which are stored within cells. The remaining Fe^{2+} contributes to a labile iron pool (LIP) in the cytoplasm.

Fth1 deficiency leads to iron dysregulation and increased oxidative stress in the heart, thereby increasing sensitivity to tissue damage caused by iron overload [10]. As the only iron exporter in the human body, ferroportin (FPN) is critical to the maintenance of systemic iron homeostasis. Fe^{2+} can be transported out of cells via FPN. Hepcidin, a peptide hormone mainly synthesized in the liver, inhibits FPN-mediated iron transport through the ubiquitination and degradation of FPN via the E3 ubiquitin ligase RNF217, thus regulating both iron absorption and recycling [15]. Cellular iron is regulated at the post-transcriptional level by an iron regulatory protein (IRP) system comprising IRP1 and IRP2 [16, 17]. These proteins bind to the 3′-untranslated region (UTR) of *TFR1* mRNA, stabilizing *TFR1* transcripts and increasing translation of TFR1 protein, cementing cell sensitivity to ferroptosis. By contrast, binding of IRP1 or IRP2 to the 5′-UTRs of *FPN* and *FTH1* prevents their translation and blocks ribosomal entry, thereby controlling cellular iron content [16, 17].

Ferritinophagy is the autophagic degradation of iron-saturated ferritin by nuclear receptor coactivator 4 (NCOA4). Knockdown of NCOA4 inhibits erastin-induced ferroptosis, whereas overexpression of NCOA4 significantly increases intracellular iron levels and promotes ferroptosis [18]. Therefore, cell processes that result in an increased LIP and abnormal expression of iron metabolism-related genes can lead to increased cell sensitivity to ferroptosis.

Ferroptosis process

The Fenton reaction plays a significant role in ferroptosis. LIP accumulates within cells when iron homeostasis is disrupted, leading to overactivation of the Fenton reaction. In this process, Fe^{2+} is oxidized to Fe^{3+}, with hydroxyl radicals produced from the decomposition of hydrogen peroxide. The ROS converted from hydrogen peroxide and lipid peroxide cause oxidative stress, leading to damage to the cell membrane and proteins, and ultimately causing ferroptosis [19]. ROS are byproducts of aerobic metabolism and include superoxide anion (O_2^-), hydroxyl radicals (OH), hydrogen peroxide (H_2O_2), and singlet oxygen. The primary sources of ROS are mitochondrial metabolism and NADPH oxidase (NOX) at the cell membrane, In the presence of mitochondrial superoxide dismutase (SOD), O_2^- is converted into H_2O_2, which subsequently diffuses from the mitochondria into the cytosol. At high concentrations of iron, which promote the fenton reaction, H_2O_2 can produce highly reactive O_2^-, leading to increased sensitivity to ferroptosis[20]. Many metabolic enzymes utilized in redox reactions and lipid peroxidation are iron dependent. Therefore, various pathways that increase free iron can lead to ferroptosis through the fenton reaction by increasing ROS generation.

Two main polyunsaturated fatty acids (PUFAs), arachidonic acid (AA) and adrenic acid (AdA), are involved in ferroptosis[21]. When extracellular diffusible AA/AdA enters cells, acyl-coenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) can activate these PUFAs by converting them to acylated forms to generate AA/AdA-CoA, which is then esterified to AA/AdA-phosphatidylethanolamine (PE) by lysophosphatidylcholine acyltransferase 3 (LPCAT3) [22]. LPCAT3 catalyzes the insertion of these acylated PUFAs into membrane phospholipids, and reduced expression of LPCAT3 has been shown to increase cellular resistance to ferroptosis [21, 23]. AA/AdA-PE, which is located on the cytoplasmic face of the membrane, undergoes iron-dependent lipid autoxidation or peroxidation through the Fenton reaction or enzyme catalysis, leading to the formation of phospholipid hydroperoxides (PLOOH). If PLOOH cannot be effectively cleared and accumulates, it can damage the integrity of the membrane and lead to ferroptosis, while also propagating the peroxidation process to neighboring PUFAs that eventually destroy membrane integrity and induce ferroptosis [24]. Lipoxygenases are iron-containing enzymes that directly oxidize PUFAs and PUFA-containing lipids in cell membranes, leading to the accumulation of lipid peroxides and directly damaging cell membranes [25].

Lipid peroxidation is an important contributing factor to ROS-induced heart injury. Several potential endogenous ROS sources exist in cardiac tissue, including the mitochondrial electron transport chain, NADPH oxidase, xanthine oxidoreductase, nitric oxide synthases, and cytochrome P450 (Fig. 1)[26].

Harmful lipid peroxides are eliminated by intracellular antioxidant systems. However, the production of ROS is not always effectively balanced by the antioxidant system. For example, when the antioxidant system is weakened, lipid peroxides cannot be cleared in a timely manner, resulting in attacks on the cell membrane and morphological changes associated with ferroptosis. Due to the presence of PUFA and iron exist in cells of the human body at certain levels, specific protective mechanisms are needed to prevent them from ferroptosis.

Pharmaceuticals that inhibit ferroptosis by decreasing lipid peroxidation and iron accumulation may influence the onset and progression of CVDs. Iron chelation therapy can be used to alleviate the burden of iron in the heart and is widely recommended for the treatment of CVDs patients with iron overload, pushing forward the treatment of CVDs.

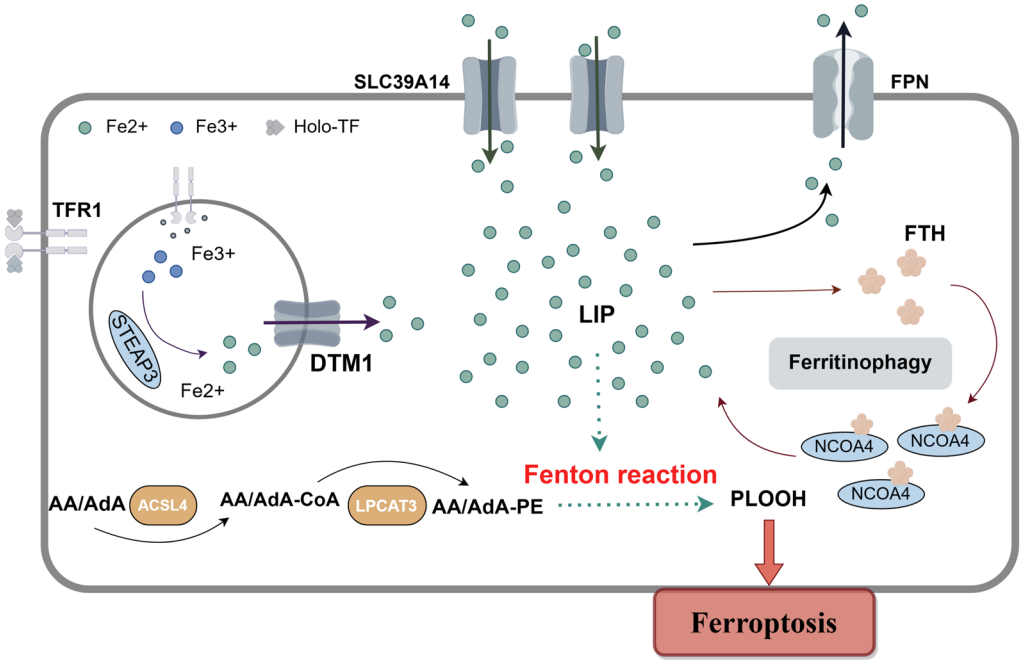

Fig. 1 Mechanism of iron homeostasis and ferroptosis occurrence. (By Figdraw.) In cardiomyocytes, iron uptake is dependent on the endocytosis of TF bound to TFR1. Excess iron is either bound to FTH or exported by FPN; iron can be released by ferritinophagy. An excessive LIP accumulates within cells when iron homeostasis is disrupted, leading to overactivation of the Fenton reaction. AA/AdA-PE undergoes iron-dependent lipid autoxidation or peroxidation through the Fenton reaction leading to the formation of PLOOH that eventually destroy membrane integrity and induce ferroptosis. TF, transferrin; TFR1,transferrin receptor protein 1;STEAP3, metalloreductase STEAP3; DMT1, divalent metal transporter 1; AA, arachidonic acid; AdA, adrenic acid; AA-CoA, arachidonic coenzyme; AdA-PE, adrenic acid-phosphatidylethanolamines; LPCAT3, lysophosphatidylcholine acyltransferase 3; PLOOH, phospholipid hydroperoxides LIP, labile iron pool; SLC39A14, solute carrier family 39 member 14 (ZIP14); FPN, ferroportin; FTH, ferritin; NCOA4, nuclear receptor coactivator 4

Main pathways that regulate ferroptosis

System Xc^--glutathione (GSH)-phospholipid hydroperoxide glutathione peroxidase 4 (GPX4) axis

GSH, which is primarily produced in the liver, is a tripeptide composed of the amino acids cysteine, glutamate, and glycine. As the main antioxidant, it is used to eliminate harmful byproducts of iron-dependent lipid peroxidation, thus protecting cell membranes from damage. Cysteine is the rate-limiting precursor in GSH synthesis. Most cells obtain cysteine primarily from the cystine–glutamate antiporter system Xc^-, which comprises the solute carrier (SLC) family 7A member 11 (SLC7A11) and SLC3A2 subunits [27]. The depletion of GSH and the inactivation of GPX4 have also been shown to promote ferroptosis [28]. Thus, inhibition of system Xc − can lead to deprivation of cellular GSH and impair the function of GPX4 to suppress lipid peroxidation and ferroptosis.

While the SLC7A11 subunit of Xc^- contains 12 transmembrane domains and primarily mediates the transporter activity of the protein complex, SLC3A2 acts as a companion protein that helps to stabilize SLC7A11 and ensure proper membrane localization of the complex. System Xc^- exports intracellular glutamate and imports extracellular cystine at a ratio of 1:1 [29]. In myocardial cells, selective overexpression of SLC7A11 can increase cellular levels of GSH and prevent iron-dependent cardiac ferroptosis mediated by ferritin H, indicating that SLC7A11 has an anti-ferroptotic function in the heart [30]. One study revealed that indicating that P53 activation diminishes the antioxidant capacity of H1299 cells. The activity of H1299 cells with silenced P53 genes did not change upon ROS treatment. However, when P53 was activated, 90% of the cells died; when treated with ROS, treatment with a ferroptosis inhibitor significantly reduced the cell death rate, suggesting that P53 also promotes ferroptosis [31].

Further studies have shown that P53 can suppress the cysteine transport function of the Xc^- system by reducing the expression of SLC7A11 and leads to reduced cystine uptake, thereby further inhibiting the activity of GPX4, resulting in a reduction in cell antioxidant capacity, accumulation of lipid ROS and ultimately leading to ferroptosis [32].

The expression and activity of GPX4, a GSH-dependent enzyme containing selenocysteine, are regulated by selenium and GSH. Selenium supplementation can increase

the expression of GPX4 and protect cells from ferroptosis [33]. GPX4 catalyzes the reduction of lipid hydroperoxides, reducing phospholipid hydroperoxides (AA/AdA-PE-OOH) to PLOH. Together with GSH, GPX4 clears harmful byproducts of iron-dependent lipid peroxidation, protecting cell membranes from damage. The Xc-GSH-GPX4 axis plays a critical role in myocardial ferroptosis. Inhibition of GPX4 activity promotes ROS formation and lipid peroxidation, leading to ferroptosis. Erastin also inhibits the Xc^- system by binding to SCL7A11, resulting in GSH depletion and GPX4 inactivation [34]. GPX4 also downregulates the levels of inflammatory factors by decreasing lipoxygenase (LOX) and cyclooxygenase (COX) [35]. In summary, inhibition of the Xc^- system impairs GPX4 function and accelerates ferroptosis.

SLC7A11 (xCT) system

System Xc^-, an amino acid transporter expressed in the mammalian cytoplasmic membrane, mainly functions through SLC7A11, which is the main active site of erastin. It has been shown that the cAMP-dependent transcription factor ATF3 can promote ferroptosis by binding to the *SLC7A11* promoter and inhibiting its expression in a p53-independent manner [36]. The Kelch-like ECH-associated protein 1 (KEAP1)–nuclear factor-erythroid 2-related factor 2 (NRF2) axis regulates a variety of genes related to GSH biosynthesis and iron metabolism and thus can also affect cellular susceptibility to ferroptosis. The transcription factor NRF2 improves the body's oxidative stress status and maintains stable viability and physiological functions of cells [37]. NRF2, a positive regulator of SLC7A11 expression, is bound by KEAP1 to promote its ubiquitination and proteasomal degradation [38]. Overexpression of NRF2 or knockout of *Keap1* increases the expression of SLC7A11, while inhibition of NRF2 expression or overexpression of Keap1 decreases the levels of SLC7A11 [38]. NRF2 also regulates cellular iron homeostasis by modulating the expression of Tfr1, FTH1, FTL, and FPN. Studies have shown that p53 inhibits the synthesis of GSH in an SLC7A11-dependent manner [32]. Additionally, p53 can increase the expression of glutaminase 2 (GLS2) to catalyze the hydrolysis of glutamine, resulting in decreased GSH, increased ROS, and increased cellular susceptibility to ferroptosis [39].

Ferroptosis suppressor protein 1 (FSP1)–Coenzyme Q10 (CoQ10)–NADPH pathway

In addition to the System Xc-GSH-GPX4 axis, the FSP1-CoQ-NADPH pathway has also been shown to inhibit ferroptosis. FSP1, formerly known as apoptosis-inducing factor mitochondria-related 2 (AIFM2), is considered to inhibit ferroptosis as an independent system working in coordination with the Xc-GSH-GPX4 pathway [40, 41]. Therefore, even in the absence of GPX4, FSP1 can eliminate lipid peroxides. CoQ10, an antioxidant, and its fully reduced form CoQH2 capture lipid peroxide radicals and prevent peroxidative damage to the membrane [41]. FSP1 reduces ubiquinone to ubiquinol through NADPH, reducing ROS and preventing lipid peroxidation to inhibit ferroptosis. Inhibition of the mevalonate pathway may decrease the level of CoQ10 and lead to ferroptosis [42]. In the inner membrane of mitochondria, dihydroorotate dehydrogenase (DHODH) converts CoQ to CoQH2. Low GPX4 activity can increase DHODH activity to raise the production of CoQH2, which can neutralize lipid peroxidation in the cell and alleviate ferroptosis in mitochondria [43]. The binding of GPX4 and DHODH in mitochondria can inhibit mitochondrial lipid peroxidation in addition to reducing CoQ. Additionally, GTP cyclohydrolase-1 (GCH1) produces tetrahydrobiopterin/dihydrobiopterin (BH4/BH2), which combats ferroptosis independent of GPX4 by inhibiting lipid peroxidation [44] (Fig. 2).

The heart is highly susceptible to oxidative damage, and the occurrence of ferroptosis and accumulation of lipid peroxidation in myocardial cells are important factors in cardiac injury. The current understanding of ferroptosis in myocardial cells has instructive significance for the mechanism and progression of CVDs. A thorough understanding of the regulatory mechanisms of iron metabolism and molecular pathways of ferroptosis in myocardial cells may improve disease outcomes. Indeed, most studies have found that epigenetic regulation and PTMs of important ferroptosis regulatory factors and pathways can alter the expression and activity of ferroptosis-related proteins, affecting the sensitivity of myocardial cells to ferroptosis and the occurrence and progression of CVDs.

Epigenetic modifications and PTMs involved in ferroptosis regulation in CVDs

Epigenetic modifications and PTMs, which regulate genes at the transcriptional and post-transcriptional levels, respectively, to control protein activity and degradation, are closely associated with the development of many diseases. In myocardial cells, these modifications help maintain the expression of ferroptosis-related genes and proteins specifically required to maintain normal cardiac function, while also regulating the occurrence and progression of CVDs. In the following sections, we elaborate on the important roles of epigenetic regulation and PTMs in the myocardial ferroptosis of common CVDs.

Ferroptosis-regulating microRNAs (miRNAs) in CVDs

The ncRNAs do not encode proteins, but rather play significant roles in regulating gene expression, cell signaling,

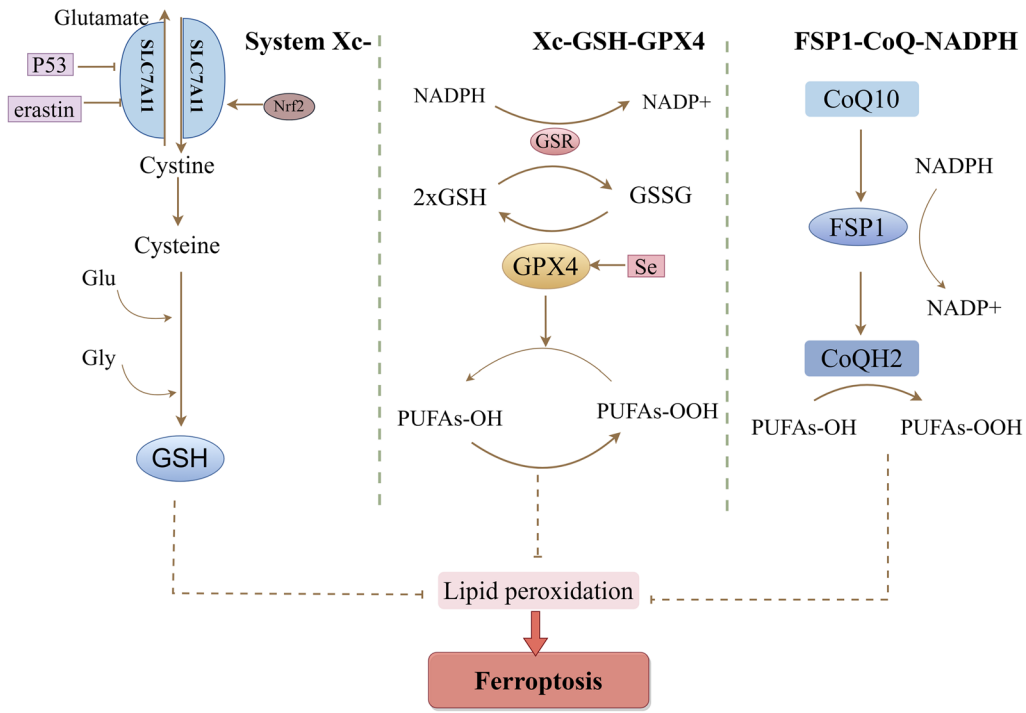

Fig. 2 Regulatory mechanisms of ferroptosis in CVDs. (By Figdraw.) Harmful lipid peroxides are eliminated by intracellular antioxidant systems. The production of ROS is not always effectively balanced by the antioxidant system. There are three major regulatory pathways regulate ferroptosis in cardiovascular diseases: the xCT System, the Xc-GSH-GPX4 axis, and the FSP1-CoQ-NADPH pathway. SLC7A11, subunit solute carrier family 7 member 11; Glu, glutamate; Gly, glycine; GSH, glutathione; GSSG, oxidized glutathione; GPX4, glutathione peroxidase 4; GSR, glutathione-disulfide reductase, Nrf2, nuclear factor-erythroid 2-related factor 2; CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; NADPH, nicotinamide adenine dinucleotide phosphate; CoQH2, ubiquinol; PUFAs-OH, lipid alcohols; PUFAs-OOH, lipid hydroperoxides; ROS, reactive oxygen species

and other biological functions in cells; ncRNA is essential for transcriptional and post-transcriptional regulation, as well as in the epigenetic modulation of gene expression. Among various types of ncRNAs, long noncoding RNAs (lncRNAs), circular RNAs (circRNAs), and especially miRNAs mediate myocardial ferroptosis and participate in the regulation of pathological processes related to CVDs, such as cardiac ischemia/reperfusion (I/R) injury, myocardial infarction (MI), atrial fibrillation (AF), and other myocardial diseases. Mechanistically, miRNAs directly target mRNA to affect gene translation, while lncRNAs and circRNAs act as miRNA sponges to regulate its gene regulation. Additionally, ncRNAs can directly bind to proteins to block their function, affecting downstream signaling pathways [45].

MicroRNAs function by hybridizing to specific regions of the mRNA's untranslated region (UTR), leading to either mRNA degradation or the inhibition of its translation. The role of microRNAs in ferroptosis involves the regulation of the antioxidant system and lipid oxidation. Most studies suggest that the overexpression of microRNAs can damage cardiomyocytes by promoting ferroptosis. However, the precise mechanisms by which microRNAs regulate ferroptosis in cardiovascular diseases (CVDs) remain unclear; we summarize the pathological and physiological roles of different microRNAs that mediate myocardial ferroptosis in CVDs (Table 1).

MI is one of the leading causes of death among patients with coronary heart disease. Early treatment of acute MI can restore blood supply to the ischemic myocardium and reduce the risk of death. However, despite the timely and effective restoration of blood flow following interruption to the myocardial blood supply, both ischemia and reperfusion can cause severe ischemic myocardial injury (myocardial I/R injury). The pathological and physiological mechanisms of myocardial I/R injury are associated with oxidative stress, intracellular calcium overload, energy metabolism disorder, cell apoptosis, endoplasmic reticulum stress, and ferroptosis [46].

GPX4 is critical for the regulation of ferroptosis. Using an in vivo myocardial I/R rat model and an in vitro hypoxia/reoxygenation (H/R)-induced H9C2 cardiomyocyte injury model, Sun et al. found that miR-135b-3p bound to and inhibited translation of *Gpx4* mRNA, thereby suppressing the GSH antioxidant system. This led to increases in ROS levels, exacerbating myocardial

Table 1 Ferroptosis-regulating microRNAs (miRNAs) in CVDs

Modification	Diseases	miRNA	Targets	Biological functions	References
miRNA	MIRI	miR-135b-3p	GPX4	miR-135b-3p promotes the myocardial I/R injury by downregulating GPX4 expression	[47]
	MIRI	miR-1224	GPX4	miR-1224 is highly expressed in H/R cardiomyocytes. Inhibition of miR-1224 affects GPX4 expression, reduces oxidative damage	[48]
	MIRI	miR-144-3p	SLC7A11	miR-144-3p negatively regulates SLC7A11 protein levels in H9C2 cells, enhances the sensitivity to ferroptosis	[49]
	MIRI	miR-190a-5p	GLS2	Overexpression of miR-190a-5p can inhibit GLS2, protect H9C2 cells from erastin and RSL3-induced ferroptosis	[50]
	MIRI	miR-199a-5p	Akt/eNOS	miR-199a-5p promotesferroptosis during OGD/R by activating the Akt/eNOS signaling pathway	[51]
	MIRI	miR-210–3p	TFR	miR-210-3p inhibiting TFR and promoting the proliferation of cardiomyocytes in H9C2 cells	[52]
	MIRI	miR-432-5p	Nrf2	miR432-5p inhibits ferroptosis by activating the Nrf2/SLC7A11 axis through degrading Keap1	[53]
	MIRI	miR-196c-3p	LOX、NOX4、P53	miR-196c-3p can regulate the expression of LOX, NOX4, P53, inhibiting ferroptosis	[54]
	AMI	miR-30d	ATG5	miR-30d can bind to ATG5 to decreased in ferroptosis after MI	[55]
	AMI	miR-15a-5p	GPX4	Overexpression of miR-15a-5p strengthened ferroptosis by affects GPX4 expression	[56]
	AMI	miR-214-3p	ME2	miR-214-3p may contribute to cardiomyocyte ferroptosis via suppressing ME2, which could significantly lower NADPH level, leading to ROS burst and ferroptosis	[58]
	AMI	miR-26b-5p	SLC7A11	Plasma exosomes from patients with AMI can downregulate miR-26b-5p and upregulation of SLC7A11 inhibited hypoxia-induced ferroptosis	[59]
	AMI	miR-23a-3p	DMT1	HUCB-MSCs-exosomes may suppress DMT1 expression via miR-23a-3p, which reduces Fe^{2+} and MDA levels, inhibits ferroptosis	[60]
	Cardiac fibrosis	miR-375-3p	GPX4	miR-375-3p downregulate GPX4 and inhibiting the oxidative clearance function of superoxide dismutase, accelerating ferroptosis and cardiac fibrosis	[66]
	Cardiac fibrosis	miR-351	MLK3	miR-351 negatively regulated the expression of MLK3, prevent myocardial fibrosis	[67]
	AF	miR-23a-3p	SLC7A11	In AF, inhibiting the secretion of exosomal miR-23a-3p by cardiac fibroblasts protects H9C2 myocardial cells from ferroptosis	[68]

MIRI: myocardMIRI: myocardial ischemia/reperfusion injury, H/R: hypoxia/reoxygenation, Keap1: Kelch-like ECH-associated protein 1, AMI: myocardial infarction, AF: atrial fibrillation, GPX4: glutathione peroxidase 4, SLC7A11: subunit solute carrier family 7 member 11, GLS2: glutaminase 2, OGD/R: oxygen glucose deprivation/reoxygenation, TFR: transferrin receptor, Nrf2: nuclear factor-erythroid 2-related factor 2, LOX: lysyloxidase, NOX: NADPH oxidases, ATG5: autophagy-related 5, ME2: malic enzyme 2, DMTI: divalent metal transporter 1, HUCB-MSCs: human umbilical cord blood mesenchymal stem cells, MLK3: mixed lineage kinase 3, MDA: malondialdehyde, TAC: transverse aortic construction

ferroptosis and myocardial I/R injury [47]. Similarly, high expression of miR-1224 in H9C2 cells has also been found to target GPX4; high expression of miR-1224 increases myocardial cell ferroptosiss [48]. In summary, ncRNAs regulate ferroptosis and protect myocardial cells by targeting GPX4 to modulate the expression of the Xc-GSH-GPX4 axis and alleviate oxidative damage by eliminating lipid peroxides on various membranes. SLC7A11, which is involved in the synthesis and maintenance of GSH, is also considered a significant target in ferroptosis. Ye et al. found that miR-144-3p targets SLC7A11; miR-144-3p overexpression inhibits SLC7A11 and reduces GSH content, leading to increases in ROS levels and sensitivity of H9C2 cells to ferroptosis[49]. GLS is a glutaminase; the regulation of GLS2 activity can modulate intracellular levels of GSH, thereby influencing the cardiomyocytes antioxidant capacity and playing a critical role in the process of ferroptosis. Zhou et al. found that miR-190a-5p targets GLS2; overexpression of miR-190a-5p inhibits GLS2 and results in decreases in ROS, malondialdehyde (MDA), and Fe^{2+} accumulation, protecting H9C2 cells from erastin and RAS-selective lethal 3 (RSL3)-induced ferroptosis [50]. In oxygen–glucose deprivation (OGD)/reoxygenation-treated H9C2 cells, an increased level of miR-199a-5p was shown to inhibit the Akt/endothelial nitric oxide synthase (eNOS) signaling pathway, downregulating the GSH/oxidized GSH (GSSG) ratio and protein expression of Gpx4, increasing ROS generation

promoting ferroptosis [51]. MiRNAs can also influence the TFR to alter iron levels in cardiomyocytes, thereby further participating in the occurrence of ferroptosis cardiovascular diseases CVDs. miR-210–3p is significantly enriched in hypoxia-conditioned cardiac microvascular endothelial cell-derived exosomes (H-exo). miR-210–3p inhibited TFR expression by directly interacting with *TFR* mRNA in H9C2 cells, reducing the content of Fe^{2+} in the LIP and decreasing iron-dependent peroxidation reactions, attenuating cell ferroptosis [52]. Geng et al. found downregulated expression of miR-432-5p in cells undergoing H/R. miR-432-5p can bind Keap1 and nuclear factor-erythroid 2-related factor 2 (Nrf2) and regulate ferroptosis of cardiomyocytes induced by RSL3, while knockdown of Nrf2 attenuated the protective effect of miR-432-5p on H/R-treated cardiomyocytes [53]. Ji et al. found that miR-196c-3p could simultaneously regulate the expression of ferroptosis-related genes *LOX*, *NOX4*, and *P53*, suppress I/R-induced ferroptosis, and reduce ferroptosis in myocardial cells [54].

In the myocardial tissue of MI, miR-30d inhibited autophagy and ferroptosis by binding to ATG5, providing a protective effect against myocardial ferroptosis [55]. Meanwhile, Fan et al. found a new signaling pathway involving factor early growth response-1 (Egr-1), miR-15a-5p, GPX4, and ferroptosis in the progression of MI; silencing of the transcription Egr-1 inhibited the level of miR-15a-5p, increasing the protein expression of GPX4, reducing ferroptosis, and alleviating myocardial injury.[56]. Liu et al. observed a significant increase in miR-214-3p in the myocardial tissue of heart failure mice that was found to inhibit, malic enzyme 2 (ME2), a member of the Myc/Max/Mad (ME) family of transcription factors that participate in cell proliferation, glutamine metabolism, lipid synthesis, and ROS generation [57]. Malic enzyme 2 (ME2), a member of the Myc/Max/Mad (ME) family of transcription factors, participates in cell proliferation, glutamine metabolism, and ROS generation. During MI, Liu et al. observed a significant increase in miR-214-3p. However, miR-214-3p was found to inhibit ME2 which results in decreased NADPH levels, thereby promoting ROS and contributing to enhanced ferroptosis during MI [58]. Jin et al. revealed that plasma exosomes have a protective effect on the heart in acute MI patients. This effect occurs through downregulating miR-26b-5p, which targets SLC7A11 and regulates the SLC7A11/GSH/GPX4 axis, alleviating myocardial cell ferroptosis [59]. DMT1, a transporter of Fe^{2+}, plays a critical role in the absorption and transportation of iron. Exosomes derived from human umbilical cord blood mesenchymal stem cells may suppress DMT1 expression via miR-23a-3p, which reduces Fe^{2+} and MDA levels, increases GSH levels, inhibits ferroptosis, and attenuates myocardial injury [60]. Blood glucose fluctuations in diabetes promote excessive ROS production [61], which is accompanied by mitochondrial dysfunction and DNA damage, leading to the progression of many CVDs, including diabetic cardiomyopathy and AF [62]. In addition to the increased ROS production, antioxidant defense systems are also depleted in diabetic myocardial cells, causing ferroptosis of these cells [63]. Two ferroptosis regulators, miR-331-3p and miR-150-5p, have been detected in cardiac cells of diabetes patients with diabetic cardiomyopathy (DbCM) and acute MI, respectively. Overexpression of these miRNAs promotes myocardial cell ferroptosis in such patients by downregulating cell cycle protein D2 (CCND2) [64, 65].

After MI, the occurrence of left ventricular enlargement and cardiac fibrosis eventually leads to heart failure (HF). Zhuang et al. found that miR-375-3p can downregulate GPX4 and inhibit the oxidative clearance function of superoxide dismutase, accelerating myocardial cell ferroptosis and cardiac fibrosis [66]. Wang et al. found that MLK3 mainly regulates NF-κB/NLRP3 signaling pathway-mediated inflammation and pyroptosis that causes myocardial fibrosis in the early stages of chronic HF. Promoting the expression of miR-351 inhibited the expression of MLK3 and significantly improved cardiac function in transverse aortic constriction (TAC) mice, effectively protecting against ventricular remodeling in heart failure (HF) caused by pressure overload [67]. Oxidative stress and fibrosis are core mechanisms that interact in the complex pathological processes of AF, the most common arrhythmia. Additionally, ncRNAs play important roles in the pathological and physiological mechanisms of AF. Liu et al. found that miR-23a-3p mainly inhibits the translation of *SLC7A11* mRNA transcripts. In AF, inhibiting the secretion of exosomal miR-23a-3p by cardiac fibroblasts protects H9C2 myocardial cells from ferroptosis, preventing the condition from developing in a persistent direction [68]. Additionally, Song et al. demonstrated that overexpression of miR-143-3p increased cell proliferation, inhibited cell death in AF cardiomyocytes. Overexpression of miR-143-3p was found to inhibit glutamic-oxaloacetic transaminase 1-mediated oxidative damage and ferroptosis [69].

Ferroptosis-regulating lncRNAs in CVDs

Defined as transcripts longer than 200 nucleotides, lncRNAs bind with DNA, mRNA, miRNA, and proteins to play crucial roles in regulating key factors involved in cell metabolism, proliferation, apoptosis, and ferroptosis. lncRNAs regulate gene expression through cis- or trans-regulation of chromatin architecture, transcription, splicing, mRNA transport, stability, and translation, thereby exerting a broad impact on various cellular processes.

Current evidence indicates that lncRNAs play important regulatory roles in the physiological and pathological processes of various CVDs, acting as competing endogenous (ce)RNAs and mediating ferroptosis in myocardial cells (Table 2) [70].

The enzyme heme oxygenase 1 (HMOX1) provides antioxidant, anti-apoptotic, and cell-protective effects through the metabolic breakdown of its products [71]. However, while HMOX1 inhibits oxidative stress, the degradation of heme by HMOX1 helps to release free iron, increasing the iron content and sensitivity to ferroptosis of myocardial cells. Tan et al. found upregulation of the lncRNAs KCNQ1OT1 and HMOX1, but downregulation of miR-377-3p, in I/R-induced myocardial injury. Inhibition of HMOX1 alleviated miR-377-3p downregulation, inducing myocardial injury. Furthermore, HMOX1 caused excess iron to accumulate in cardiomyocytes, exacerbating the I/R damage to myocardial cells [72]. ACSL4 can promote lipid peroxidation of PUFAs to promote ferroptosis and is also an important target of many microRNAs; Sun et al. identified lncAABR07025387.1 was highly expressed in MI/RI myocardial tissues; it negatively regulating miR-205 expression, leading to an increase in ACSL4 levels. Overexpression of ACSL4 promoted ferroptosis and exacerbated myocardial injury, increasing the cardiac damage caused by I/R [73]. Wu et al. demonstrated that the lncRNA SEMA5A-IT1 could regulate the expression of B-cell chronic lymphocytic leukemia/lymphoma 2 (BCL2) and SLC7A11 through miR-143-3p, reduced ROS, and protected myocardial cells from apoptosis and ferroptosis[74]. Zhang et al. found high expression of the lncRNA Mir9-3hg in mouse bone marrow mesenchymal stem cell-derived exosomes, which increased GSH content and reduced iron ion concentrations and the levels of ROS and ferroptosis marker proteins in H/R-treated myocardial cells, interference with Mir9-3hg reversed these effects, thereby protecting the myocardial cells.

Table 2 Ferroptosis-regulating lncRNA, circRNAs in CVDs

Modification	Diseases	lncRNA、circRNA	Targets	Biological functions	References
lncRNA	MIRI	lncRNA KCNQ1OT1	HMOX1	LncRNA KCNQ1OT1 targets HMOX1 cause the accumulation of excess iron in cardiomyocytestends to induce ferroptosis	[72]
	MIRI	lncAABR07025387	ACSL4	LncAABR07025387.1 negatively regulated miR-205 expression, leading to an increase in ACSL4 levels and promote ferroptosis	[73]
	MIRI	lncRNA SEMA5A-IT1	BCL2/SLC7A11	LncRNA SEMA5A-IT1 regulate the expression of BCL2 and SLC7A11 through sponging miR-143-3p, upregulated SEMA5A-IT1 can protect cells from ferroptosis	[74]
	MIRI	lncRNA Mir9-3hg	GSH	BMSCs-Exo increased GSH content and reduced ferroptosis marker protein levels, thereby protected cardiomyocytes against ferroptosis	[75]
	MI	lncRNA Gm47283	Ptgs2	LncRNA Gm47283 participated in MI by targeting miR-706. Overexpression of miR-706 could inhibit the expression of Ptgs2 and the activity of ferroptosis	[76]
	AMI	lncRNA AC005332.7	ACSL4	LncRNA AC005332.7 inhibited ferroptosis of OGD-induced AC16 cells by regulating the miR-331-3p/CCND2 axis	[65]
	Cardiac hypertrophy	lncRNA AAB	TFR1	LncRNA AAB sponges and isolates miR-30b-5p to induce MMP9/TIMP1 imbalance, which further affects the expression of TFR-1, increases the level of Fe2 + in CMECs, and promotes ferroptosis	[77]
	DbCM	lncRNA-ZFAS1	CCND2	LncRNA-ZFAS1 acted as a ceRNA sponge for miR-150-5p and downregulated CCND2, promoting myocardial cell ferroptosis and DbCM development	[64]
circRNA	MIRI	circRNA FEACR	Fth1	circRNA FEACR can regulate the expression of FTH1 through the FEACR/NAMPT/Sirt1/FOXO1 axis and protect cardiomyocytes from I/R injury	[78]
	MI	circRNA1615	LRP6	circRNA1615 could regulate myocardial cell autophagy through the miRNA1523p/LRP6 axis to suppress ferroptosis	[79]
	HF	circRNASnx12	FTH1	The low expression of circSnx12 and high expression of miR-224-5p could downregulate the expression of FTH1, leading to myocardial cell ferroptosis	[80]

I/R: ischemia/reperfusion, MI: myocardial infarction, DbCM: diabetic cardiomyopathy, HMOX1: heme oxygenase 1, ACSL4: acyl-coA synthetase long-chain family member 4, BCL2: B-cell chronic lymphocytic leukemia/lymphoma 2, GSH: giutathione, BMSCs-Exo: bone mesenchymal stem cells exosomes, Ptgs2: prostaglandin endoperoxide synthase-2, OGD: oxygen–glucose deprivation, CCND2: cell cycle protein D2, TFR1: TF receptor protein 1, CMECs: cardiac microvascular endothelial cells, MMP9: matrix metalloproteinase 9, TIMP1: TIMP metallopeptidase Inhibitor 1, Fth1: ferritin light chain, NAMPT: nicotinamide phosphoribosyl transferase, Sirt1: sirtuin-1, FOXO1: forkhead box protein O1, LRP6: lipoprotein receptor-related protein 6

The Pumilio RNA-binding family member 2 (Pum2) protein can promote the aforementioned functions of Mir9-3hg in myocardial cells [75]. Gao et al. found the lncRNA Gm47283 participates in MI by regulating cardiomyocyte ferroptosis activity through miR-706, which could target *Ptgs2*, a regulator of ferroptosis, while overexpression of miR-706 inhibited Ptgs2 expression and ferroptosis activity to reduce lipid peroxidation toxicity [76]. Dai et al. found that the lncRNAs AC005332.7 and CCND2 were downregulated, while miR-331-3p was upregulated, in both in vivo and in vitro models of acute MI. Furthermore, AC005332.7 interacted with miR331-3p and inhibited ferroptosis of OGD-induced AC16 cells. Increasing AC005332.7 reduced the levels of ROS, MDA, iron, preventing ferroptosis and improving myocardial cell damage in acute MI [65]. Dysregulation of lncRNA has recently been recognized as a key mechanism leading to cardiac hypertrophy. Pilong Shi et al. found that the lncRNA AAB was upregulated in rats with cardiac hypertrophy and in angiotensin II-induced cardiac microvascular endothelial cells (CMECs), further affecting the protein expression of TFR-1, increasing the level of Fe^{2+}, and promoting ferroptosis in CMECs. Furthermore, silencing of AAB using small interfering RNA and overexpression of miR-30b-5p was developed as a novel therapy for cardiac hypertrophy [77]. Ni et al. identified upregulated expression of the lncRNA ZFAS1 in both DbCM and high glucose-treated myocardial cells. While ZFAS1 was found to act as a ceRNA sponge for miR-150-5p and downregulate CCND2, promoting myocardial cell ferroptosis and DbCM development, inhibition of ZFAS1 led to reductions in collagen, weakening the progression of DbCM [64].

Ferroptosis-regulating circRNAs in CVDs

CircRNAs regulate ferroptosis and the expression of various ferroptosis-related genes by binding to miRNA or RNA-binding proteins. CircRNAs also participate in the pathological processes of CVDs. Ju et al. identified a ferroptosis-associated circRNA (FEACR) that directly binds to nicotinamide phosphoribosyltransferase (NAMPT), increasing NAMPT-dependent Sirtuin1 expression and reducing the acetylation of forkhead box protein O1 (FOXO1) to promote FOXO1 transcriptional activity. FOXO1 was shown to upregulate *FTH1* transcription and protect myocardial cells from cardiomyocyte ferroptosis in I/R.[78]. Li et al. found that circRNA1615 regulated the expression of lipoprotein receptor-related protein 6 (LRP6) through sponge adsorption of miR-152-3p, preventing LRP6-mediated autophagy-related ferroptosis in MI [79]. Zheng et al. found that circSnx12 acts as an endogenous sponge that binds to miR-224-5p to interfere with its mRNA activity. FTH1 is a direct target of miR-224-5p with low expression of circSnx12 and high expression of miR-224-5p downregulating FTH1 expression, leading to myocardial cell iron overload and ultimately causing myocardial ferroptosis.[80].

Ferroptosis-regulating methylation in CVDs

DNA methylation is an important epigenetic modification that controls gene expression. It is catalyzed by DNA methyltransferases (DNMTs), which use S-adenosylmethionine as a donor to add a methyl group to the 5′-carbon end of cytosine, generating 5-methyl-cytosine (5mC). DNA methylation can cause changes in chromatin structure, DNA conformation and stability, and the mode of DNA–protein interactions, thus regulating ferroptosis-related gene expression (Table 3) [81].

The role of DNA methylation in ferroptosis in CVDs is being uncovered at an ever-increasing rate. Wang et al. found that protein arginine methyltransferase 4 (PRMT4) interacts with Nrf2 to promote its enzymatic methylation, thereby limiting the nuclear translocation of Nrf2 and subsequently suppressing the transcription of GPX4, accelerating ferroptosis in doxorubicin-induced cardiomyopathy (DIC) [82]. More than half of diabetes patients suffer from CVDs, and DNA methylation has also been shown regulate ferroptosis in DdCM [83]. Li et al. discovered that inhibition of DNMT-1 could reduce ferroptosis during diabetic myocardial I/R injury, possibly with the participation of NCOA4-mediated ferritinophagy [84]. The roles of RNA m6A modification have been elucidated in many physiological processes and diseases, including cell autophagy and proliferation, stem cell renewal and differentiation, tumor development, and CVDs [85]. In recent years, several studies have shown that the involvement of RNA m6A marks in ferroptosis affects the progression of HF, MI, cardiac hypertrophy, and abdominal aortic aneurysm, indicating that an increase in RNA m6A methylation may be a mark of CVDs. Consistently, Li et al. found that the protein expression of methyltransferase-like 3 (METTL3) was significantly upregulated in the aorta of patients with thoracic aortic aneurysm and dissection, showing negative correlations with the aortic expression levels of SLC7A11 and FSP1; upregulation of METTL3 could promote the degradation of *SLC7A11* and *FSP1* mRNA transcripts, thereby promoting ferroptosis in human aortic smooth muscle cells [86].

In a study of DIC, Zhuang et al. demonstrated that doxorubicin treatment led to upregulation of METTL14, which catalyzed the m6A modification of the lncRNA KCNQ1OT1, a miR-7-5p sponge. The lack of miR-7-5p expression led to increased levels of TFR1, increasing ferroptosis [87]. Yang et al. showed that downregulation of fat mass and obesity-associated protein (FTO) was associated with doxorubicin-induced cardiotoxicity. FTO

Table 3 Ferroptosis-regulating methylation in CVDs

Modification	Diseases	Targets	Biological functions	References
Methylation	DIC	Nrf2/GPX4	PRMT4 interacts with Nrf2 to limit the nuclear translocation of Nrf2 and suppressing the transcription of GPX4	[82]
Methylation	DdCM	NCOA4	Inhibition of DNMT-1 could reduce ferroptosis by participation of NCOA4-mediated ferritinophagy	[82]
m6A	AD	SLC7A11	METTL3 was significantly upregulated in the aorta of patients with thoracic aortic aneurysm and dissection, it can promote ferroptosis by inhibiting the expression of SLC7A11 and FPS1	[86]
m6A	DIC	TFR	Doxorubicin led to upregulation of METTL14, catalyzed the m6A modification of the lncRNA KCNQ1OT1, which led to increased levels of TFR1, thereby increasing ferroptosis in DIC	[87]
m6A	DIC	P53	FTO mediates m6A demethylation of P53 or P21/Nrf2 in a human antigen R-dependent manner, inhibiting doxorubicin-induced ferroptosis through the activation of P21/Nrf2	[88]
m6A	Sepsis-induced myocardial	SLC7A11	METTL3-mediated methylation of SLC7A11 could result in YTHDF2 mediated mRNA degradation of SLC7A11.thereby upregulating ferroptosis in sepsis-induced myocardial injury	[89]

DIC: doxorubicin-induced cardiomyopathy, AD: aortic aneurysm and dissection, PRMT4: protein arginine methyltransferase 4, FSP1: ferroptosis suppressor protein 1, FTO: fat mass and obesity-associated protein, YTHDF2: YTH N6-methyladenosine RNA-binding protein F2

mediates m6A demethylation of P53 or P21/Nrf2 in a human antigen R-dependent manner, inhibiting doxorubicin-induced ferroptosis through the activation of P21/Nrf2 [88]. In sepsis-induced myocardial injury, Tang et al. found METTL3 resulting in a high methylation level of *SLC7A11* mRNA. Additionally, the m6A reader YTHDF2 mediated degradation of *SLC7A11* mRNA by directly binding to the m6A modification site of *SLC7A11*, thereby upregulating ferroptosis [89].

Ferroptosis-regulating ubiquitination in CVDs

Ubiquitination is a key step in cellular proliferation, differentiation, and death, and its importance in ferroptosis has been gradually uncovered. Reversible ubiquitination, known as deubiquitination, is carried out by deubiquitylating enzymes [90, 91]. Protein ubiquitination involves a series of coordinated reactions mediated by E1 (ubiquitin-activating enzyme), E2 (ubiquitin-conjugating enzyme), and E3 (ubiquitin ligase) [92]. Ubiquitination modification of ferroptosis-related genes plays an important role in CVDs (Table 4).

USP22, a member of the deubiquitinase family, USP22-mediated deubiquitination can stabilize the expression of SIRT1. Ma et al. found that SIRT1 overexpression brought about a reduction in p53 acetylation, thereby led to upregulation of SLC7A11, reduced lipid peroxides, and inhibited ferroptosis in myocardial I/R injury [93]. Using I/R-treated rat hearts, Tang et al. identified a novel ubiquitin-specific protease (USP)7/p53/TfR1 pathway. Knockdown of USP7 enhanced the ubiquitination of p53 and led to decreased levels of p53 and TFR1, reducing myocardial cell I/R injury and ferroptosis [94]. Meanwhile, Zhang et al. found that the increased expression of USP11 during myocardial I/R injury stabilized TRAF3 via deubiquitination; overexpression of TRAF3 reversed the effect of USP11 on H/R-induced H9C2 cell injury in ferroptosis [95].

One byproduct of lipid peroxidation, 4-hydroxy-2-nonenal (4-HNE), is an important marker of cell apoptosis. Liu et al. discovered OTUD5 serves as a novel deubiquitinase for GPX4. Upregulation of OTUD5 deubiquitinates and stabilizes GPX4, thus reversing 4-HNE-induced ferroptosis and alleviating myocardial I/R injury [96]. As a key transcriptional effector of the Hippo pathway, Yes-associated protein (YAP) is involved in myocardial I/R injury [97]. Using myocardial I/R injury models, Qiu et al. found that YAP interacts with TEA domain family member 4 (TEAD4) to promote the transcription and expression of developmentally downregulated 4-like (NEDD4L) in neural precursor cells, consequently leading to ubiquitination and degradation of ACSL4, thereby limiting ferroptosis and alleviating myocardial I/R injury [98].

Frataxin is a widely expressed mitochondrial protein that participates in the biosynthesis of iron-sulfur clusters to regulate the activity of iron-sulfur proteins [99]. Zhang et al. found the frataxin involvement in the regulation of cardiomyocyte ferroptosis. As an E3 ligase, NHL repeat-containing 1 (NHLRC1) directs the ubiquitination and degradation of frataxin, which regulates the sensitivity to ferroptosis in I/R [100]. In DIC, the E3 ubiquitin ligase TRIM21 interacts with and ubiquitylates p62 and negatively regulates the p62-Keap1-Nrf2 antioxidant pathway, with TRIM21 ablation protecting against doxorubicin-induced cardiotoxicity [101]. Another E3 ubiquitin ligase, MITOL, can control and stabilization of mitochondrial function. MITOL knockdown reduced the ratio of GSH/GSSG, promoted the accumulation of lipid peroxides in mitochondria, and increased ferroptosis in cardiomyocytes [102]. Zhou et al. discovered the spermatogenesis-associated protein 2 (SPATA2)/CYLD

Table 4 Ferroptosis-regulating ubiquitination in CVDs

Modification	Diseases	Targets	Biological functions	References
Ubiquitination	MIRI	SIRT1/p53/SLC7A11	SIRT1 overexpression brought about a reduction in p53 acetylation, led to upregulation of SLC7A11, inhibits ferroptosis	[93]
	MIRI	P53、TFR1	Knockdown USP7 can enhanced the ubiquitination of p53 and led to decreased levels of p53 and TFR1, reducing myocardial cell I/R injury and ferroptosis	[94]
	MIRI	TRAF3	USP11 improved myocardial I/R injury by downregulating TRAF3 expression	[95]
	MIRI	GPX4	Upregulation of OTUD5 deubiquitinates and stabilizes GPX4, thus reversing 4-HNE-induced ferroptosis and alleviating myocardial I/R injury	[96]
	MIRI	ACSL4	YAP interacts with TEAD4 to promote the expression of NEDD4L, leading to ubiquitination of ACSL4, thereby limiting ferroptosis	[98]
	MIRI	Frataxin	Reduced NHLRC1 expression can decrease frataxin ubiquitination and inhibit ferroptosis via the IRP1 pathway	[100]
	DIC	Keap1	Ubiquitin E3 ligase TRIM21 negatively regulates the p62-Keap1-Nrf2 antioxidant pathway and protects doxorubicin-induced cardiotoxicity	[101]
	DIC	GPX4	MITOL knockdown reduced the ratio of GSH/GSSG to regulate GPX4 expression, increase ferroptosis in cardiomyocytes	[102]
	DIC	NCOA4	SPATA2 can recruit CYLD to reduce NCOA4 ubiquitination and reducing ferroptosis in doxorubicin-induced cardiotoxic cells	[103]
	HF	Keap1/Nfr2	Upregulation of PGAM5 reduce Keap1 protein ubiquitination through the Keap1/Nrf2 signaling pathway, thereby reducing ferroptosis in HF	[105]

USP7: ubiquitin-specific protease 7, TRAF3: tumor necrosis factor receptor-associated factor 3, OTUD5: ovarian tumor deubiquitinase 5, 4-HNE: 4-hydroxy-2-nonenal, IRP1: iron regulatory protein 1, NHLRC1: NHL repeat-containing 1, MITOL: mitochondrial ubiquitin ligase, NCOA4: nuclear receptor coactivator 4, SPATA2: spermatogenesis-associated protein 2, PGAM5: phosphoglycerate mutase 5

pathway, which involves the deubiquitination of NCOA4. Knockout of *SPATA2* reduced expression of the deubiquitinating enzyme CYLD, thereby reducing NCOA4 ubiquitination and reducing ferroptosis in cells with DIC [103]. Phosphoglycerate mutase 5 (PGAM5) is an atypical mitochondrial serine/threonine phosphatase [104]. Li et al. found upregulation of PGAM5 reduced Keap1 protein ubiquitination through the Keap1/Nrf2 signaling pathway and reduced Nrf2 inhibition, thereby reducing ROS and ferroptosis in HF [105].

Ferroptosis-regulating phosphorylation in CVDs

Phosphorylation also plays an important role in the progression of ferroptosis in cardiovascular diseases. Phosphorylation of ferroptosis-related proteins via the addition of a phosphate group alters its structure and function, thereby regulating the ferroptosis pathway (Table 5) [4]. HIP-55 is a novel adaptor protein to integrate ferroptosis into the classic AKT cell survival pathway and the MAP4K1 cell death pathway in MI injury. Jiang et al. found that AKT phosphorylates HIP-55 at the S269/T291 sites and that HIP-55 negatively regulates the MAP4K1-dependent JNK/GPX4 ferroptosis pathway, significantly reducing the myocardial damage caused by ferroptosis [106]. Beclin 1 (BECN1), an endogenous SLC7A11-binding protein, is a key regulator of ferroptosis [107]. Cao et al. confirmed that NaHS could attenuate sepsis-induced myocardial cell and tissue injury by significantly inhibiting the phosphorylation of BECN1 and significantly increasing expression levels of SLC7A11 and GPX4 [108].

Upregulation of ferroptosis-associated genes and proteins is accompanied by ion of in the doxorubicin-treated mouse heart. In the doxorubicin-treated mouse heart, AMPKα2 phosphorylation downregulates; AMPKα2 phosphorylation was shown to decrease mortality by promoting mitochondrial injuries, diminishing expression of ferroptosis-associated proteins, and reducing the accumulation of LDH and MDA [109]. Recent studies have found that ferroptosis plays a role in high-fat diet-induced cardiac injury. Zhu et al. discovered that, in high-fat diet-induced cardiac injury, STAT3 phosphorylation increased NCOA4 activity and promoted NCOA4-mediated ferritinophagy, which eventually triggered lipid peroxidation and ferroptosis of cardiomyocytes [110].

Ferroptosis-regulating acetylation and glycosylation in CVDs

Emerging study has shown that acetylation and glycosylation participate in cellular signaling pathways of ferroptosis. Studies by Han Su et al. suggested SIRT3-mediated cardiac fibrosis is partly exerted through a mechanism involving p53 acetylation-induced ferroptosis in H9C2 myofibroblasts [111]. Zhong et al. found that glycosylated CD147 interacts with TNF receptor-associated factor 2 (TRAF2) to activate the downstream TRAF2/TGFβ-associated kinase (TAK1) signaling pathway, promoting ferroptosis and oxidative stress, and plays a role in

Table 5 Ferroptosis-regulating phosphorylation, acetylation, and glycosylation in CVDs

Modification	Diseases	Targets	Biological functions	References
Phosphorylation	MI	MAP4K1/GPX4	HIP-55 negatively regulates MAP4K1-dependent JNK/GPX4 ferroptosis pathway, reducing the damage caused by MI	[106]
Phosphorylation	**Sepsis-induced cardiomyopathy**	BECN1/SLC7A11	NaHS could attenuate sepsis-induced myocardial cell and tissue injury by significantly inhibiting the phosphorylation of BECN1 and significantly increasing expression levels of SLC7A11 and GPX4	[106]
Phosphorylation	DIC	AMPKa2	AMPKα2 phosphorylation can promote ferroptosis-associated mitochondrial injuries, diminish ferroptosis-associated proteins and genes expression	[109]
Phosphorylation	HFD-induced cardiac injury	NCOA4	STAT3 phosphorylation increased NCOA4 activity and promoted NCOA4-mediated ferritinophagy in HFD-Induced cardiac injury	[110]
Acetylation	Cardiac fibrosis	p53	SIRT3-mediated cardiac fibrosis through a mechanism involving p53 acetylation-induced ferroptosis	[111]
Glycosylation	Cardiac hypertrophy	TRAF2	CD147 activates the TRAF2-TAK1 signaling pathway, promoting pathological cardiac remodeling in cardiac hypertrophy	[112]

HFD: high-fat diet, MAP4K1: mitogen-activated protein kinase kinase kinase kinase 1, BECN1: beclin 1, STAT3: signal transducer and activator of transcription 3, TAK1:TGF-β-associated kinase 1

pathological cardiac remodeling and dysfunction associated with myocardial hypertrophy [112].

Conclusion and future perspectives

CVD has always been a major threat to human health. Iron is an essential trace element in cardiacmuscle. Excessive iron can lead to ferroptosis-mediated myocardial cell death, which prompted us to investigate the potential link between myocardial ferroptosis and CVDs. We discovered that the mechanisms underlying myocardial ferroptosis involve iron homeostasis, regulation of different iron metabolism pathways, and balancing of the antioxidant system. Many CVDs involve differential expression of the aforementioned molecules and pathways.

The discovery of epigenetic modification, gene regulation, and PTMs of ferroptosis-related proteins and pathways invites new perspectives on the pathophysiological progression of CVDs. Novel drugs need be developed to target ferroptosis-related genes, which can accurately influence iron metabolism processes, guiding precise clinical interventions.

The epigenetic regulation and PTMs involved in myocardial ferroptosis are part of an emerging field of CVD research. Could there be additional, as yet undiscovered modes of epigenetic regulation that participate in regulating the ferroptosis of myocardial cells? If inherited CVDs linked to genetic similarities in the regulation of epigenetic modifications and PTMs of ferroptosis molecules? How can we achieve quantitative detection and early monitoring of iron levels in myocardial cells? Does the occurrence of ferroptosis interfere with the stability of other elements in myocardial cells and affect the progress of CVDs? All of these questions require exploration. We anticipate that continuous research on the molecular mechanisms, epigenetic regulation, and PTMs of ferroptosis will lead to the development of molecular-targeted, disease-specific drugs, and ultimately a cure for CVD.

Abbreviations

MIRI	Myocardial ischemia/reperfusion injury
H/R	Hypoxia/reoxygenation
Keap1	Kelch-like ECH-associated protein 1
AMI	Myocardial infarction
AF	Atrial fibrillation
GPX4	Glutathione peroxidase 4
SLC7A11	Subunit solute carrier family 7 member 11
GLS2	Glutaminase 2
OGD/R	Oxygen glucose deprivation/reoxygenation
TFR	Transferrin receptor
Nrf2	Nuclear factor-erythroid 2-related factor 2
LOX	Lysyloxidase
NOX	NADPH oxidases
ATG5	Autophagy-related 5
ME2	Malic enzyme 2
DMTI	Divalent metal transporter 1
HUCB-MSCs	Human umbilical cord blood mesenchymal stem cells
MLK3	Mixed lineage kinase 3
MDA	Malondialdehyde
TAC	Transverse aortic construction
I/R	Ischemia/reperfusion
MI	Myocardial infarction
DbCM	Diabetic cardiomyopathy
HMOX1	Heme oxygenase 1
ACSL4	Acyl-coA synthetase long-chain family member 4
BCL2	B-cell chronic lymphocytic leukemia/lymphoma 2
GSH	Giutathione
BMSCs-Exo	Bone mesenchymal stem cells exosomes
Ptgs2	Prostaglandin endoperoxide synthase-2
OGD	Oxygen–glucose deprivation
CCND2	Cell cycle protein D2
TFR1	TF receptor protein 1
CMECs	Cardiac microvascular endothelial cells
MMP9	Matrix metalloproteinase 9
TIMP1	TIMP metallopeptidase inhibitor 1
Fth1	Ferritin light chain
NAMPT	Nicotinamide phosphoribosyl transferase

Sirt1	Sirtuin-1
FOXO1	Forkhead box protein O1
LRP6	Lipoprotein receptor-related protein 6
DIC	Doxorubicin-induced cardiomyopathy
AD	Aortic aneurysm and dissection
PRMT4	Protein arginine methyltransferase 4
FSP1	Ferroptosis suppressor protein 1
FTO	Fat mass and obesity-associated protein
YTHDF2	YTH N6-methyladenosine RNA-binding protein F2
USP7	Ubiquitin-specific protease 7
TRAF3	Tumor necrosis factor receptor-associated factor 3
OTUD5	Ovarian tumor deubiquitinase 5
4-HNE	4-Hydroxy-2-nonenal
IRP1	Iron regulatory protein 1
NHLRC1	NHL repeat-containing 1
MITOL	Mitochondrial ubiquitin ligase
NCOA4	Nuclear receptor coactivator 4
SPATA2	Spermatogenesis-associated protein 2
PGAM5	Phosphoglycerate mutase 5.HFD: high-fat diet
MAP4K1	Mitogen-activated protein kinase kinase kinase kinase 1
BECN1	Beclin 1
STAT3	Signal transducer and activator of transcription 3
TAK1	TGF-β-associated kinase1
O_2^-	Superoxide anion
OH	Hydroxyl radicals
H_2O_2	Hydrogen peroxide
SOD	Superoxide dismutase

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Author contributions
Chunlu Jing involved in writing—review & editing, writing—original draft. Yupeng Wu took part in writing—review & editing, investigation. Yuzhu Zhang involved in writing—review & editing, validation. Zaihan Zhu involved in writing—review & editing, methodology. Yong Zhang took part in writing—review & editing, investigation. Zhen Liu involved in writing—review & editing, conceptualization. Dandan Sun involved in writing—review & editing, conceptualization.

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No datasets were generated or analyzed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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