New developments in the role of ferroptosis in sepsis-induced cardiomyopathy (Review)

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Abstract. Sepsis is a life-threatening organ dysfunction disorder caused by dysfunctional host response to infection. Sepsis-induced cardiomyopathy (SIC) is a common and serious complication of sepsis, and it is associated with increased mortality rates; however, its specific pathogenesis is still unclear. Ferroptosis, which is an iron-dependent form of programmed cell death, is involved in the pathophysiology of SIC. Further study on the mechanism and therapeutic targets of ferroptosis in SIC may provide new strategies for clinical diagnosis and treatment of this condition. The present article reviews the mechanisms between SIC and ferroptosis, summarizes the progress in research of the involvement of ferroptosis in SIC and provides new potential strategies for further research and treatment in the future.

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Abbreviations: SIC, sepsis-induced cardiomyopathy; ROS, reactive oxygen species; ATP, adenosine triphosphate; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; CoQ10, coenzyme Q10; NAD(P)H, reducer nicotinamide adenine dinucleotide (phosphate); FSP1, ferroptosis suppressor protein 1; MBOAT1/2, membrane-bound O-acyltransferase domains 1/2; METTL3, methyltransferase-like 3; LPS, lipopolysaccharide; SIRT1, sirtuin1; HO-1, heme oxygenase 1; Nrf2, nuclear factor erythroid 2-related factor 2

Key words: sepsis, sepsis-induced cardiomyopathy, ferroptosis, mitochondrial dysfunction, reactive oxygen species

1. Introduction

Sepsis is a serious infectious disease caused by the invasion of bacteria, viruses, fungi and other pathogens into human tissues (1). In severe cases, sepsis can lead to systemic inflammatory response syndrome, multiple organ failure and mortality (2-4). Sepsis is a global health problem and, according to a previous study, in 2017, there were an estimated 48.9 million cases of sepsis worldwide, and nearly 11 million sepsis-related mortalities were reported, which accounted for 19.7% of the total global mortality (5). In the United States, >1.7 million adults develop sepsis each year, and sepsis results in mortality of nearly >350,000 adults annually (6). In China, from 2017 to 2019, 4.8 to 6.1 million patients were hospitalized with sepsis each year, and there were ~800,000 sepsis-related mortalities, with complications occurring in >70% of cases (7). Sepsis-induced cardiomyopathy, a common and serious complication of sepsis, is a key cause of mortality in critically serious patients in the intensive care unit, and can increase the mortality rate of sepsis in patients by two to three fold (8). The pathogenesis of SIC is complex and may be associated with various factors, such as inflammation, apoptosis and energy metabolism disorders (9). However, the specific molecular mechanisms are still unclear, and further research is required.

Ferroptosis was first reported in the study by Dixon *et al* (10) in 2012. Ferroptosis is an iron-dependent form of programmed cell death, which is different from pyroptosis, apoptosis and autophagy. Ferroptosis is characterized by iron-catalyzed lipid peroxidation (11). The mechanism of ferroptosis is complex and diverse, and is associated with various cellular structures.

At the organelle level, mitochondria are closely associated with the occurrence of ferroptosis (12). Excess iron in cells can be absorbed by mitochondria, promoting the Fenton reaction to produce reactive oxygen species (ROS) that cause mitochondrial lipid peroxidation and damage, thus affecting cellular energy production (13,14). Mitochondria are abundant in cardiomyocytes and damage to mitochondria seriously effects their normal function (15).

In previous years, numerous studies have revealed that ferroptosis has a key role in the occurrence of SIC (16,17). Therefore, further research on ferroptosis may be beneficial for the diagnosis, treatment and prognosis of SIC. The present review briefly describes the molecular mechanisms of ferroptosis. Additionally, the present review focuses on the research progress of the possible mechanisms of action in SIC to provide new ideas for the treatment of SIC in the future.

2. SIC

SIC has not been clearly defined since it was first proposed and its complex pathophysiological processes hinder diagnosis. New advances in cardiac imaging have increased the uncertainty in defining SIC; moreover, the potential for myocardial dysfunction and the need for acute intervention adds further complexity (18). A 2019 review proposed that SIC is an acute cardiac dysfunction caused by sepsis, which is a reversible complication. The clinical symptoms of SIC mainly manifest as ventricular dilatation, reduced ventricular contractility and/or right and left ventricular dysfunction, and a reduced response to volume infusion (19). These symptoms are largely associated with cardiac function and hemodynamic changes (20). Wang *et al* (21) proposed using echocardiographic changes to explain the possible pathophysiological mechanism of cardiac function changes in SIC. To date, although there have been numerous studies and reviews of SIC (16,22-24), the understanding of SIC is still insufficient, and thus there is an unmet clinical need in the diagnosis and treatment of SIC. The present review provides a brief overview of current research on the mechanisms of SIC (Fig. 1).

Inflammatory reaction. SIC is associated with an excessive inflammatory response, through which the release of inflammatory mediators is a key factor. Studies have revealed that in patients with sepsis, the expression of pro-inflammatory factors, such as tumor necrosis factor-α, IL-1β and IL-6 are increased (8,25,26). These inflammatory factors are mainly mediated by Toll-like receptor-4 to recognize different pathogen-associated molecular patterns and damage-associated molecular patterns (27). Toll-like receptor-4 activates intracellular signaling pathways such as the MyD88-dependent pathway (28). This activation leads to the translocation of NF-κB into the nucleus, where it promotes the transcription of target genes, including pro-inflammatory cytokines and chemokines which attract and activate inflammatory cells such as macrophages and neutrophils (29). Macrophages, upon activation, secrete more pro-inflammatory cytokines, creating a positive feedback loop that exacerbates the inflammatory response (30). Neutrophils, attracted to the site of injury, release ROS and proteases, which directly damage cardiomyocytes, compromising the integrity of the cell membrane and leading to cell content leakage (31). This direct damage, along with metabolic disturbances and altered gene expression in cardiomyocytes induced by the inflammatory response, results in necrosis and apoptosis of cardiomyocytes (32). Additionally, the inflammatory response stimulates the activation and proliferation of cardiac fibroblasts, leading to myocardial fibrosis, which replaces normal myocardial tissue and impairs cardiac function (33). These above processes eventually lead to myocardial damage and dysfunction.

Mitochondrial dysfunction. Mitochondrial dysfunction is a key characteristic of SIC. The main role of mitochondria is to produce adenosine triphosphate (ATP) but they also have roles in other cellular functions, such as calcium homeostasis, body temperature regulation, cell signal transduction and apoptosis (34). The manifestations of mitochondrial dysfunction are complex and diverse in SIC, mainly in the electron transport chain and oxidative phosphorylation abnormalities, mitochondrial structure abnormalities, oxidative and nitrite stress, mitochondrial calcium overload, mitochondrial autophagy dysregulation, and mitochondrial dynamics imbalance (35-37).

The electron transport chain within mitochondria is a pivotal component of cellular respiration and energy generation. During SIC, disruptions of this chain lead to reduced ATP synthesis, thereby impairing the regular operation of cardiomyocytes (38). Deviations in mitochondrial morphology and structure, such as swelling, shortening and the loss of cristae, can also compromise mitochondrial function. Furthermore, heightened levels of ROS and reactive nitrogen species generated by mitochondria can initiate oxidative and nitrosative stress, exacerbating damage to both mitochondria and cardiomyocytes (39). Calcium has a key role in mitochondrial function and is a primary regulator of oxidative phosphorylation (40). In SIC, elevated levels of calcium ions within the mitochondria contribute to reduced mitochondrial antioxidant capacity and heightened production of ROS (41). Additionally, autophagy, which is responsible for the elimination of damaged mitochondria, may become dysregulated, resulting in the accumulation of dysfunctional mitochondria and thus cellular malfunction (42).

Mitochondrial division and fusion are key processes that preserve the dynamic equilibrium of the mitochondrial network. When this equilibrium is disrupted, it can adversely affect mitochondrial function and distribution. Failure of the mitochondrial antioxidant system increases susceptibility of the body to inflammation, immune response, hormone metabolism and bioenergetic response activation (43). This failure mainly leads to increased production of ROS, which can damage mitochondrial components (44). The accumulation of ROS triggers a series of detrimental processes: It activates inflammatory pathways, causing the release of pro-inflammatory cytokines and initiating an inflammatory response; stimulates the immune system, potentially leading to an overactive immune response; disrupts hormone synthesis and metabolism, causing hormonal imbalances; and reduces ATP production efficiency, impairing the cell's ability to meet its energy demands and affecting various bioenergetic processes (45,46). These processes create a vicious cycle, where initial mitochondrial dysfunction leads to oxidative stress, which further exacerbates mitochondrial issues and increases ROS production, ultimately resulting in an irreversible condition of oxidative stress and mitochondrial dysfunction that impacts the cell's overall health and function (47).

Regulatory cell death. Cell death is another key feature of SIC. All types of damage can result in irreversible damage of myocardial cells and promote the progression of cardiac

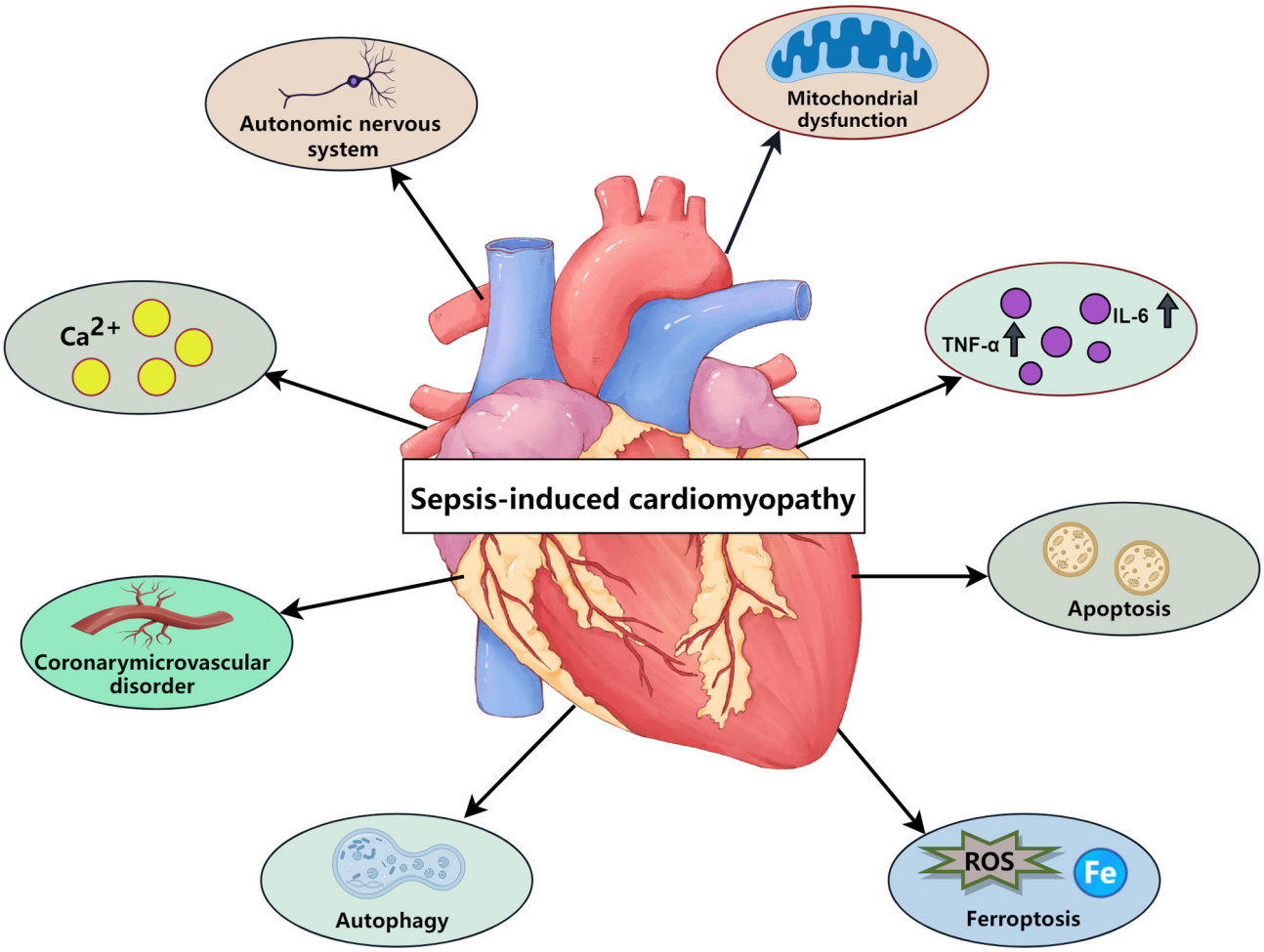

Figure 1. Mechanism of sepsis-induced cardiomyopathy. Pathogenesis of sepsis-induced cardiomyopathy may include changes in the expression of mitochondrial dysfunction, pro-inflammatory factors, regulatory cell death (for example, autophagy, apoptosis and ferroptosis), abnormal calcium processing, autonomic nervous system dysfunction and coronary microvascular disorders. The figure was generated using Figdraw. ROS, reactive oxygen species; Fe, iron.

dysfunction (48). Most cardiomyocyte death is accomplished through regulatory molecular pathways, including autophagy and apoptosis, pyroptosis, ferroptosis and necrosis. These forms of regulatory cell death are the main characteristics of the pathogenesis of SIC (49).

Autophagy is a cellular process that involves the recycling of materials, and is typically initiated during nutrient deprivation or other stressful conditions to aid in the elimination of damaged proteins and organelles (50). Apoptosis is an orderly process of cellular demise, often initiated by internal signals. In SIC, autophagy can be hyperactivated or suppressed and inflammatory mediators along with oxidative stress can induce apoptosis, both of which contribute to the death of cardiomyocytes (51). Pyroptosis, another mode of cell death, is triggered by inflammatory vesicles and is characterized by the discharge of substantial quantities of proinflammatory cytokines, such as IL-18 and IL-1β. Pyroptosis is particularly pronounced in SIC as it can amplify inflammatory responses, resulting in tissue damage and organ dysfunction (52). Ferroptosis, a more recently discovered form of cell death, is closely associated with intracellular iron metabolism and lipid peroxidation. During sepsis, ferroptosis may be initiated by disruptions in iron metabolism and heightened oxidative stress, leading to damage and death of cardiomyocytes (53). Additionally, necrosis is an uncontrolled form of cell death that can interact with other forms of cell death, ultimately contributing to myocardial tissue damage (9). Understanding the regulatory mechanisms underlying these cell death pathways is key for the advancement of novel therapeutic strategies for SIC.

Other mechanisms of SIC. In addition to the aforementioned mechanisms, calcium dysregulation, autonomic nervous system dysfunction and coronary microvascular disorders may be involved in SIC (54). Disturbances in intracellular calcium homeostasis have been studied in septic hearts (55). Most models of sepsis show a decrease in cytosolic calcium transients, the difference between systolic and diastolic calcium, which may be associated with an increase in diastolic cytoplasmic calcium and a decrease in sarcoplasmic reticulum calcium content (8,56). In sepsis, the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system are the two main pathways of neuromodulation (57). Hyperactivation of the sympathetic nervous system and elevated levels of circulating endogenous catecholamines ultimately culminate in the desensitization of adrenergic receptors, which in turn affects cardiac function (58). Alterations in the coronary microvasculature may affect myocardial blood flow and oxygen supply. This occurs mainly due to disruption of the glycocalyx in

the endothelium leading to vascular leakage, coagulation and inflammation, with the heterogeneous microvascular flow and myocardial edema (59).

3. Ferroptosis

The occurrence and development of numerous diseases, such as various types of cancer, neurodegenerative diseases, diseases involving tissue or organ damage and inflammation, and infectious diseases, are inseparable from ferroptosis (60). The morphological and mechanistic characteristics of ferroptosis are different from those of traditional cell death. In terms of morphology, ferroptosis mainly manifests as a reduction in the levels of mitochondria, an increase in mitochondrial membrane density, a reduction in the number of mitochondrial cristae and rupture of the mitochondrial outer membrane. However, for all cells undergoing ferroptosis, there is no considerable association between change in nuclear size or nuclear chromatin with ferroptosis (61). It is necessary for particular lipids to experience oxidation, and concurrently, the physiological defenses that inhibit the aggregation of oxidized lipids must be dysfunctional. The mechanism of ferroptosis is complex and varied but it is essentially an imbalance between oxidation and antioxidant systems, resulting in cellular lipid peroxidation (62). The main pathways resulting in ferroptosis are discussed in the present review.

Cystine/glutamate anti-transport system and glutathione peroxidase 4. Cystine/glutamate antiporter is a transmembrane amino acid transporter, also known as system Xc^-, which is distributed in phospholipid bilayers in certain cell types, such as neurons, immune cells and cancer cells (63). The transporter protein, xCT, in the transporter is formed of two chains, solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2), connected by disulfide bonds (64). Glutathione (GSH) is a key antioxidant substance in cells, and cystine is one of the raw materials needed for its synthesis. By inhibiting activation of system Xc^-, the absorption of cystine is reduced and the synthesis of GSH is diminished. As a result, the antioxidant capacity of cells decreases and a large amount of ROS accumulates, leading to oxidative damage and ferroptosis (65). Thus, ferroptosis can occur by reducing or depleting GSH: The P53 gene can affect GSH synthesis and activity by downregulating the expression of SLC7A11 (66). Beclin1 can directly bind to SLC7A11 and contribute to the depletion of GSH and the level of lipid peroxidation (67). The ATP-binding cassette family of transporters of the multidrug resistance protein 1 can enable the release of GSH into the extracellular space, leading to GSH depletion (68). These result in ROS accumulation (Fig. 2). The ferroptosis inducer erastin acts by restraining expression of SLC7A11 (69).

GSH peroxidase 4 (GPX4) is one of the key components of the antioxidant system *in vivo*, and it can convert GSH to oxidized GSH and reduce cytotoxic lipid peroxides to corresponding alcohols (70). GPX4 is a key regulator of ferroptosis that mainly inhibits the formation of lipid peroxides. By directly inhibiting the activity of Gpx4 or reducing the quantity of GPX4, causes an increase in intracellular lipid peroxides, which induces a decrease in cellular antioxidant capacity and ROS accumulation, ultimately leading to the occurrence of ferroptosis (71). Thus, GPX4 inhibitors can induce the onset of ferroptosis (Fig. 2). Previous studies have revealed that small molecules that use chloroacetamido groups as electrophilic moieties may be effective covalent GPX4 inhibitors (72,73). For instance, RAS-selective lethal 3 (RSL3), another classical inducer of ferroptosis, directly inhibits GPX4 (74). Recent studies have reported that both A16 and C18 have a similar role in inducing ferroptosis (73,75). In another study, GPX4 synthesis has been revealed to be associated with system Xc^- as a target of rapamycin complex 1 (76).

Iron metabolism. Disturbances in iron metabolism can also trigger ferroptosis. Iron is a vital trace element in the body (77). Therefore, abnormal iron distribution and content affect normal physiological processes, such as oxygen transport, DNA synthesis and ATP production (78). Excessive absorption or decreased use of iron in cells leads to an imbalance in iron ion concentrations for various reasons, and this results in iron overload. Excess iron then undergoes the Fenton reaction, and hydrogen peroxide produces hydroxyl free radicals and oxygen free radicals. These react with lipid components in cells and this generates a large number of lipid ROS eventually resulting in ferroptosis (Fig. 2) (60,79).

Cellular iron homeostasis in organisms is tightly regulated. Extracellular iron ions, usually in the form of trivalent iron, bind to transferrin and enter the cell via receptor for transferrin-1 (Fig. 2) (80). After the reduction of trivalent iron to divalent iron by the metalloreductase six-transmembrane epithelial antigen of the prostate 3, various iron complexes or storage iron are formed. When the complex becomes saturated, excess iron divalent accumulates in the cell and form an unstable iron pool, which is known as iron overload (81). Therefore, the regulation of iron metabolism for ferroptosis is dependent on the regulation of the capacity of the unstable iron pool. Heat shock protein β-1 can reduce iron uptake and control capacity of the iron pool by inhibiting TFR-1 expression levels (82). In addition, ferroportin and ferritin transfer protein, Prominin 2, can transport iron ions and ferritin to the extracellular compartment through each group of pathways, respectively, and their reduced expression levels have been shown to promote ferroptosis (83,84).

Gpx4-independent regulatory system. GPX4 is a central inhibitor of ferroptosis (85). However, there are other systems that do not rely on GPX4 to regulate ferroptosis. Ubiquinone 10, also referred to as coenzyme Q10 (CoQ10), is present in the membrane lipids of various cells and has antitumor, anti-aging and antioxidant properties (Fig. 2) (86). The studies by Doll *et al* (87) and Bersuker *et al* (88) report that CoQ10 can behave as a lipophilic free radical-trapping antioxidant that diminishes the accumulation of lipid peroxides and attenuates the occurrence of ferroptosis. Additionally, ferroptosis suppressor protein 1 (FSP1) can catalyze the regeneration of CoQ10 using reducer nicotinamide adenine dinucleotide (phosphate) (NAD(P)H). This is an independent antioxidant system that synergizes with GPX4 and GSH to inhibit phospholipid peroxidation and ferroptosis (89,90).

The other is dihydroorotate dehydrogenase (DOHDH). As a flavin-dependent enzyme located in the inner mitochondrial membrane, DOHDH reduces ubiquinone CoQ10

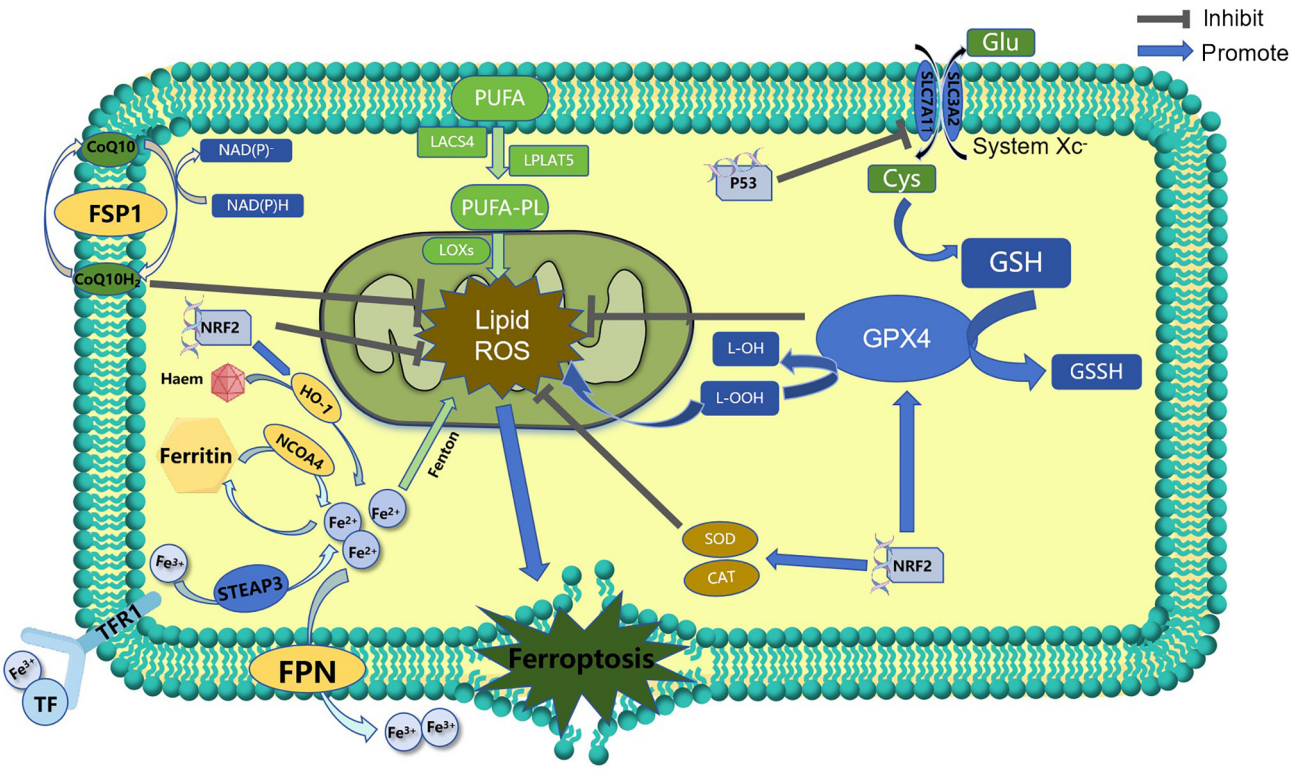

Figure 2. Regulatory mechanism of ferroptosis. Ferroptosis can be divided into three categories. The first is GSH/GPX4 metabolism, which is mainly regulated by system Xc-. Erastin acts on system Xc- and RSL3 inhibits GPX4 to induce ferroptosis. The second category is iron metabolism, associated with ferritin and HO-1. When iron metabolism is disrupted, it promotes the Fenton reaction, leading to the production of a large amount of lipid ROS, ultimately triggering ferroptosis. The third category is associated with lipid metabolism pathways. In addition, the FSP1-CoQ10-NAD(P)H pathway exists as an independent parallel system to inhibit phospholipid peroxidation and ferroptosis. ROS, reactive oxygen species; Glu, glutamate; Cys, cystine; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GSSG, glutathione disulfide; GPX4, glutathione peroxidase 4; NRF2, nuclear factor-erythroid 2-related factor 2; SOD, superoxide dismutase; CAT, Catalase; FPN, ferroportin; TF, transferrin; TFR1, TF receptor protein 1; STEAP3, six-transmembrane epithelial antigen of prostate 3; NCOA4, nuclear receptor coactivator 4; HO-1, heme oxygenase 1; CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; NAD(P)H, reducer nicotinamide adenine dinucleotide (phosphate); PUFA-PL, polyunsaturated fatty acid-containing phospholipid; LACS4, long-chain fatty-acid CoA ligase 4; LPLAT5, lysophospholipid acyltransferase 5; LOX, lipoxygenase.

to dihydro-ubiquinone, which traps oxidants in the cell membrane to prevent lipid peroxidation and thus inhibit ferroptosis (91). DOHDH has a similar role to FSP1 on the outer mitochondrial membrane (92). On this basis, a subsequent study has revealed that DOHDH inhibitors make cells more sensitive to ferroptosis by inhibiting FSP1 but not DHODH (93) (Fig. 3).

A recent study has found that membrane-bound O-acyltransferase domains 1,2 (MBOAT1 and 2) can reduce intracellular phosphatidylethanolamine polyunsaturated fatty acids. And since phosphatidylethanolamine polyunsaturated fatty acid is the preferred substrate for phospholipid peroxidation and a key determinant of ferroptosis sensitivity, MBOAT1 and MBOAT2 can effectively inhibit ferroptosis through a phospholipid remodeling mechanism (94). MBOAT1 and MBOAT2 are transcriptionally upregulated by the estrogen receptor (ER) and the androgen receptor (AR), respectively. The combination of ER or AR antagonists with ferroptosis induction can significantly inhibit the growth of ER-positive breast cancer or AR-positive prostate cancer. This finding provides new ideas for the treatment of cancers with specific genetic backgrounds (94,95). In addition, GTP cyclohydrolase 1 (GTPCH1) and GSH transferase pi inhibit ferroptosis independently (Fig. 3) (96,97).

Lipid metabolism. Lipid metabolism is an essential process of ferroptosis. Polyunsaturated fatty acids in cell membranes or organelles generate lipid peroxides in response to oxygen free radicals. When an antioxidant imbalance occurs in the body, the accumulated lipid peroxides eventually destroy the structure and function of the membranes, leading to cell damage and death (98). Furthermore, lipoxygenases and cyclooxygenases, such as long-chain acyl-CoA synthetase 4, lysophospholipid acyltransferase 5 and lipoxygenase, facilitate lipid peroxidation and ferroptosis (99).

Ferroptosis in SIC. Ferroptosis is a common feature of several cardiovascular diseases and a key process in mediating the pathogenesis and progression of heart diseases (100,101). These diseases include atherosclerosis, myocardial ischemia-reperfusion injury, SIC, drug-induced heart failure, arrhythmia and diabetic cardiomyopathy (102). SIC is a cardiac disease caused by sepsis, presenting significant difficulties in both clinical diagnosis and treatment (9). By summarizing the research on ferroptosis, progress can be made in the treatment of patients with SIC.

Mitochondrial function in SIC. Mitochondria are characterized as the energy factories of eukaryotic cells and have a variety of important functions in different physiological

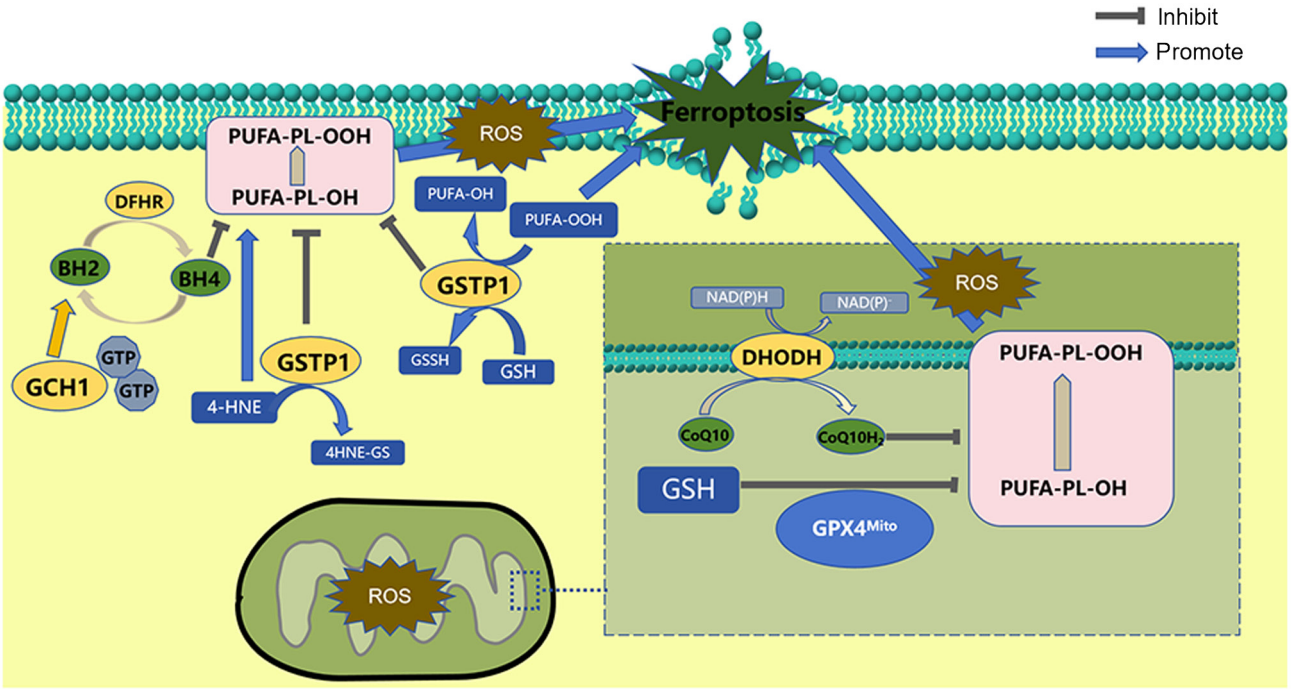

Figure 3. Gpx4-independent regulatory system. GCH1/BH4: GCH1 is a key enzyme in the biosynthesis pathway of BH4. Increased expression of GCH1 enhances BH4 biosynthesis, reducing ROS production and thus inhibiting ferroptosis; GSTP1/4-HNE: GSTP1 is involved in the detoxification process of 4-HNE, a product of lipid peroxidation. GSTP1 neutralizes 4-HNE by binding with GSH, reducing oxidative damage and protecting cells from ferroptosis; DHODH/CoQ10: DHODH catalyzes the reduction of CoQ10 to generate CoQ10H2, which participates in the electron transport chain and maintains mitochondrial function, indirectly affecting ROS production. The DHODH-CoQH2 regulatory system blocks mitochondrial lipid peroxidation, thereby inhibiting ferroptosis. ROS, reactive oxygen species; GTP, guanosine triphosphate; GCH1, guanosine triphosphate cyclohydrolase 1; BH2, dihydrobiopterin; DFHR, dihydrofolate reductase; PUFA-PL-OOH, polyunsaturated fatty acid-containing phospholipid hydroperoxide; GSTP1, glutathione S-transferase Pi; 4-HNE-GS, 4-hydroxynonenal-glutathione; GSH, glutathione; GSSG, glutathione disulfide; GPX4Mito, mitochondrial glutathione peroxidase 4; DHODH, dihydroorotate dehydrogenase; CoQ10, coenzyme Q10; NAD(P)H, reducer nicotinamide adenine dinucleotide (phosphate).

cellular processes (103). Mitochondrial dysfunction is a catalyst for a variety of diseases with widespread cell death (104). During SIC, mitochondrial dysfunction in cardiomyocytes results from heightened oxidative stress due to the release of inflammatory factors. A previous study has shown that morphological changes due to mitochondrial damage in the lipopolysaccharide (LPS)-induced myocardium are consistent with mitochondrial changes characterized by ferroptosis (105). Therefore, mitochondrial homeostasis in SIC can be maintained by targeting ferroptosis (Fig. 4) (17,35).

Liu *et al* (106) synthesized a nanomaterial from melanin, which was found to suppress ferroptosis by reducing cardiomyocyte ROS levels and inhibiting iron accumulation in a mouse model of LPS-induced septic cardiomyopathy. The study by Liu *et al* (106) also revealed a decline in cytochrome *c* release from mitochondria into the cytoplasm and a decrease in intra-mitochondrial JC-1 monomers, which protected mitochondrial function, thus improving survival and cardiac function in mice. This study revealed that low-dose olaparib effectively inhibits ferroptosis by attenuating markers associated with ferroptosis and promoting mitochondrial autophagy, which improves mitochondrial mass (107). Additionally, all-trans retinoic acid enhances the host immune response to LPS. Its derivative 4-amino-2-trifluoromethylphenyl retinoate expands the number of mitochondrial cristae and maintains mitochondrial membrane integrity, alleviating ferroptosis and myocardial injury (108). Located on the outer membrane of mitochondria, voltage-dependent anion channel 2 has a role in the regulation of mitochondrial metabolism and capacity and participates in the regulation of cell life cycle signal transmission. It is an important transmembrane channel that mediates the transport of ions and metabolites between the mitochondria and the cytoplasm (109). She *et al* (110) have found that malonyl-coenzyme A can induce the volt-dependent anion channel 2 malonylation in septic mice, which changes the structure of the N-terminal of the channel, causing mitochondrial dysfunction, increasing mitochondrial ROS levels, leading to ferroptosis and aggravating SIC (Fig. 4).

Xc- system and GPX4. Inhibition of xCT protein or GPX4 leads to ferroptosis, which provides a possible therapeutic target for the treatment of septic myocardial injury (Fig. 4). Methyltransferase-like 3 (METTL3) is a core catalytic subunit for RNA N6-methyladenosine (m6A) modification. METTL3 has a key role in several biological processes, such as embryonic development, immune responses and the occurrence and progression of tumors (111). METTL3-mediated m6A methylation causes the mRNA of SLC7A11 to have increased levels of methylation. YTH domain family member 2 directly binds to the m6A modification site to mediate mRNA degradation and promote the decay of SLC7A11 mRNA, thus upregulating ferroptosis in myocardial injuries caused by sepsis (112). The study by Cao *et al* (113) found that Beclin 1, which is an endogenous SLC7A11 binding protein, can regulate ferroptosis. Sodium hydrosulfide can inhibit the phosphorylation of Beclin 1, increase SLC7A11 and GPX4 expression levels, and reduce

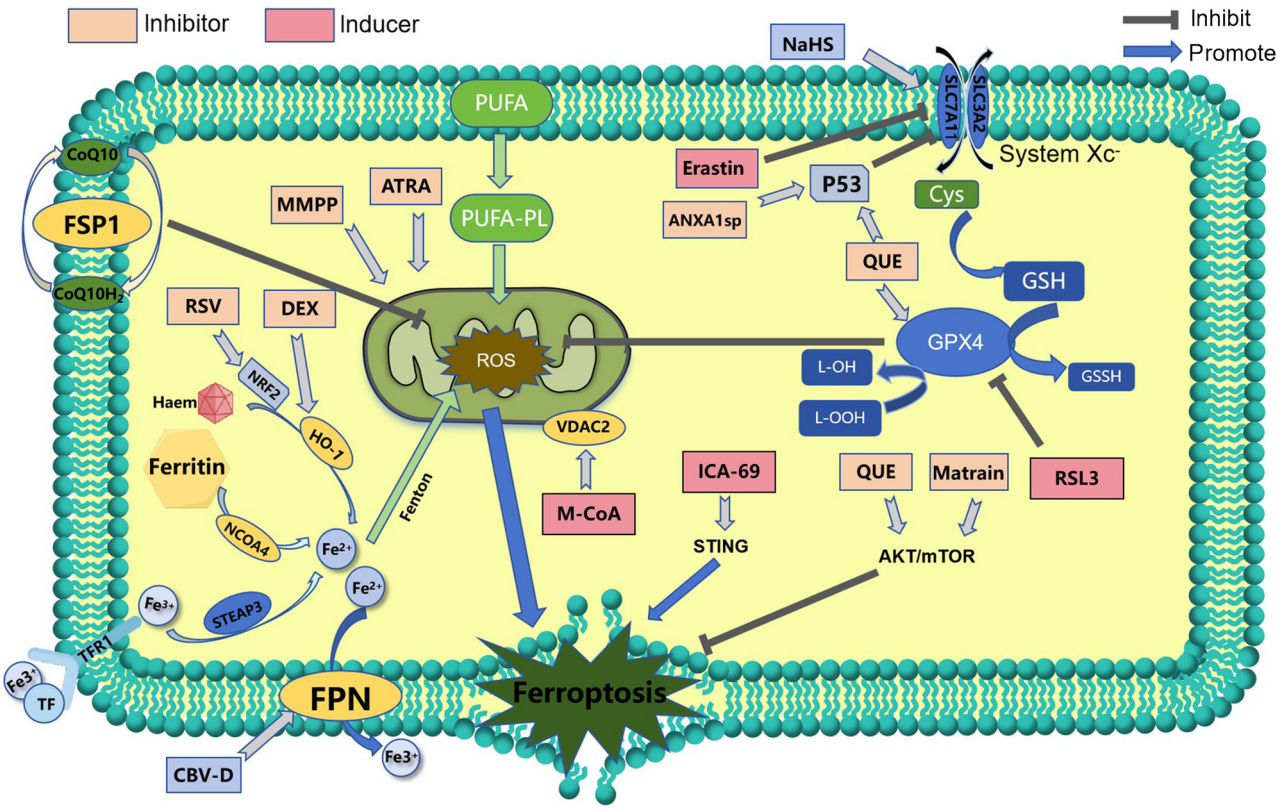

Figure 4. Ferroptosis inhibitors and promoters and their targets of action. The diagram shows that in cardiomyocytes, both ferroptosis promoters and inhibitors have their specific sites of action to regulate ferroptosis, forming a complex regulatory network. Light pink boxes indicate inducers and yellow boxes indicate inhibitors. ROS, reactive oxygen species; Cys, cystine; SLC7A11, solute carrier family 7 member 11; GSH, glutathione; GSSG, glutathione disulfide; GPX4, glutathione peroxidase 4; NRF2, nuclear factor-erythroid 2-related factor 2; FPN, ferroportin; TF, transferrin; TFR1, TF receptor protein 1; STEAP3, six-transmembrane epithelial antigen of prostate 3; NCOA4, nuclear receptor coactivator 4; HO-1, heme oxygenase 1; CoQ10, coenzyme Q10; FSP1, ferroptosis suppressor protein 1; NAD(P)H, reducer nicotinamide adenine dinucleotide (phosphate); PUFA-PL, polyunsaturated fatty acid-containing phospholipid; NaHS, sodium hydrosulfide; ANXA1sp, annexin A1 small peptide; QUE, quercetin; ICA-69, islet cell autoantigen 69; M-CoA, malonyl-coenzyme A; VDAC2, voltage-dependent anion channel 2; RSV, resveratrol; DEX, dexmedetomidine; MMPP, nanomaterial from melanin; ATRA, all-trans retinoic acid.

the incidence of cardiac ferroptosis, thus protecting against sepsis-induced cardiomyocyte injury (113). Furthermore, YiQiFuMai injection has been found to ameliorate SIC by inhibiting ferroptosis via the xCT/GPX4 axis (Fig. 4) (114).

The *p53* gene, a prominent oncogene in tumors, has been shown to specifically inhibit the xCT system by downregulating expression of SLC7A11, causing ferroptosis (Fig. 4) (115). Additionally, studies have revealed p53-dependent mitochondrial dysfunction in SIC (8,116,117). Therefore, there may be corresponding mechanisms or pathways in SIC that can be used as therapeutic targets. The study by Lin *et al* (118) found that quercetin reduces intracellular iron and prostaglandin peroxidase synthase 2 levels, and upregulates GPX4 and ferritin levels through the sirtuin1 (SIRT1)/*p53*/SLC7A11 signaling pathway. This results in amelioration of ferroptosis and thus alleviates SIC (118). Annexin A1 small peptide, which is a member of the membrane-associated protein superfamily of proteins, can protect cardiomyocytes from ferroptosis through sirtuin 3-dependent *p53* deacetylation (Fig. 4) (119).

Iron metabolism processes. Previous studies have shown that ferroptosis is affected by regulation of iron metabolism in SIC. Ferritin autophagy mediated by nuclear receptor coactivator 4 promotes ferroptosis by controlling intracellular iron homeostasis (9,120,121). On this basis, expression of intracellular nuclear receptor coactivator 4 and iron are increased in an LPS-induced cardiac injury model (122). This is largely due to the fact that nuclear receptor coactivator 4 can directly interact with ferritin and degrade it in a ferritin autophagy-dependent manner, subsequently releasing a large amount of iron, which leads to iron accumulation (123). Excess iron in the cytoplasm further stimulates the expression of ferritin on the mitochondrial membrane, which in turn transports cytoplasmic iron into the mitochondria, stimulating mitochondrial ROS production and ferroptosis. These findings suggests that ferritin autophagy-mediated ferroptosis is involved in SIC (Fig. 4) (124).

Heme oxygenase 1 (HO-1) is an intracellular enzyme that catalyzes the production of ferrous iron, carbon monoxide and bilirubin from heme. HO-1 is one of the downstream targets of nuclear factor erythroid 2-related factor 2 (Nrf2) (Fig. 4). Nrf2 has antioxidant roles, and increased HO-1 expression reduces oxidative damage and inflammation (125). HO-1 is also involved in scavenging free radicals and modulating immune responses. However, overactivation of HO-1 can contribute to the accumulation of a large amount of iron in the cytoplasm, promoting ROS production and ultimately ferroptosis (126,127). Dexmedetomidine, which is an α_2-adrenergic receptor agonist,

can diminish ferroptosis by restricting HO-1 overexpression, decreasing iron concentrations and increasing levels of antioxidants such as GPX4, which defend against sepsis-induced cardiomyocyte injury (128). Recombinant ferroportin, which is located in the cell membrane, has a key role in iron metabolism. Ferroportin is able to transport iron ions from the intracellular to the extracellular compartments, thus modulating the distribution and use of iron in the body (129). Cyclovirobuxine D increases the upregulation of ferroportin-1, which reduces LPS-induced iron overload in the cytoplasm, thereby alleviating lipid peroxidation and ferroptosis in sepsis (130).

Other drugs or structural mechanisms. Other drugs and mechanisms have been identified that may be implicated in the development of ferroptosis in SIC (Fig. 4). Islet cell autoantigen 69, which is a molecule that regulates inflammatory and immune responses in a variety of diseases, is highly expressed in cardiomyocytes in wild-type mice with LPS-induced sepsis (131). This molecule triggers the production of stimulator of interferon genes, further contributing to lipid peroxidation and ferroptosis in cardiomyocytes.

Transmembrane protein 43 is a quaternary transmembrane protein that is mainly localized in the endoplasmic reticulum and inner nuclear membrane and is associated with cardiovascular diseases (132). The study by Chen *et al* (133) revealed that transmembrane protein 43 could be used as a beneficial factor to effectively inhibit ferroptosis of cardiomyocytes and alleviate myocardial injury.

Transient receptor potential melastatin 7, a transmembrane protein with the dual functions of cation channel and kinase activity, can mediate endoplasmic reticulum stress and ferroptosis. It may be a potential strategy for the treatment of SIC (134).

Currently, biological agents and their synthetics are available in a variety of applications and are gradually being used to examine ferroptosis. The study by Jiang *et al* (135) designed cerium dioxide nanozymes ligated with curcumin by self-assembly of human serum albumin. The formed cerium dioxide nanozymes ligated with curcumin acquired superoxide dismutase-like and catalase-like activities of cerium dioxide nanozymes, which could scavenge ROS (135). This study also reversed ferroptosis induced by RSL3 and showed an inhibitory effect on ferroptosis. Additionally, it revealed a reduction in pro-inflammatory factor release, which substantially relieved myocardial injury and restored cardiac function. The study by Jiao *et al* (136) revealed that platelet-rich plasma not only reduces inflammation, but also mitigates oxidative stress and ferroptosis by modulating the AKT/mTOR signaling pathway.

Several chemical extracts have been studied in animal or cellular experiments (Fig. 4). Puerarin protects against sepsis-induced myocardial injury through AMPK-mediated ferroptosis signaling (137). Matrine modulates ferroptosis by upregulating GPX4 expression, downregulating acyl-coenzyme A synthetase long-chain family member 4 and PI3K/AKT pathway-related molecules (138). Tectorigenin attenuates ferroptosis by silencing the expression of mothers against decapentaplegic homolog 3 (139). Resveratrol, which is a naturally occurring agonist of silencing information regulatory factor 1, initiates the SIRT1/NRF2 signaling pathway (140). A study had showed that resveratrol inhibits ferroptosis by ameliorating LPS-induced cardiomyocyte injury with upregulation of miR-149 and downregulation of high-mobility group box protein 1 (141).

Gene intervention. Numerous studies have investigated ferroptosis-related genes in search of potential diagnostic and therapeutic targets (142,143). The study by Huang *et al* (144) revealed that the *Lcn2* gene is associated with iron metabolism through bioinformatics analysis. This study also revealed that knockdown of LncRNA Lcn2-204 has a cardioprotective effect through the inhibition of iron overload and ferroptosis in SIC. They study by Song *et al* (145) showed that the cuproptosis- and ferroptosis-related genes *POR*, *SLC7A5* and *STAT3* are associated with SIC, and could also be used to predict therapeutic agents against these targets. The study by Zou *et al* (146) identified eight key ferroptosis-related genes and ferroptosis signatures through the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/) database. The study concluded that the aforementioned ferroptosis-related genes exhibit excellent diagnostic ability for SIC and that some of these genes are associated with the prognosis of SIC and have potential as therapeutic drugs. The study by Lin *et al* (147) screened the expression of six circadian genes to reveal that the *Bmal* gene inhibits the progression of ferroptosis in SIC. Furthermore, *Hmox1* and *SLC7A11* are target genes for ferroptosis in sepsis-induced myocardial injury (148).

4. Conclusion and perspectives

In summary, ferroptosis is key in the development of SIC, but several questions remain to be answered in this field of research. Despite the well-known regulatory pathways of ferroptosis, such as the GSH/GPX4 regulatory pathway, the FSP1/CoQ10 pathway, and iron metabolism and lipid metabolism, whether there are other regulatory mechanisms is unclear. Additionally, there is a lack of specific markers for the occurrence of ferroptosis in SIC.

Currently available established models of SIC are limited to animal and cellular experiments. For instance, Lu *et al* (149) established a mouse model of SIC by cecum ligation and puncture, including Nrf2 knockout ($Nrf2^{+/-}$) and wild-type ($Nrf2^{+/+}$) mouse, demonstrating that Daohe Chengqi decoction can inhibit ferroptosis and alleviate SIC. Another Lu *et al* (150) created a model of SIC by injecting Sprague-Dawley rats with LPS, showing that nicorandil, a drug used in the clinical treatment of cardiac diseases such as acute myocardial infarction and acute heart failure (151), can modulate ferroptosis and protect the myocardium. These models represent the promotion or inhibition of ferroptosis by drugs and chemical compounds, and provide new therapeutic ideas and targets for intervention. However, they are not supported by clinical data and have not been truly translated into real-world clinical problems. Most research has only demonstrated an effect on ferroptosis in models of LPS-induced cardiomyopathy, and no reliable mechanism or pathway has been identified to date.

Furthermore, the subcellular organelles that drive ferroptosis are also essential in SIC. Some studies have investigated the role of subcellular organelles associated with ferroptosis in sepsis-related organ injuries, such as the lung (152,153). However, to the best of our knowledge, few studies have focused the heart. Therefore, further investigation is warranted.

As research progresses, the mechanisms and therapeutic targets associated with ferroptosis in SIC are being revealed at the genetic level. Therefore, bioinformatics analysis, technology and genomics should be the priority direction for future research. Research on this topic can be more convincing and influential by applying the central law, from transcription and translation of genes to the establishment of animal and cellular models for validation. In conclusion, ferroptosis has broad developmental prospects, and it is expected to be a new approach for treating SIC by precisely manipulating its molecular mechanism.

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Availability of data and materials

Not applicable.

Authors' contributions

DW drafted the manuscript and prepared the figures. XQ revised the manuscript and participated in the design of the figures. ZZ designed the present study and revised the manuscript. GZ designed the present study and revised the manuscript. All authors have read and approved the final manuscript. All authors are responsible for all aspects of the work and approve the submission in its current form. Data authentication is not applicable.

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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