Ferroptosis and its impact on common diseases

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ABSTRACT

Ferroptosis is a novel form of programmed cell death characterized by iron accumulation, lipid peroxidation, and a decline in antioxidant capacity, all of which are regulated by gene expression. The onset of numerous diseases is closely associated with ferroptosis. Common diseases affect a large population, reduce the quality of life, and impose an increased burden on the healthcare system. The role of ferroptosis in common diseases, its therapeutic potential, and even its translation into clinical drug treatments are currently significant research topics worldwide. This study preliminarily explores the theoretical basis of ferroptosis, its mechanism and treatment prospect in common diseases including ischaemia-reperfusion injury, inflammatory bowel diseases, liver fibrosis, acute kidney injury, diabetic kidney disease, stroke, Alzheimer's disease, cardiovascular disease, immune and cancer. This review provides a theoretical foundation for the further study and development of ferroptosis, as well as for the prevention and treatment of common diseases.

Subjects Biochemistry, Cell Biology, Molecular Biology
Keywords Ferroptosis, Mechanism, Inducer, Inhibitor, Treatment

INTRODUCTION

Death is the ultimate fate of all cells. Scholars originally believed that cell death was unregulated until the concept of programmed cell death was raised in the 1960s (*Hirschhorn & Stockwell, 2019*). Unlike non-programmed cell death, which is caused by intense stress (such as severe heat shock, the use of detergents, pore-forming agents, or highly active alkylating agents), programmed cell death refers to a pattern of cell death that relies on specific molecular involvement and can be regulated by specific pharmacological and genetic means (*Galluzzi et al., 2018*). The discovery of programmed cell death patterns has aroused great interest among scholars. Subsequently, researchers found a series of programmed cell death such as autophagy, apoptosis and necroptosis. Unlike previous patterns of cell death, ferroptosis first proposed by *Dixon et al. (2012)* in 2012 is a novel cell death model. It is characterized by excess iron accumulation in the cytoplasm, lipid peroxidation of the cell membrane, mitochondrial morphology, and changes in genes related to ferroptosis. The reactive oxygen species (ROS) initiated ferroptosis include iron-mediated Fenton reactions, mitochondrial ROS, and the NOX protein family-mediated ROS. Polyunsaturated fatty acid (PUFA)-containing phospholipids are the main substrates of lipid peroxidation in ferroptosis, which is active by enzymes, such as

Submitted 6 September 2024
Accepted 23 November 2024
Published 19 December 2024

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Academic editor
Vladimir Uversky

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DOI **10.7717/peerj.18708**

ACSL4, LPCAT3, LOX. The decrease of anti-lipid peroxidation ability of System xc-, glutathione-GPX4 axis, *etc*., is also an important manifestation of ferroptosis (*Liu, Kang & Tang, 2022*). In 2018, the Committee on Cell Death Nomenclature (NCCD) added ferroptosis to the family of programmed cell death (*Galluzzi et al., 2018*). At present, ferroptosis has been found to exist in many common diseases including ischaemia-reperfusion injury, inflammatory bowel diseases, liver fibrosis, acute kidney injury, diabetic kidney disease, stroke, Alzheimer's disease, cardiovascular disease, immune and cancer. This provides insights into the pathogenesis and treatment of common diseases. By reviewing the mechanism and treatment of ferroptosis in common diseases, we aim to summarize the achievements and shortcomings of current ferroptosis research, so as to better guide the direction of future research..

SURVEY METHODOLOGY

We searched related literature by pubmed using the key words (ferroptosis) AND (intestine)/(ferroptosis) AND (liver)/(ferroptosis) AND (kidney)/(ferroptosis) AND (cerebrovascular disease)/(ferroptosis) AND (cardiovascular disease)/(ferroptosis) AND (tumor)/(ferroptosis) AND (neutrophils)/(ferroptosis) AND (B cell)/(ferroptosis) AND (T cell)/(ferroptosis) AND (macrophages). These terms were selected to better capture a view of ferroptosis across different organ systems and immune cell types. However, the articles included only published materials and excludednot research articles or reviews.

Ferroptosis and intestinal disease

Ischaemia-reperfusion (I/R) injury is defined as the paradoxical exacerbation of cellular dysfunction and death, following restoration of blood flow to ischemic tissues. Although, reestablishment of blood flow is essential to salvage ischemic tissues, reperfusion would paradoxically further injury the function and viability of organ (*Sorby-Adams et al., 2024*). Intestinal I/R injury is common in various clinical diseases, such as trauma, hemorrhagic shock, mesenteric ischemia, small intestine torsion and so on. Necrotizing enterocolitis is a common disease in newborns, and I/R injury is an important pathogenesis of this condition (*Klinke et al., 2020*; *Knowles et al., 2021*).

The damage of I/R to the intestinal tract is multifactorial, such as damage to the intestinal mucosal barrier, inflammation, and ectopia of the flora. The damage of intestinal mucosal barrier, inflammation and ectopic flora could start from the death of intestinal epithelial cells. I/R injury can lead to various forms of cell death, including necrosis, apoptosis, and autophagy (*Li et al., 2023c*; *Xi et al., 2024*). In recent years, researchers have found that ferroptosis can also be induced by I/R. Reactive oxygen species (ROS) are highly reactive forms of molecular oxygen, including the superoxide anion radical, hydrogen peroxide, singlet oxygen, and hydroxyl radical (*Sahoo et al., 2022*). During I/R, a large amount of ROS may be produced, and ROS is an important initiation of lipid peroxidation and ferroptosis. Malondialdehyde (MDA) is a product of lipid peroxidation and a marker of ferroptosis (*Qiu et al., 2022*). I/R leads to the increase of ROS and MDA, the decrease of Glutathione (GSH), which protected reactive molecules in living cells against oxidative damage. In addition, I/R damage can increase the iron content of intestinal tissues or cells,

and iron accumulation is also necessary for ferroptosis (*Dong et al., 2021*). *Hu et al. (2018)*, *Ozkan et al. (2009)*, *Stefanutti et al. (2008)*, *Li et al. (2019b)* showed that intestinal I/R could induce ferroptosis in the early stage. They also found that the degree of intestinal damage induced by I/R was improved by the use of the ferroptosis inhibitor liproxstatin-1 (Lip-1). Although it has been reported that lipid peroxidation and iron accumulation are important role of ferroptosis in intestinal I/R injury, the mechanism of ferroptosis still need to be further studied (*Xu et al., 2021*).

Inflammatory bowel diseases (IBDs), which include ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disease of the gastrointestinal tract most diagnosed in adolescence and young adulthood, with an increasing incidence in pediatric populations. However, because its pathogenesis is not clear, the current treatment for IBDs is not effective. *Chen et al. (2020)* found that ferrostain-1 (Fer-1) can alleviate the symptoms of dss induced colitis, and NRF2/HO-1 signaling pathway plays an important role in inhibiting the process of intestinal ferroptosis. In addition, ferroptosis suppressant drugs Lip-1 and deferoxamine (DFO) can also treat dss induced colitis, reduce disease symptoms and increase colon length (*Xu et al., 2020*, *2021*). *Kobayashi et al. (2019)* have found that high iron intake increases the risk of UC, and the use of DFO can reduce ROS production and improve colonic symptoms of UC (*Millar, Rampton & Blake, 2000*; *Minaiyan, Mostaghel & Mahzouni, 2012*). Acyl-CoA synthetase long-chain family member 4 (ACSL4) is an important isozyme for polyunsaturated fatty acids (PUFAs) metabolism that dictates ferroptosis sensitivity (*Cui et al., 2021*). Glutathione peroxidase 4 (GPX4) is a selenoenzyme that uses GSH as a co-factor to regulate lipid peroxidation of cell membranes by eliminating phospholipid hydroperoxides (*Xue et al., 2023*). *Gao, Sun & Kong (2023)* found that vitamin D can improve UC by inhibiting ACSL4 and upregulating GPX4 expression in the ferroptosis pathway. Another exciting discovery is that Curculigoside, naturally occurring compounds can mitigate DSS-induced UC in mice by promoting GPX4 expression in a manner that depends on selenium (*Wang et al., 2020*).

Ferroptosis and liver disease

The liver is an important organ for iron storage and metabolism. Primary and secondary abnormalities in iron levels can affect the normal function of liver cells and liver diseases. *Zhou et al. (2019)* showed that in alcoholic liver disease, fat-specific lipin-1 overexpression accelerates iron accumulation, causes lipid peroxidation, reduces GSH, induces ferroptosis and thus promotes liver injury in mice. Concurrently, adipose lipin-1 overexpression induced defective adiponectin signaling pathways in ethanol-fed mice, including impaired adiponectin-SIRT1 signaling and disrupted adiponectin-FGF15 axis after ethanol administration in mice. Unlike the relatively mild liver damage caused by alcohol, acute liver failure is a clinical critical disease characterized by rapid loss of liver function with high mortality. The common inducing factors in clinic are virus, drug and alcohol. It had been reported that the nonsteroidal anti-inflammatory drug acetaminophen can induce ferroptosis and lead to liver damage, and ferroptosis inhibitors can improve liver cell death (*Lorincz et al., 2015*). *Carlson et al. (2016)* showed that GPX4 content and vitamin E administration could protect liver function. It is suggested that

hepatocyte-specific Gpx4$^{-/-}$ pups were found to die by 48 h due to the lipid peroxidation-mediated cell death. The supplemented vitamin E form gestation period and newborns could protect membranes from oxidative damage, with the decreasing plasma levels of MDA. Ferroptosis inhibitor Lip-1 can improve I/R liver function, suggesting that ferroptosis plays an important role in ischemia-perfusion-related liver diseases (*Chen et al., 2022b*).

Liver fibrosis is a chronic progressive process, and the end-stage can lead to a series of liver dysfunction and cirrhosis symptoms. The persistent liver damage due to infection of chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) is an important cause of liver fibrosis. *Kanda et al. (2019)* found that both HBV and HCV infections change hepcidin levels and other iron-related parameters, which are closely linked to ferroptosis. Liver fibrosis is characterized by excessive accumulation of extracellular matrix (ECM) proteins. ECM secreted by myofibroblasts proteins are mainly transformed from hepatic stellate cells (HSCs). *Sui et al. (2018)* showed that the knockout of HO-1 could inhibit the ferroptosis of liver trait cells, thus aggravating the liver fibrosis process. *Kong, Liu & Cheng (2019)* showed that artesunate alleviated carbon tetrachloride (CCl4)-induced liver fibrosis in mice by promoting the ferritinophagy-mediated ferroptosis pathway of HSCs. Sorafenib, well known for its anti-tumour effect, was also found to exhibit anti-fibrosis effect in liver by inhibiting proliferation and promoting apoptosis of HSCs. Ttransmembrane protein of solute carrier 7A11 (SLC7A11), combined with solute carrier 3A2 (SLC3A2), are the composition unit of system XC- for exchanging extracellular cysteine with intracellular glutamate (*Ma et al., 2021*). After being transported into the cell by system xc−, cystine is oxidizedto cysteine, which is then used for glutamate-cysteine ligase catalytic subunit (GCLC/GCL)-mediated GSH synthesis. Recently, it was observed that sorafenib attenuated liver injury and ECM accumulation in CCl4-induced fibrotic livers *via* HIF-1α/SLC7A11 (*Yuan et al., 2022*). Induction of ferroptosis by RSL3 treatment in HSCs results in decreased glutathione peroxidase 4, glutathione deficiency, reactive oxygen species generation, and lipid peroxidation. Moreover, RSL3 treatment upregulated the expression of plasminogen activator inhibitor-1, a representative fibrogenic marker of HSCs (*Cho et al., 2022*). Regulatory molecules of ferroptosis in HSCs, including p53, ELAV-like protein 1 (ELAVL1), and zinc finger protein 36 (ZFP36), have been reported as promising targets in preventing liver fibrosis (*Chen et al., 2022b*). Another exciting finding is that ginsenoside Rb1 (GRb1), a major active component extracted from *Panax ginseng*, inhibits HSC activation by promoting SLC7A11 expression (*Lin et al., 2024*). On the contrary, however, hepatic iron accumulation and ferroptosis deteriorate liver injury and fibrosis induced by acetaminophen, which can be regressed by ferrostatin-1 (Fer-1) (*Wang et al., 2017*). It seems that ferroptosis play a bidirectional role in the development of liver fibrosis. However, the role and effect of ferroptosis in the early stages of liver fibrosis is unclear. In the future, early prevention of liver fibrosis and even reversal of liver fibrosis may be an important research direction. Ferroportin (Fpn), also known as SLC40A1, is a the only known iron exporter and plays an essential role in iron homeostasis by releasing ferrous ion (Fe2+) from cells (*Jiang et al., 2021a*; *Shen et al., 2023*). In addition, it's worth mentioning that the liver can secrete hepcidin to regulate the level of FPN protein in itself

and other organs (*Collins, Wessling-Resnick & Knutson, 2008*). This suggested that the regulation of ferroptosis may be a multi-system or intercellular process, rather than confined to a single organ or cell.

Ferroptosis and kidney disease

Acute kidney injury (AKI) is commonly seen in clinical conditions such as bleeding, dehydration, postoperative hypoperfusion, sepsis and shock. *Linkermann et al. (2014)* found that the function of kidney injury induced by I/R could be relieved by administration of Fer-1. In renal I/R, the iron accumulation, through the Fenton reaction, may generate a large amount of ROS (also increased by mitochondrial dysfunction and NOX family activity) that can severely enhance intra-cellular oxidative stress and lipid peroxidation (*Granata et al., 2022*). Fer-1 can prevented AKI in lipid levels of ferroptosis, such as the decrease in PE and lyso-sulfatide species, without changing the gene expression of lipid metabolism enzymes (*Martin-Saiz et al., 2022*). It is also suggested that Fer-1 reduce iron content and some critical ferroptosis-related proteins in AKI, such as GPX4, SLC7A11, NRF2, and FTH1 (*Zhao et al., 2023*). *Su et al. (2019)* further demonstrated that ferroptosis inhibitors could also protect cells from hypoxic damage in isolated tubule cells. Ferroptosis suppressor protein 1 (FSP1) and GPX4 are important molecules in the body to play an antioxidant role in resisting ferroptosis. Ferroptosis suppressor protein 1 (FSP1), operating independently of the canonical system xc-/GPX4 pathway, is an NAD(P)H-ubiquinone oxidoreductase that reduces ubiquinone to ubiquinol (*Lee & Roh, 2023*). It has been shown that loss of function of GPX4 or FSP1 proteins can increase susceptibility of mice to ferroptosis during acute kidney injury (*Tonnus et al., 2021*). It is worth mentioning that the damage of renal cell morphology and function is rapid in acute renal injury. In the case of ferroptosis cells, the researchers found that ferroptosis cells could impair the surrounding cells in a lipid peroxide- and iron-dependent manner (*Kim et al., 2016*; *Linkermann et al., 2014*). *Riegman et al. (2020)* showed that the rupture of ferroptostic cells was due to plasma membrane pores, similar to cell lysis in pyroptosis and necroptosis. Ferroptosis inducers can cause transmission of intercellular death, which does not directly depend on GPX4 inhibition. Changes in ferroptosis signaling precede cell rupture, leading to cell swelling and intercellular transmission in a lipid peroxide and iron-dependent manner (*Riegman et al., 2020*). Excitingly, it has shown that acute kidney injury can be mitigated by targeted delivery of vitamin E using nanoparticles, which is related to its strong ability to inhibit ROS production and ferroptosis (*Zhang et al., 2024a*).

Diabetic kidney disease (DKD) is a common chronic complication of diabetes and has become the leading cause of end-stage kidney disease (*Ma et al., 2023*). Diabetic kidney disease has a high global disease burden and the single strongest predictor of mortality in patients with diabetes (*Reidy et al., 2014*). However, existing treatments are less effective and there is still a risk of worsening (*Tuttle et al., 2022*). Current therapeutic regimens, such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), can only alleviate diabetic nephropathy to a certain extent. Based on the huge population of diabetes and may result in heavy financial burden, increase the pathogenesis and treatment of diabetic nephropathy the urgent demand

(*Wang et al., 2023a*). Previous studies have shown that iron overload is directly related to proteinuria and tubule injury in DKD patients and STZ-induced type 1 diabetes rat models (*Dominguez, Liu & Kelly, 2015*; *Howard, Buddington & Alfrey, 1991*). *Matsumoto et al. (2013)* found that limiting iron intake in diabetic mice could delay the development of diabetic nephropathy, indicating that iron overload could aggravate kidney damage in DKD. In addition to iron overload, lipid peroxidation also plays an important role in DKD. In China, *Wang et al. (2022b)* found that GPX4 was mainly expressed in renal tubule interstitium, especially in tubular epithelial cells of patients with diabetic nephropathy. GPX4 decreased significantly in diabetic nephropathy patients, which was strongly associated with worsening renal function in type 2 diabetic nephropathy, including urinary protein, Scr, eGFR, and sclerosed glomerular percentage in renal specimens. In particular, GPX4 levels in the renal tubulointerstitium have been shown to be an independent predictor of renal prognosis (*Wang et al., 2022b*). In addition to the decrease of antioxidant capacity, ROS levels in the kidney will also be significantly increased in diabetic nephropathy due to various NADPH oxidase and mitochondrial dysfunction (*Jha et al., 2016*), thus aggravating the process of lipid peroxidation. In addition to ferroptosis inhibitors like Fer-1 and DFO, many traditional Chinese herb components have a beneficial effect in suppressing ferroptosis in DKD (*Wang et al., 2023a*). Schisandrin A, isolated from the fruits of *Schisandra chinensis*, protect against kidney injury by reducing ROS production, alleviating mitochondrial damage through NRF2/HO-1/GPX4 pathway in HFD/STZ-induced diabetic mice (*Wang et al., 2022a*). Germacrone, the main bioactive component of Rhizoma Curcuma, improve ferroptosis induced kidney injury in mice by the ROS/GSH/GPX4 axis (*Jin et al., 2022*).

Ferroptosis and cerebrovascular disease

Stroke is an acute cerebrovascular syndrome with a high incidence, disability and recurrence rate, especially in elderly patients. Studies have shown that ferroptosis process exists in both ischemic stroke and hemorrhagic stroke (*Cui et al., 2021*; *Karuppagounder et al., 2018*). The severity of ischemic stroke and hemorrhagic stroke can be improved by the use of ferroptosis inhibitors DFO and Fer-1, respectively (*Hanson et al., 2009*; *Zhang et al., 2018*). Ischemic stroke contains ischemia and reperfusion injury (IRI). In ischemic stroke, iron accumulation has emerged after ischemia through inhibiting the expression of tau (*Tuo et al., 2017*). The excess iron would also flow into the brain parenchyma through the interrupted blood brain barrier, boosting the generation of ROS *via* Fenton reaction, ultimately inducing ferroptosis (*Zhang et al., 2021*). Hemorrhagic stroke was defined as a rupture of cerebral vessels that causes blood to flow into subarachnoid space, brain parenchyma, or ventricular system. The blood accumulates and compresses the surrounding brain tissue, causing tissue damage and neuronal death. Hemoglobin (Hb) released from lysed erythrocytes can be taken into microglia and metabolized into ferrous/ferric iron, which induces lethal reactive oxygen species (ROS) and lipid membranes damage (*Li et al., 2017*). In addition, the ferroptosis, including increased iron, the increased iron, MDA and shrunken mitochondria can be found in the early stage (3h) of the hemorrhagic stroke mouse (*Chen et al., 2019a*). Inhibition of ferroptosis exerts a

long-term cerebroprotective effects in the hemorrhagic stroke (*Chen et al., 2019a*). Although hemorrhagic stroke and ischemic stroke have different pathologic processes, there is still crossover in the pathogenesis of ferroptosis. The inactivation of GPX4 plays an important role in both hemorrhagic and ischemic diseases, and supplementation of GSH and selenoprotein plays an important role in the activation and treatment of GPX4 (*Wei, 2024*). The existence of blood-brain barrier is an important factor restricting the effect of stroke treatment. How to improve the efficiency of drugs entering the blood-brain barrier is the key to improve the therapeutic effect. Excitingly, the researchers found that the assembly of recombinant human heavy chain ferritin (rHF) through nanomaterials can improve the efficiency of drug entry into the blood-brain barrier and reduce infarct size by anti-ROS and ferroptosis effect (*Qi et al., 2024*). In hemorrhagic stroke, *Li et al. (2024)* found that Selenium nanoparticles can improve the cognitive deficits and ameliorate the damage of hippocampal by promoting NRF2/GPX4 axis expression neuron.

In addition to Stork, acute cerebrovascular syndrome, cerebrovascular chronic diseases and the resulting damage are also of concern. Alzheimer's disease, which is also common in the elderly, is a progressive neurodegenerative disease of development, characterized by dementia symptoms, including memory impairment and aphasia. Most patients with AD have Aβ amyloid angiopathy, degenerative capillaries changes and ischaemic parenchymal abnormalities. It is suggested that hypoperfusion exists in the early and late stages of Alzheimer's disease (*Love & Miners, 2016*). It is also suggested that ferroptosis exits in Alzheimer's disease (*Lane et al., 2021*). Neurons in forebrain regions (cerebral cortex and hippocampus) are severely afflicted in AD patients, which might be vulnerable to ferroptosis. *Hambright et al. (2017)* generated Gpx4BIKO mouse, a mouse model with conditional deletion in forebrain neurons of Gpx4. It is suggested that Gpx4BIKO mice have significant imperfection in spatial learning and memory function *vs.* control mice as estimated by the Morris water maze task. Further examinations revealed that Gpx4BIKO mice exhibited hippocampal neurodegeneration (*Hambright et al., 2017*). Moreover, *Hambright et al. (2017)* also found Lip-1 can improve Gpx4BIKO mice ameliorated neurodegeneration, while the vitamin E had an expedited rate of hippocampal neurodegeneration and behavior dysfunction. In addition, studies have also found that the hippocampus of Alzheimer's patients is severely damaged and its iron content is significantly elevated, which increases the risk of Fenton reaction in brain tissue (*Lane, Ayton & Bush, 2018*; *Raven et al., 2013*). In recent studies, new therapeutic agents, such as thonningianin A and selenium nanosphere, were also found to improve cognitive function in mice with Alzheimer's disease by promoting GPX4 expression (*Wang et al., 2023b*; *Yong et al., 2024*).

Ferroptosis and cardiovascular disease

Myocardial ischemia is a common disease of the cardiac system. Studies have shown that ferroptosis plays an important role in the onset and progression of myocardial ischemia. Ischemia can lead to the increase of ROS and lipid peroxidation in myocardium (*Hausenloy & Yellon, 2013*). *Fang et al. (2019)* showed that ischemia reperfusion resulted

in the increase of non-heme iron and Fth in the heart, and intervention in the process of ferroptosis could improve cardiac function. *Dabkowski, Williamson & Hollander (2008)* showed that decreased expression of anti-lipid peroxidation protein GPX4 could improve the function of cardiac contraction after ischemia/reperfusion injury. Myocardial infarction is a serious complication of myocardial ischemia. *Park et al. (2019)* showed that ferroptosis process existed in myocardial cells during myocardial infarction. The protein level of GPX4 was significantly down-regulated in the early and middle stages of myocardial infarction by proteomic analysis of the heart tissue in mice that were lapped to simulate myocardial infarction. Toll-like receptor 4(TLR4), a transmembrane receptor, plays a central role in the innate immune response (*Kim et al., 2023*). Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4) is a constitutive enzyme and primarily contributes to the growth in ROS, and exerts an important role in the regulation of oxidative stress and downstream signals (*Li et al., 2023b*). In the process of heart failure, when ferroptosis occurs, TLR4 and NOX4 are up-regulated, and inhibition of TLR4 or NOX4 can reduce cardiomyocyte death through ferroptosis and autophagy (*Chen et al., 2019b*). It is worth mentioning that coenzyme Q10(COQ10), as a clinical drug commonly used to improve myocardial ischemia, has also been found to improve the lipid peroxidation process in ferroptosis (*Awad, Sayed & Banach, 2022*; *Li et al., 2023a*; *Liang, Ping & Ge, 2017*). As a clinical drug, the rationale of the use of CoQ10 in cardiovascular diseases is that the loss of contractile function due to an energy depletion status in the mitochondria and reduced levels of NO for vasodilatation. Clinical evidence shows that CoQ10 supplementation for prolonged periods is safe, well-tolerated. Moreover, CoQ10 supplementation reduces mortality in cardiovascular causes and improves clinical outcome in from and patients undergoing coronary artery bypass graft surgery, including decreased vascular stiffness and hypertension (*Rabanal-Ruiz, Llanos-Gonzalez & Alcain, 2021*). COQ10, existing in oxidized form (ubiquinone) and reduced form (ubiquinol), is a vitamin-like endogenously produced isoprenyl benzoquinone compound. It is an essential part of the mitochondrial respiratory chain and works as a powerful antioxidant by neutralizing free radicals in various membrane structures (*Kuang et al., 2020*). FSP1-CoQ10-NAD(P)H pathway operates independently from the GPX4 pathway, functioning to scavenge lipid radicals by reducing ubiquinone to ubiquinol (*Doll et al., 2019*).

Cardiomyopathy is a type of abnormal mechanical and electrical activity of the heart caused by different causes, which is manifested by improper hypertrophy or dilation of the ventricles. The most common cardiomyopathy were hypertrophic cardiomyopathy and dilated cardiomyopathy. *Fang et al. (2019)* found that the lipid peroxidation pathway in mitochondria mediated ferroptosis plays an important role in cardiomyopathy. The use of mitochondria-targeted antioxidant MitoTEMPO improved doxorubicin (DOX) -induced cardiomyopathy. In addition to heart disease, there is also an ferroptosis process in the process of blood vessel damage. Some cardiovascular risk factors, such as smoking and PM2.5, can damage smooth muscle cells and endothelial cells in blood vessels by inducing ferroptosis (*Sampilvanjil et al., 2020*).

Ferroptosis and immune disease

Ferroptosis broadly regulates immune system function. On the one hand, ferroptosis can affect the function and number of immune cells. On the other hand, ferroptosis cells and their products can be recognized by immune cells, and thus induce an immune response. Macrophages are an important part of innate immunity. Under normal physiological effects, macrophages are an important mechanism for the clearance of senescent red blood cells in the body. *Youssef et al. (2018)* showed that ferroptosis inhibitors could reduce the phagocytosis of macrophages on red blood cells in the spleen. Toll-like Receptor 2 (TLR2) is a protein coding gene that belongs to the Toll-like receptor family and plays a role in pathogen recognition and innate immunity. *Luo et al. (2021)* showed that ferroptostic cells could produce oxidized phosphatidylethanolamine, which was recognized and cleared by TLR2 on macrophages. The polarization function of macrophages is also regulated to some extent by ferroptosis. Neutrophils are another important part of innate immunity. Recruitment of neutrophils in the early stages of inflammation can inhibit infection and clear pathogens. It is shown that ferroptostic cells in heart transplantation can initiate neutrophils recruitment by activating TLR4/Trif signals, thus leading to tissue damage, and further use of ferroptosis inhibitor Fer-1 can inhibit the expansion of inflammation (*Li et al., 2019a*). T cells and B cells are important parts of adaptive immunity. *Muri et al. (2019)* showed that B1 cells and marginal B cells but not follicular B2 cells needed GXP4 to inhibit lipid peroxidation and ferroptosis, and knocking out GPX4 in B1 and marginal B cells caused ferroptosis and IgM antibody response. Similarly, loss of GPX4 expression plays an important role in the induction of ferroptosis in T cells. It is shown that the occurrence of ferroptosis can lead to the failure of CD4+ or CD8+ T cells to expand in the case of acute infection, but the ability to expand can be restored by administering the anti-lipid peroxidation drug vitamin E (*Matsushita et al., 2015*). Infection is an important factor leading to immune cell activation and tissue damage. It is reported that infection can induce ferroptosis. The main ways of infection induced ferroptosis include: (1) transcriptional regulation of the ferroptosis-related proteins, mainly GPX4; (2) control of lipid ROS generations through lipid, iron, and mitochondria metabolism (*Gao et al., 2023*). *Dar et al. (2018)* found that Gram-negative *Pseudomonas aeruginosa* could induce lipid peroxidation and ferroptosis in human lung epithelial cells. Cecal ligation and puncture (CLP) and Lipopolysaccharide (LPS) are methods to make sepsis mouse models and acute tissue injury (*Xu et al., 2018*). Myeloid cell-specific Gpx4-deficient mice are sensitive to LPS or CLP induced septic death with increasing lipid peroxidation (*Kang et al., 2018*). *Chu et al. (2023)* found neutrophils in sepsis-associated acute lung injury accumulation, which is strongly associated with ferroptosis and decrease GPX4. Ferroptosis inhibitors (*e.g.*, Fer-1) prevent CLP or LPS-induced tissue damage (*Li et al., 2020c*; *Wei et al., 2020*). It is worth mentioning that in the non-infectious inflammatory response, the increase of TLR4 level caused by heart failure is closely related to ferroptosis, and inhibition of TLR4 or NOX4 can reduce myocardial cell death through ferroptosis and autophagy (*Chen et al., 2019b*). Although the previously reported results support the important role of ferroptosis

in immune cells and infection, there are still many questions to be solved about the process and mechanism of ferroptosis in immune cells caused by infection.

Ferroptosis and tumor

In many diseases, the existence of ferroptosis aggravates the disease process, and it is necessary to intervene in the process of ferroptosis to inhibit its occurrence. In tumor-related diseases, the effect of ferroptosis on tumor cells is complex and even two-sided. Loss of GPX4 in tumor cells leads to an increase in lipid peroxidation products such as 5-HETE, 11-HETE, and 15-HETE (*Friedmann Angeli et al., 2014*). These lipid peroxidation substances can assist immune cells to detect tumor cells and regulate the activity of immune cells (*Li & Li, 2020*). On the other hand, immune cells can also regulate the ferroptosis of tumor cells. It is reported that CD8+T cells can release the cytokine interferon gamma (IFNγ), which in turn down-regulates the expression of SLC3A2 and SLC7A11. The absence of SLC3A2 and SLC7A11 led to the impairing the uptake of cystine and decrease of GSH synthesis in tumor cells, which in turn reduced the anti-lipid peroxidation effect of GPX4, thus inducing ferroptosis in tumor cells. In fact, clinical studies have shown that the decreased expression of SLC3A2 and the increased IFN-γ in patients treated with anti-tumor drugs can help improve the clinical therapeutic effect (*Wang et al., 2019*). At present, many studies have found that classical anti-tumor drugs can affect the target of ferroptosis pathway and played the role of anti-tumor therapy. Sulfasalazine and sorafenib can affect the content of GSH in tumor cells by inhibiting system xc-, but cannot well inhibit lipid peroxidation during ferroptosis (*Dixon et al., 2014*; *Louandre et al., 2015*; *Sleire et al., 2015*). Lapatinib can induce ferroptosis by inhibiting iron transport in breast cancer cells, thus playing a therapeutic role. In addition to the therapeutic effect, ferroptosis is also deeply involved in the occurrence, development, metastasis and invasion of tumors. Knockout of ACSL4 reduced 17β-estradiol induced migration, proliferation, and invasion of cancer cells, while increasing ACSL4 enhanced tumor growth and proliferation (*Belkaid, Ouellette & Surette, 2017*; *Wu et al., 2015*, *2013*). In mechanism, the silence of ACSL4 decrease the uptake of in arachidonic acid, eicosapentaenoic acid and the activation of Akt/GSK3β/E-cadherin pathway, which is the requisites for migration and invasion capacities. It is exciting to see that nanotechnology and traditional Chinese medicine extract ingredients, such as Formosanin C, can effectively promote iron death and thus improve the treatment of breast cancer (*Chen et al., 2022a*; *Mu et al., 2024*; *Shi et al., 2024*; *Zhang et al., 2024b*). In addition, studies have shown that GPX4 expression can influence tumor cell invasion and metastasis. Overexpression of GPX4 in L929 cells can reduce the metastatic ability of tumor cells, whereas increasing the level of GXP4 in B16BL6 cells can increase the ability of lung metastasis to colonize (*Heirman et al., 2006*). The increase of NRF2 inhibits the increase of vascular cell adhesion molecule-1 (VCAM-1), thereby reducing vascular inhibition and tumor migration (*Banning & Brigelius-Flohe, 2005*). Iron chelating agent and promotion of SLC40A1 expression can reduce the migration of tumor cells (*Guo et al., 2015*; *Wang et al., 2014*).

Induction and treatment of ferroptosis

In 2003, *Dolma et al. (2003)* discovered a new compound, erastin, which has a selective lethal effect on RAS expressing cancer cells. Subsequently, *Yang & Stockwell (2008)* and *Yagoda et al. (2007)* showed that this cell death pattern could be inhibited by iron chelating agent (DFO), while RAS-selective lethal 3 (RSL3), could cause this cell death pattern. Various substances that induce ferroptosis mainly include four categories (*Li et al., 2020a*): (1) Erastin; (2) RSL3 and DPI7; (3) FIN56; (4) FINO2. Erastin is induced mainly by action on GPX4. Erastin can also directly inhibit System Xc-, thus inhibiting cystine import and depriving cells of cysteine, an essential composition of GSH. The lack of GSH inactivate GPX4, leading to phospholipid hydroperoxides (PLOOHs) accumulate, causing damage of plasma membrane, leading to ferroptosis cells (*Jiang, Stockwell & Conrad, 2021b*). Recent studies have also found that Erastin activation of ferroptosis can increase the level of lysosomal associated membrane protein 2a, thereby promoting chaperone protein-mediated autophagy and further promoting GPX4 degradation (*Wu et al., 2019*). Erastin can also induce mitochondrial dysfunction through the volt-dependent anion channels pathway, thus producing the ROS, Fenton reaction, and lipid peroxidation, leading to ferroptosis cells (*Li et al., 2020b*). RSL3 and DPI7 directly inhibit GPX4 activity and induce ferroptosis. FIN56, which has two ways of inducing ferroptosis. On the one hand, FIN56 promotes the degradation of GPX4. Another way of acting, FIN56 binds to squalene synthetase, leading to depletion of endogenous antioxidant COQ10. This process enhances the sensitivity of cells to FIN56-induced iron poisoning (*Liang et al., 2019*). FINO2, an organic peroxide that shares many characteristics with artemisinin, causes iron poisoning due to the combined action of direct oxidation of unstable iron and inactivation of GPX4 (*Liang et al., 2019*). For the treatment of ferroptosis, in addition to the use of iron chelating agents to target the accumulation of iron in cells, there are many inhibitors that target the lipid process in the final stage of ferroptosis, such as Fer-1, Lip-1, and vitamin E.

Issues and prospects

The role of ferroptosis causing pathological cell death associated with I/R injury, IBDs, liver fibrosis, AKI, DKD, stroke, degenerative diseases, cardiovascular disease, immune and cancer is increasingly being recognized. However, the specific role of ferroptosis in disease and its mechanisms are still poorly understood. In tumor, ferroptosis can promote tumor growth and may also promote tumor formation, depending on the type, stage and microenvironment of the tumor (*Kuang et al., 2020*). On the other hand, we noted that during liver fibrosis, the ferroptosis can both promote liver fibrosis and inhibit liver fibrosis, which is related to the specific cell type (*Chen et al., 2022b*). Therefore, focusing on the effects of ferroptosis at different stages of the disease process and on specific cell functions is a very important to provide us with more precise prevention and treatment strategies. Moreover, while GPX4, FSP1, and SLC7A11 are known to play an important role in ferroptosis, the specific mechanism of regulating the change of these molecular at the gene level is still not clear. In addition to the genetic level, the clinical risk factors that induce ferroptosis still need to be further explored. Although iron overload is thought to be

Table 1 Therapeutic targets of ferroptosis in common diseases.

Disease	Model	Key mechanism	Drug	Reference
Ulcerative colitis	*In vivo*	Downregulate NRF2/HO-1, GPX4, FTH1; Upregulate ACSL4;	Inhibitor: Ferrostain-1, Liproxstatin-1, Deferoxamine	*Chen et al. (2020)*
	In vivo/*In vitro*	Downregulate NF-κBp65	Inhibitor: Ferrostain-1	*Xu et al. (2020)*
	In vivo/*In vitro*	Downregulate GPX4	Inhibitor: Curculigoside Ferrostain-1	*Wang et al. (2020)*
	In vivo/*In vitro*	Upregulate ACSL4; Downregulate GPX4	Inhibitor: Vitamin D	*Gao, Sun & Kong (2023)*
	In vivo/*In vitro*	Downregulate GPX4	Inhibitor: Curculigoside	*Wang et al. (2020)*
Acute liver failure	*In vivo*	Downregulate GPX4	Inhibitor: Vitamin E	*Xue et al. (2023)*
I/R Liver	*In vivo*	Upregulate ACSL4	Inhibitor: Liproxstatin-1	*Rokop et al. (2024)*
Liver fibrosis	*In vivo*	Downregulate HO-1	—	*Sui et al. (2018)*
	In vivo/*In vitro*	Downregulate HIF-1α/SLC7A11	Inducer: Sorafenib	*Yuan et al. (2022)*
	In vitro	Downregulate GPX4	Inducer: RSL3, Erastin	*Cho et al. (2022)*
	In vivo	Downregulate SLC7A11	Inhibitor: Ferrostatin-1; Inducers: iron	*Wang et al. (2017)*
	In vivo/*In vitro*	Downregulate SLC7A11	Inhibitor: Ginsenoside Rb1	*Lin et al. (2024)*
Acute kidney injury	*In vivo*	Imbalance of lipid composition and gene expression of lipid metabolism enzymes	Inhibitor: Ferrostatin-1	*Martin-Saiz et al. (2022)*
	In vivo/*In vitro*	Downregulate GPX4, SLC7A11, NRF2, FTH1	Inhibitor: Ferrostatin-1	*Zhao et al. (2023)*
	In vivo/*In vitro*	Downregulate GPX4, FSP1	Inhibitor: Ferrostatin-1 Nec-1f	*Tonnus et al. (2021)*
	In vivo/*In vitro*	Upregulate ROS	Inhibitor: Vitamin E nanoparticles	*Zhang et al. (2024a)*
Diabetic kidney disease	*In vivo*	Downregulate NRF2/HO-1/GPX4	Inhibitor: Schisandrin A	*Wang et al. (2022a)*
	In vivo	Downregulate GPX4	Inhibitor: Germacrone	*Jin et al. (2022)*
	In vivo/*In vitro*	Downregulate NRF2,SLC7A11, GPX4	Inhibitor: Ferroastatin-1	*Kim et al. (2021)*
	In vitro	Downregulate GPX4,FTH1, SLC7A11	Inhibitor: Deferoxamine	*Huang et al. (2022)*

Table 1 (continued)

Disease	Model	Key mechanism	Drug	Reference
Ischemic stroke	*In vivo*	Iron accumulation	Inhibitor: Deferoxamine	*Hanson et al. (2009)*
	In vivo	Downregulate Tau, Iron accumulation	Inhibitor: Liproxstatin-1, Ferrostatin-1	*Tuo et al. (2017)*
	In vivo/*In vitro*	Upregulate ROS	Inhibitor: Recombinant human heavy chain ferritin nanoparticles	*Qi et al. (2024)*
Hemorrhagic stroke	*In vivo*	Downregulate GPX4	Inhibitor: Ferrostatin-1	*Zhang et al. (2018)*
	In vivo/*In vitro*	Downregulate NRF2/GPX4	Inhibitor: Selenium nanoparticles	*Li et al. (2024)*
	In vivo	Downregulate cyclooxygenase-2	Inhibitor: Ferrostatin-1	*Li et al. (2017)*
Ischemic stroke and Hemorrhagic stroke	*In vitro*	Downregulate GPX4	Inhibitor: GSH, Selenoprotein	*Wei (2024)*
Alzheimer's disease	*In vivo*	Downregulate GPX4	Inhibitor: Liproxstatin-1 Inducer: Vitamin E	*Hambright et al. (2017)*
	In vivo/*In vitro*	Downregulate GPX4	Inhibitor: selenium nanosphere	*Wang et al. (2023b)*
	In vivo/*In vitro*	Downregulate GPX4	Inhibitor: Thonningianin A	*Yong et al. (2024)*
Myocardial infarction	*In vivo*/*In vitro*	Downregulate GPX4	Inhibitor: Liproxstatin-1 Ferrostatin-1 Inducer: RSL3	*Park et al. (2019)*
Myocardial ischemia	*In vivo*/*In vitro*	Upregulate ROS/AMPK/mTOR	Inhibitor: Idebenone (CoQ10 analog)	*Li et al. (2023a)*
I/R heart	*In vitro*	Downregulate antioxidative stress	Inhibitor: COQ10	*Awad, Sayed & Banach (2022)*, *Liang, Ping & Ge (2017)*
	In vivo	Downregulate GPX4	—	*Dabkowski, Williamson & Hollander (2008)*
Heart failure	*In vivo*/*In vitro*	Downregulate SLC7A11	Inhibitor: Liproxstatin-1 Inducers: Erastin	*Ma et al. (2020)*
	In vivo	Upregulate TLR4, NOX4; Downregulate GPX4, FTH1	—	*Chen et al. (2019b)*
Cardiomyopathy	*In vivo*	Upregulate NRF2, HO-1	Inhibitors: MitoTEMPO, Zinc protoporphyrin IX, Ferrostatin-1, Deferoxamine	*Fang et al. (2019)*

(Continued)

Table 1 (continued)

Disease	Model	Key mechanism	Drug	Reference
Aortic aneurysm and dissection	*In vivo*/*In vitro*	Downregulate GPX4; Upregulate Ptgs2	Inducer: Cigarette, RSL3 Inhibitor: Liproxstatin-1, Ferrostatin-1, Deferoxamine	*Sampilvanjil et al. (2020)*
Sepsis	*In vitro*	Downregulate GPX4	Inducer: RSL3 Inhibitor: Irisin	*Wei et al. (2020)*
	In vivo/*In vitro*	Upregulate NCOA4, Ferritinophagy	Inhibitor: Ferrostatin-1	*Li et al. (2020c)*
Fibrosarcoma	*In vitro*	Downregulate SLC3A2, SLC7A11	Inducer: RSL3, Erastin Inhibitor: Nivolumab, Liproxstatin-1	*Wang et al. (2019)*
Fibrosarcoma, Prostate cancer	*In vitro*	Downregulate SLC7A11	Inducer: Sorafenib, Erastin	*Dixon et al. (2014)*
Glioblastomas	*In vivo*/*In vitro*	Downregulate SLC7A11	Inducer: Sulfasalazine	*Sleire et al. (2015)*
Breast cancer	*In vitro*	Upregulate FPN	Inducer: Lapatinib	*Ma et al. (2016)*
	In vitro	Downregulate ACSL4	Inducer: 17β-estradiol	*Belkaid, Ouellette & Surette (2017)*
	In vitro	Upregulate GSH/GPX4	Inducer: GSH-depleted photodynamic nanoadjuvant	*Shi et al. (2024)*
	In vivo/*In vitro*	Downregulate ROS	Inducer: Mitochondria-targeted nanoreactor (Ce3+, EGCG and IR780)	*Mu et al. (2024)*
	In vitro	Upregulate SlC7A11, FPN; Downregulate Ferritinophagy	Inducer: Formosanin C	*Chen et al. (2022a)*

the key factor to trigger ferroptosis, whether other metal ions are involved in ferroptosis remains unclear, as the latest researchhas revealed that copper and calcium may be also associated with the initiation of ferroptosis (*Maher et al., 2018*; *Xue et al., 2023*).

Another unresolved important issue is that whether there is a synergistic or antagonistic effect of ferroptosis with other modes of cell death. It has been shown that ferroptosis, autophagy,and apoptosis will occur together in neuronal death after ICH *via* ultrastructural analysis (*Zhang et al., 2021*). In the ATG5-ATG7-NCOA4 pathway, the process of ferritin-associated autophagy that is mediated by NCOA4 can increase the content of unstable iron in cells, thus promoting ferroptosis (*Li et al., 2020a*). These results suggest that ferroptosis can coexist with other forms of cell death, and that other forms of cell death have an effect on ferroptosis.

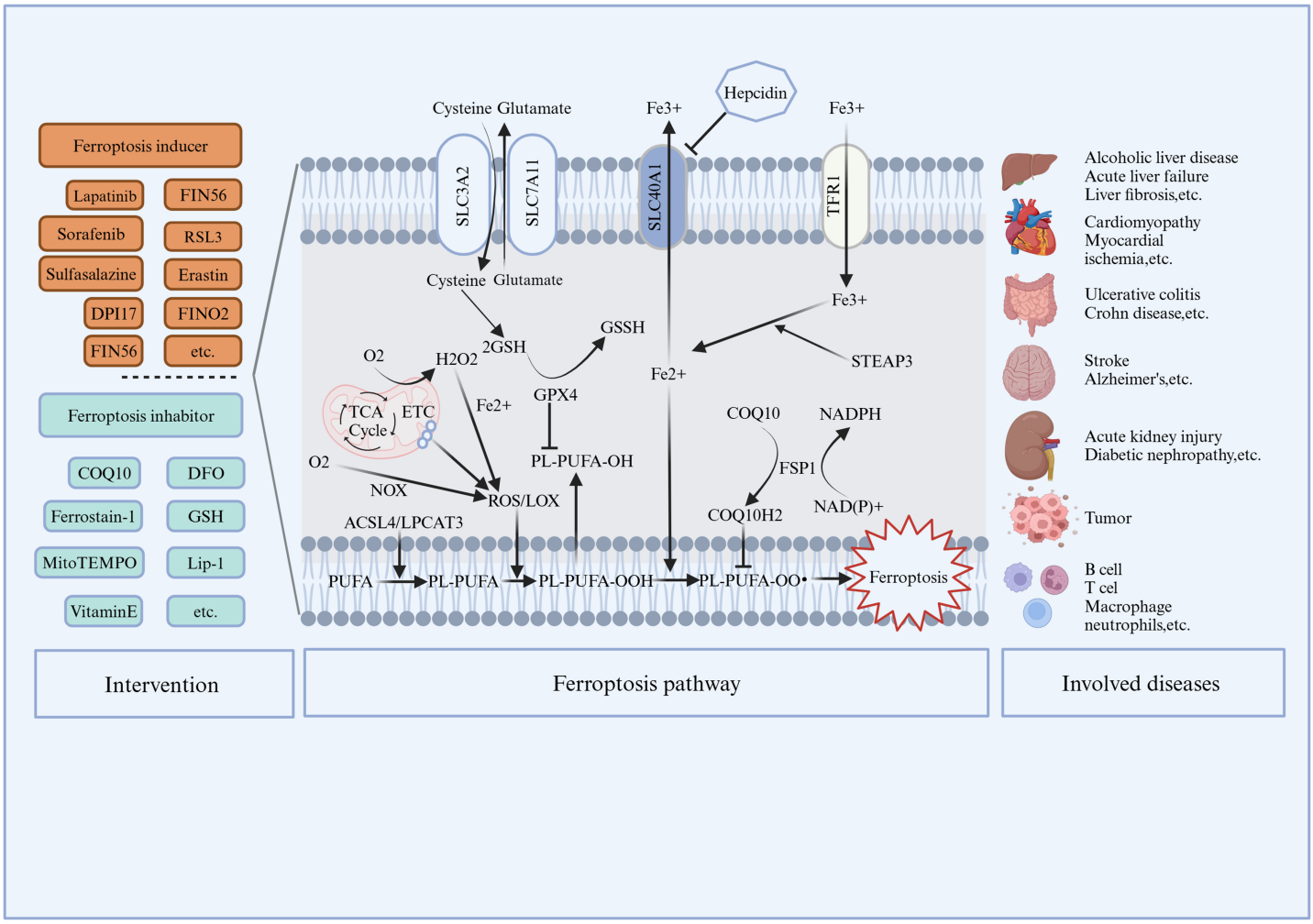

Figure 1 **Intervention, mechanism and related diseases of ferroptosis.** Full-size DOI: 10.7717/peerj.18708/fig-1

The discovery and proposal of ferroptosis greatly promoted the understanding and research of programmed cell death. Firstly, description of ferroptosis as a unique cell death modality brings together into a cohesive network previously disparate elements of cell metabolism, involving iron, selenium, amino acids, lipids and redox chemistry (*Jiang, Stockwell & Conrad, 2021b*). In addition, since the introduction and identification in 2012, there has been a rapid increase in the number and results of studies on ferroptosis. In addition to the classical system xc−(SLC7A11/SLC3A2) and GPX4/GSH pathways, we have successively discovered FSP1/COQ10 and GCH1/BH4 pathways. In terms of drug therapy, unlike Fer-1, Lip-1 used to treat drugs in animals, some metabolites in the new target, such as GSH and COQ10, have been safely applied clinically, which provides a theoretical basis for the new application of old drugs. A successful example is that researchers found that Bitopertin originally developed to treat schizophrenia successfully treat osteoporosis by inhibiting the ferroptosis pathway and with fewer side effects (*Dong et al., 2024*). We summarized preliminarily summarized ferroptosis and disease (Table 1). Further, for more accurate treatment, the researchers proposed to design

developing nanoparticles to target ferroptosis from multiple levels (*Sun et al., 2023*). Thus, as our increasing understanding of ferroptosis regulatory pathways such as iron metabolism, lipid metabolism and new drug targets, ferroptosis may provide new opportunities for the treatment of many currently incurable diseases.

CONCLUSION

In summary, ferroptosis, as a new programmed cell death mode, plays an important role in the occurrence and development of a wide range of diseases (*e.g.*, Ischaemia-Reperfusion injury, liver fibrosis, neurodegenerative diseases, cancer, *etc.*) (Fig. 1). The targets of iron metabolism, lipid peroxidation and key pathways during ferroptosis provide new ideas for disease occurrence and treatment. To explore the role and specific mechanism of ferroptosis pathway in various stages of disease has revolutionize clinical significance to change the treatment strategy and curative effect of existing diseases. Further research on ferroptosis drugs and their clinical transformation may be important research directions in the future.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

The authors received no funding for this work.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Pengjian Zou performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
- Qiuming He performed the experiments, authored or reviewed drafts of the article, and approved the final draft.
- Huimin Xia analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
- Wei Zhong conceived and designed the experiments, authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a literature review.

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