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REVIEW

Zooming in and out of ferroptosis in human disease

Xue Wang[1,2,*], Ye Zhou[3,*], Junxia Min (✉)[1], Fudi Wang (✉)[1,2]

[1]The Second Affiliated Hospital, The First Affiliated Hospital, Institute of Translational Medicine, School of Public Health, State Key Laboratory of Experimental Hematology, Zhejiang University School of Medicine, Hangzhou 310058, China; [2]The First Affiliated Hospital, Basic Medical Sciences, School of Public Health, Hengyang Medical School, University of South China, Hengyang 421001, China; [3]Department of Endocrinology and Metabolism, Ningbo First Hospital, Ningbo 315000, China

Abstract **Ferroptosis is defined as an iron-dependent regulated form of cell death driven by lipid peroxidation. In the past decade, it has been implicated in the pathogenesis of various diseases that together involve almost every organ of the body, including various cancers, neurodegenerative diseases, cardiovascular diseases, lung diseases, liver diseases, kidney diseases, endocrine metabolic diseases, iron-overload-related diseases, orthopedic diseases and autoimmune diseases. Understanding the underlying molecular mechanisms of ferroptosis and its regulatory pathways could provide additional strategies for the management of these disease conditions. Indeed, there are an expanding number of studies suggesting that ferroptosis serves as a bona-fide target for the prevention and treatment of these diseases in relevant pre-clinical models. In this review, we summarize the progress in the research into ferroptosis and its regulatory mechanisms in human disease, while providing evidence in support of ferroptosis as a target for the treatment of these diseases. We also discuss our perspectives on the future directions in the targeting of ferroptosis in human disease.**

Keywords ferroptosis; human disease; iron metabolism; lipid peroxidation; antioxidation

Introduction

Cell death has been implicated in the pathogenesis of many diseases that constitute the leading causes of death and disability worldwide. Unlike unregulated cell death, programmed cell death, such as apoptosis, necroptosis, pyroptosis and autophagy, involves a tightly regulated signal cascade and a molecular-defined effect mechanism, which has unique morphological and biochemical characteristics.

Ferroptosis is driven by iron-dependent lethal lipid peroxidation, which can be suppressed by blocking lipid peroxidation or through depleting iron, and thus meets the criteria for programmed cell death [1]. This type of cell death was first reported in RAS mutant tumor cells, which were sensitive to the small molecule erastin, an inhibitor of solute carrier family 7A member 11 subunit (SLC7A11) [1]. The occurrence of this type of cell death requires the production of iron-induced reactive oxygen species (ROS), but does not depend on the activation of the caspase protease family or need ATP. A further study reported that iron chelating agent deferoxamine (DFO) can effectively inhibit this type of cell death [2].

Importantly, ferroptosis has been increasingly considered to mediate the pathogenesis and development of multiple diseases, and, thus, it could be a potential target for clinical translation for therapy. In this review, we summarize the mechanisms involved in the regulation of lipid peroxidation, the antioxidation system, and iron metabolism that together contribute to ferroptosis. We also review the current knowledge regarding the role of ferroptosis in various diseases, including cancers, neurodegenerative diseases, cardiovascular diseases, lung diseases, liver diseases, kidney diseases, endocrine metabolic diseases, iron-overload diseases, orthopedic diseases and autoimmune-mediated diseases (Fig. 1). We also provide critical perspectives on the potential of targeting ferroptosis as a new clinical therapy.

Ferroptosis and its characteristics

Ferroptosis differs from those of other known forms of programed cell death in terms of its morphological and

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Correspondence: Fudi Wang, fwang@zju.edu.cn;
Junxia Min, junxiamin@zju.edu.cn

*These authors contributed equally.

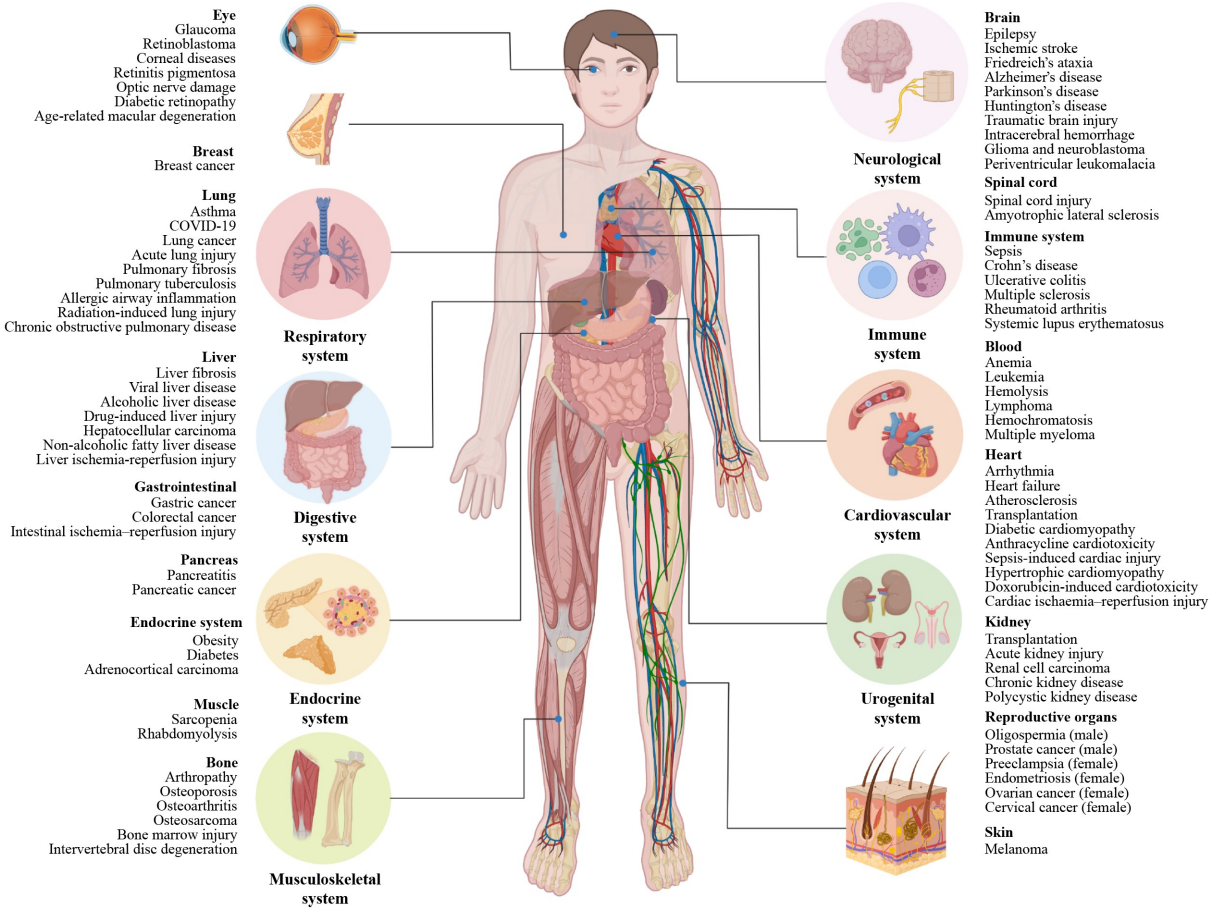

Fig. 1 The relationship between ferroptosis and various diseases. Ferroptosis is implicated in the regulation of multiple systemic diseases, including cancers, neurological diseases, cardiovascular diseases, respiratory diseases, liver diseases, digestive system diseases, urogenital system diseases, endocrine system diseases, iron overload diseases, musculoskeletal system diseases and autoimmune system diseases, and diseases of the visual system.

physiologic characteristics [3]. In general, mitochondria in cells that are undergoing ferroptosis exhibit a shrunken and abnormal change in their morphology, including decreased cristae, dissipated membrane potential and increased permeability [2,4]. Under ferroptotic stress, cells become rounded and swollen, followed by cell rupture with chromatin condensation and intact nuclei [5]. Notably, ferroptosis can propagate rapidly through cell populations in a wave-like manner [6], and the pathways involved in lipid metabolism, glutathione synthesis and iron metabolism converge to control the initiation and execution of ferroptosis. During ferroptosis, specific lipids localized to membranes undergo peroxidation, while simultaneously the endogenous antioxidation system becomes compromised. Characteristically, iron can regulate ferroptosis sensitivity.

In the following sections, we summarize the mechanisms that mediate ferroptosis, including lipid peroxidation, the antioxidation system, and iron regulation (Fig. 2).

The peroxidation of membrane lipids drives ferroptosis

Specific lipids for ferroptosis

Ferroptosis is ultimately driven by the peroxidation of membrane lipids (phospholipids (PLs), ether lipids, and other glycerol-derived lipids). The susceptibility of a membrane lipid to peroxidation depends on the strength of its C–H bonds. Membrane lipids that contain polyunsaturated fatty acids (PUFAs), but not monounsaturated fatty acids (MUFAs) or saturated fatty acids (SFAs), can exert lethal effects upon peroxidation, as there are extremely weak C–H bonds between adjacent C=C double bonds in PUFAs. Among these PUFAs, the number of bisallylic groups also determines the susceptibility of PUFAs to peroxidation. Usually, PUFAs having two bisallylic groups, such as arachidonic acid (AA, 20:4), are preferentially oxidized than those only having a single bisallylic group, such as linoleic acid (LA, 18:2) [7]. In contrast, MUFAs have been demonstrated to

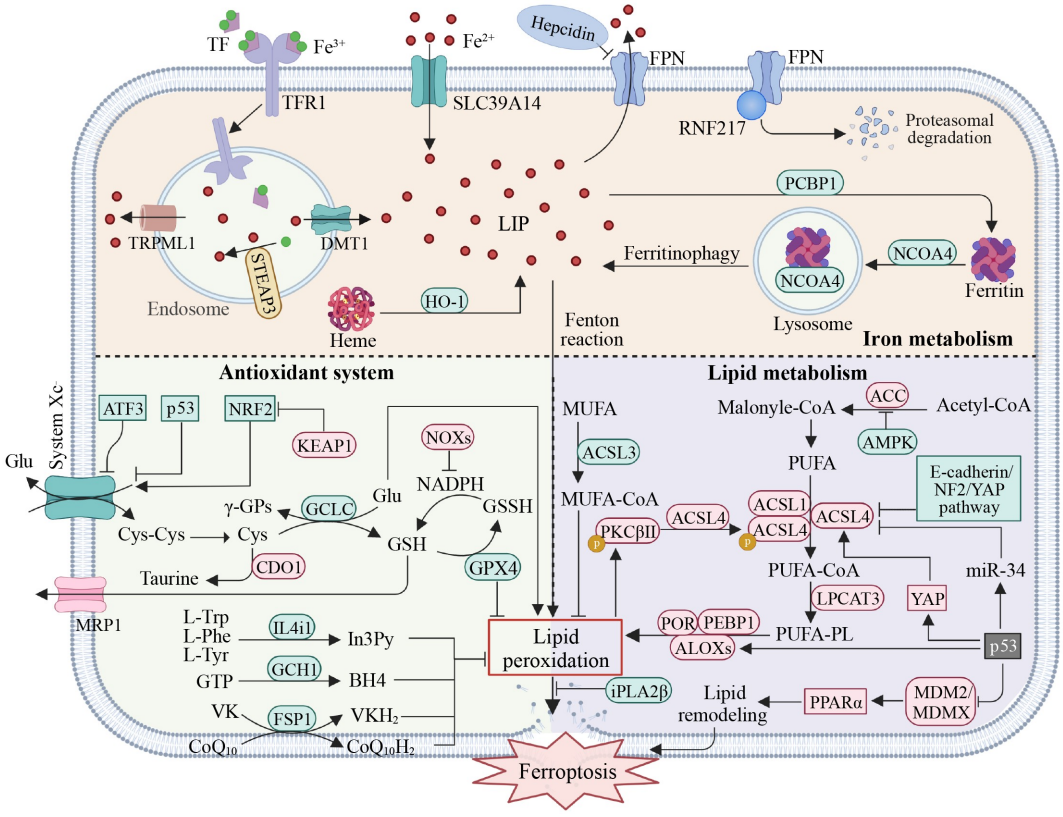

Fig. 2 The molecular mechanisms of ferroptosis. The metabolic pathways that mediate ferroptosis mainly include iron metabolism, the antioxidant system and lipid metabolism. Iron metabolism: non-heme iron binds to TF and is released into the cytoplasm by TFR1 and can also be transported into cells through non-TF-bound iron uptake mediated by metal transporter SLC39A14. The metalloreductase STEAP3 reduces Fe^{3+} to Fe^{2+} in endosomes. Iron can be released from TF and exported to the cytoplasm by DMT1 or TRPML1. Heme releases iron under the catalyzed degradation of HO-1. Ferritin also releases a large amount of iron by ferritinophagy mediated by NCOA4. Further, hepcidin inhibits FPN to reduce the release of iron from the cell. Together, these processes can increase the LIP, thereby sensitizing cells to ferroptosis via the Fenton reaction. Antioxidant system: this pathway mainly involves the cysteine-GSH-GPX4 axis and FSP1-CoQ_{10} axis. Cystine is transported into the cell via system Xc^-, and promotes the synthesis of GSH. Coenzyme Q_{10} and VK can be reduced to $CoQ_{10}H_2$ and VKH_2, respectively, by FSP1, inhibiting lipid peroxidation by trapping lipid peroxidation free radicals. Lipid metabolism: MUFAs incorporate into phospholipids in an ACSL3-dependent manner to inhibit lipid peroxidation. PUFAs are metabolized by ACSL4/ACSL1, and LPCAT and then oxidized by PEBP1, POR, and ALOXs to promote lipid peroxidation and ferroptosis. In addition, PKCβII senses initial lipid peroxidation events and phosphorylates ACSL4 to drive pACSL4 activation to promote PUFA incorporation into PLs. Abbreviations: TF, transferrin; TFR1, transferrin receptor protein 1; SLC39A14, solute carrier family 39 member 14; TRPML1, transient receptor potential mucolipin 1; DMT1, divalent metal transporter 1; LIP, labile iron pool; NCOA4, nuclear receptor coactivator 4; FPN, ferroportin; GSH, glutathione; GTP, guanosine triphosphate; BH4, tetrahydrobiopterin; VKH_2, vitamin K hydroquinone; GCLC, glutamate-cysteine ligase catalytic subunit; GPX4, glutathione peroxidase 4; IL4i1, interleukin-4-induced-1; GCH1, GTP cyclohydrolase-1; FSP1, ferroptosis suppressor protein 1; MRP1, multidrug resistance protein 1; ACC, acetyl CoA carboxylase; AMPK, adenosine-monophosphate-activated protein kinase; PUFA-PL, polyunsaturated fatty acid-containing phospholipid; LPCAT3, lysophosphatidylcholine acyltransferase 3; ACSL, acyl-CoA synthetase long-chain family; ALOXs, arachidonate lipoxygenases; POR, P450 oxidoreductase; PKCβII, protein kinase C beta type isoform 2; MUFA, monounsaturated fatty acid; PEBP1, phosphatidylethanolamine-binding protein 1; iPLA2β, group VI calcium-independent phospholipase A2β.

limit lipid peroxidation of membrane lipid and thus block ferroptosis [8], although the underlying mechanism remains unclear.

In addition, the species of a membrane lipid also determines its susceptibility to peroxidation. For example, specific phosphatidylethanolamines (PEs) preferentially promote ferroptosis compared to other PLs [7]. Studies have further shown that ether lipids promote ferroptosis in cancer cells [9], but play a protective role in *C. elegans* [10]. The differences in ether lipid composition of *C. elegans* and mammals might explain these contrasting findings. Interestingly, the synthesis of plasmalogens, a subclass of ether lipids, suppresses ferroptosis [11].

Sphingolipids are important components of cellular membranes. A few studies have shown a correlation between sphingolipids and ferroptosis. Inhibition of sphingolipid synthesis significantly decreases erastin- or glutamate-induced ferroptosis in hippocampal neuronal

cells [12]. Moreover, the generation of ceramide, a type of sphingolipid, is required for acid sphingomyelinase-mediated ferroptosis in cancer cells [13].

Cholesterol is another essential lipid component of mammalian membranes and is susceptible to peroxidation [14]. Inhibition of the synthesis of cholesterol protects cancer cells from ferroptosis [15]. Moreover, cholesterol and its metabolites can act as signaling molecules regulating the uptake of fatty acids that induce lipid peroxidation and ferroptosis in cancer cells [16]. All these results indicate that cholesterol content is positively correlated with ferroptosis.

Key modulators responsible for lipid remodeling in ferroptosis

ACSL4 and LPCAT3

Free PUFAs are not drivers of ferroptosis, but rather they rely on the catalytic activity of acylcoenzyme A (CoA) synthetase long-chain family member 4 (ACSL4) and lysophospholipid CoA acyltransferase 3 (LPCAT3) for their metabolism and incorporation into membrane-localized lipids, which can undergo oxidation [17]. In particular, ACSL4 attaches the long-chain PUFA to CoA, and then LPCAT catalyzes the esterification of fatty coenzyme A to the SN2 position of lysophospholipids to produce PLs. In addition to its catalytic activity, ACSL4 also participates in a feed-forward loop to execute ferroptosis. Notably protein kinase C beta type isoform 2 (PKCβII) senses initial lipid peroxides and amplifies lipid peroxidation through the phosphorylation and activation of ACSL4, leading to the incorporation of PUFAs into PLs, which drives ferroptosis [18]. Moreover, ACSL4 is also a point of regulation in ferroptosis via neurofibromin 2-yes-associated protein 1 (NF2-YAP) signaling pathways in response to intercellular interactions [19]. Similarly, another ACSL enzyme, ACSL1, is required for exerting the pro-ferroptotic activity of conjugated linolenic acids, such as α-eleostearic acid, in some plants [20].

Notably, it has been shown that LPCAT3 deficiency leads to a dramatic decrease in membrane AA levels during ferroptosis [21]. RAS-selective lethal 3 (RSL3) is a chemical inhibitor of GPX4, and thus can promote ferroptosis. However, knockdown or knockout of LPCAT3 protects mouse lung epithelial cells and mouse embryonic cells from RSL3-induced ferroptosis, which shows the important role of LPCAT3 in ferroptosis [7,17].

p53

The tumor suppressor protein p53 is a key transcription factor contributing to lipid remodeling in ferroptosis. One study has shown that mouse double minute 2 homolog (MDM2), and its homolog MDMX, are negative regulators of p53 and amplify ferroptosis through peroxisome proliferator-activated receptor alpha (PPARα)–mediated lipid remodeling [22]. Further, p53 promotes the expression of microRNA-34 (miR-34), which post-transcriptionally downregulates ACSL4 levels [23,24], and thus may repress ferroptosis by limiting lipid peroxidation substrates. Nevertheless, other studies have claimed that p53 upregulates ACSL4 levels [25,26]. The exact roles of ACSL4 in p53-mediated ferroptosis need more investigation. In addition to regulating lipid remodeling, another important role of p53 is inhibiting SLC7A11 expression and therefore regulating cystine metabolism, the antioxidation system, and ferroptosis [27].

Other important genes

There are also other genes that inhibit ferroptosis by remodeling of lipids. For example, in contrast to ACSL4 and ACSL1, ACSL3 exerts anti-ferroptotic effects by participating in the synthesis of MUFAs [8]. In addition, Group VI calcium-independent phospholipase A2 β (iPLA2β) suppresses p53-driven ferroptosis by removing oxidized PUFA tails from PLs [28]. Moreover, limiting PUFA biosynthesis through activation of adenosine-monophosphate-activated protein kinase (AMPK) and its control of acetyl CoA carboxylase (ACC) inhibits ferroptosis [29].

Key sites of lipid peroxidation in ferroptosis: the endoplasmic reticulum (ER) and the plasma membrane

Ferroptosis is defined as the peroxidation of membrane PLs. Imaging of the localization of inhibitors of ferroptosis revealed that these compounds accumulate in lysosomes, mitochondria, and the ER [30]. However, the functional relevance of lysosomes and mitochondria to ferroptosis suppression indicated that neither is required for inhibiting ferroptosis, suggesting that suppressing lipid peroxidation in the ER is sufficient to block ferroptosis. The larger volume of the ER compared to other organelles supports the notion that the ER is the most critical site of lipid peroxidation during ferroptosis [31,32].

Plasma membrane lipid peroxidation is an essential late step in ferroptosis. As is common in other types of cell death, the end stage of ferroptosis involves permeabilization of the plasma membrane. In this process, the activation of the ESCRT III complex repairs damage to the plasma membrane and protects cells from ferroptosis [33].

Reduced oxidized lipids are anti-ferroptotic

The role of the GPX4 system in inhibiting lipid peroxidation in ferroptosis

For ferroptosis to occur natural mechanisms for blocking the accumulation of oxidized lipids must become compromised. Therefore, the intracellular reducing power of cells via their antioxidant enzymes are particularly important for them to resist ferroptosis. The GPX (phospholipid hydroperoxide glutathione peroxidase, PHGPx) system is a central inhibitor of ferroptosis and is mainly composed of GPX4, glutathione (GSH), and the xCT system. Among these, GPX4 is an important antioxidant enzyme as it can directly reduce phospholipid hydroperoxide. Its catalytic reaction requires the use of reduced GSH, a tripeptide composed of glutamate, cysteine, and glycine, as a hydrogen donor to convert hydroperoxide into water ($2GSH + H_2O_2 \rightarrow GSSH+2H_2O$) and can also reduce many toxic organic hydroperoxides (ROOH) to non-toxic hydroxyl compounds (ROH, $2GSH + ROOH \rightarrow GSSH + 2ROH$). The xCT system (the cystine-glutamate antiporter) consists of SLC7A11 and the SLC3A2 subunit (also known as 4F2HC), which exports intracellular glutamate and imports extracellular cystine at a 1:1 ratio. The newly imported cystine is then converted to cysteine in the cytosol via an NADPH-consuming reduction reaction [34]. Perturbed cystine absorbance decreases downstream GSH biosynthesis, thus diminishing GPX4's ability to antagonize ferroptosis. Erastin and RSL3 are small molecule chemical inhibitors of the GPX4 system as they inhibit the xCT system and GPX4 activity, respectively. Some transcription factors, such as p53, can repress *SLC7A11* transcription, thereby promoting ferroptosis [27]. The cAMP-dependent transcription factor ATF3 has also been shown to promote ferroptosis by binding to the *SLC7A11* promoter to repress its expression in a p53-independent manner [35]. Conversely, the transcription factor NRF2 can positively regulate the expression of *SLC7A11* [36]. Both the genetic deletion of *NRF2* and overexpression of Kelch-like ECH-associated protein 1 (KEAP1, which binds to and facilitates the ubiquitination and proteasomal degradation of NRF2) have been shown to promote ferroptosis in cancer cells [37].

In addition to perturbing the uptake of cystine by inhibiting SLC7A11 to reduce GSH, high levels of multidrug resistance protein 1 (MRP1)-mediated GSH efflux can increase sensitivity to ferroptosis in cancer cells [38]. Also, high levels of cystine dioxygenase 1 (CDO1) leads to a depletion of cystine and, in turn, GSH, which drives sensitivity to ferroptosis [39]. In contrast, glutamate (Glu)-cys ligase (GCLC) inhibits ferroptosis by synthesizing GSH, but it also acts in a glutathione-independent, non-canonical manner by promoting the conversion of Glu, a ferroptosis inducer, to γ-glutamylpeptides [40]. One recent study reports that $NADPH^+$-dependent malic enzyme 1 (ME1) inhibits ferroptosis via mediating the production of NADPH [41].

In addition to the inhibition of GPX4 enzymatic activity to promote ferroptosis, a study screened for caspase-independent lethal compounds and found that a compound termed ferroptosis-inducer-56 (FIN56) induces GPX4 degradation to drive increased sensitivity to ferroptosis [42]. Also, the degradation of GPX4 can be promoted by chaperone-mediated autophagy to induce ferroptosis [43].

The role of the CoQ_{10} system in reducing lipid peroxidation in ferroptosis

In addition to the GPX4 system, there are other GPX4-independent systems that suppress ferroptosis. Ubiquinone-10 (CoQ_{10}) has a crucial electron-carrying role in mitochondrial energy production. Reduced CoQ_{10} acts as a lipophilic radical-trapping antioxidant that halts the propagation of lipid peroxides, causing the oxidation of CoQ_{10} and the protection against lipid peroxidation and, thus, ferroptosis. A recent study found that a reduced form of vitamin K (VKH_2) is another quinone different from CoQ_{10} that inhibits ferroptosis by inhibiting lipid peroxidation [44].

Some mitochondria enzymes play an important role in CoQ_{10} and VKH_2 synthesis, thereby playing a role in ferroptosis progression. The mitochondria protein ferroptosis suppressor protein 1 (FSP1) is recruited to the plasma membrane where it functions to regenerate the reduced form of CoQ_{10} and VKH_2 through the use of NADPH, therefore mediating resistance to ferroptosis [44–46]. Dihydroorotate dehydrogenase (DHODH), a mitochondrial protein located in the inner membrane, acts analogously to the function of FSP1 in the extramitochondrial membranes to generate reduced mitochondrial CoQ_{10} [47]. Cells with high expression of DHODH are more resistant to ferroptosis, while those with a low expression are more sensitive to ferroptosis. Therefore, DHODH is a mitochondrial suppressor of ferroptosis.

GTP cyclohydrolase-1 (GCH1) is the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis [48]. A study found that GCH1 overexpressing cells show a significant enrichment in reduced CoQ_{10} levels after treatment with an inducer of ferroptosis, which possibly contributes to the protection of these cells from ferroptosis [49]. This elevation of CoQ_{10} levels could be the result of the increased BH4 in the cells, which converts phenylalanine into tyrosine that can be further converted to 4-OH-benzoate, a precursor to CoQ_{10}. As CoQ_{10} protects against lipid peroxidation, cells with high

expression of GCH1 are more resistant to ferroptosis, while those with a low expression are more sensitive [49,50].

The role of endogenous metabolites in inhibiting lipid peroxidation in ferroptosis

Some endogenous metabolites can also protect against lipid peroxidation. As mentioned above, GCH1 generates the lipophilic antioxidant BH4, which functions analogously to CoQ_{10} to prevent lipid peroxidation and ferroptosis [49]. Moreover, the metabolite indole-3-pyruvate (In3Py), which is generated by the amino acid oxidase interleukin-4-induced-1 (IL4i1), suppresses ferroptosis both through a radical scavenging mechanism and by regulating gene expressions that attenuates ferroptosis [51].

Iron-driven lipid peroxidation

Free iron induces lipid peroxidation

Ferroptosis is driven by iron-dependent lethal lipid peroxidation. Thus, the regulation of iron homeostasis plays an important role in ferroptosis. Iron uptake via solute carrier family 39 member 14 (SLC39A14; also known as metal cation symporter ZIP14) sensitizes cells to ferroptosis [52]. Moreover, iron uptake in cells is dependent on the endocytosis of diferric transferrin (TF) bound to its receptor transferrin receptor protein 1 (TFR1) [53]. Next, iron is released from TF in endolysosomes and exported to the cytoplasm by natural resistance-associated macrophage protein 2 (NRAMP2/DMT1) after a metalloreductase STEAP3-mediated reduction [54]. Excess Fe^{2+} is either bound to ferritin heavy chain (FTH) after delivery by the iron chaperone poly(rC) binding protein 1 (PCBP1) [55], or it is exported to the extracellular space by ferroportin (FPN), the only known iron exporter in mammals [56–58]. ROS can be generated by the Fenton reaction ($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$) directly from free iron, but not from iron bound to TF or FTH. Therefore, iron chelators, such as DFO, can prevent ferroptosis by reducing the size of the labile iron pool (LIP).

Lysosomes and the Golgi contribute to free iron content

Some organelles play an important role in elevating the intracellular LIP, thus contributing to ferroptosis. Lysosomes are reservoirs of iron and in principle can initiate ferroptosis. Iron stored in FTH can be released via nuclear receptor coactivator 4 (NCOA4)-mediated autophagic degradation of ferritin, a process known as ferritinophagy, which occurs in lysosomes. In addition to contributing to the LIP, the lysosome itself can accumulate iron that can also induce ferroptosis in neurons [59].

The Golgi is another organelle that contributes to the LIP. When ferroptosis occurs, TFR1 localized in the Golgi is translocated to the plasma membrane and to the closely associated endosomal recycling compartment, promoting additional iron-loaded TF uptake, which eventually further enhances ferroptosis. The re-localization of TFR1 can be regarded as one marker of ferroptosis [60].

Mitochondrial iron overload contributes to ferroptosis

In addition to intracellular iron, mitochondrial iron homeostasis is also associated with the occurrence of ferroptosis (Fig. 3). Mitoferrin 1 (also known as SLC25A37) and mitoferrin 2 (also known as SLC25A28) are key mitochondrial iron importers responsible for heme and Fe–S biogenesis [61]. In vertebrates, mitoferrin 1 functions as the principal mitochondrial iron importer in erythroblasts, while mitoferrin 2 functions as the principal mitochondrial iron importer in non-erythroid cells [62]. Enhanced activity of SLC25A28 leads to an abnormal accumulation of redox-active iron in mitochondrial and sensitizes cells to ferroptosis, while SLC25A28 knockdown prevents erastin-induced ferroptosis [63]. Activation of heme oxygenase 1 (HO1), a mitochondrial enzyme that catalyzes the degradation of heme to produce ferrous iron, leads to mitochondrial iron overload and increases ferroptosis [64–66]. However, mild upregulation of HO1 has a protective role against ferroptosis [67]. Overexpression of mitochondrial ferritin (FTMT) causes ferroptosis resistance both *in vitro* and *in vivo* [68], indicating that similar to cytosolic ferritin FTMT can actually be cytoprotective.

Several Fe–S proteins have a role in lipid peroxidation during ferroptosis. For example, suppression of NFS1 (cysteine desulfurase, mitochondrial), an essential enzyme that harvests sulfur from cysteine to synthesize Fe–S clusters (ISCs), sensitizes cancer cells to ferroptosis [69]. Moreover, ferroptosis in cancer cells is promoted by the deletion of the Fe–S binding proteins mitoNEET (also known as CISD1) and NAF1 (also known as CISD2), reported to participate in mitochondrial iron transportation [67,68]. Increased expression of mitoNEET prevents erastin-induced ferroptosis in hepatocellular carcinoma cells [70], while NAF1 overexpression similarly leads to resistance to sulfasalazine-induced ferroptosis *in vivo* [71].

Iron-containing enzymes promote lipid peroxidation

The LIP not only facilitates the Fenton reaction to propagate lipid peroxidation [72], but it also acts as an

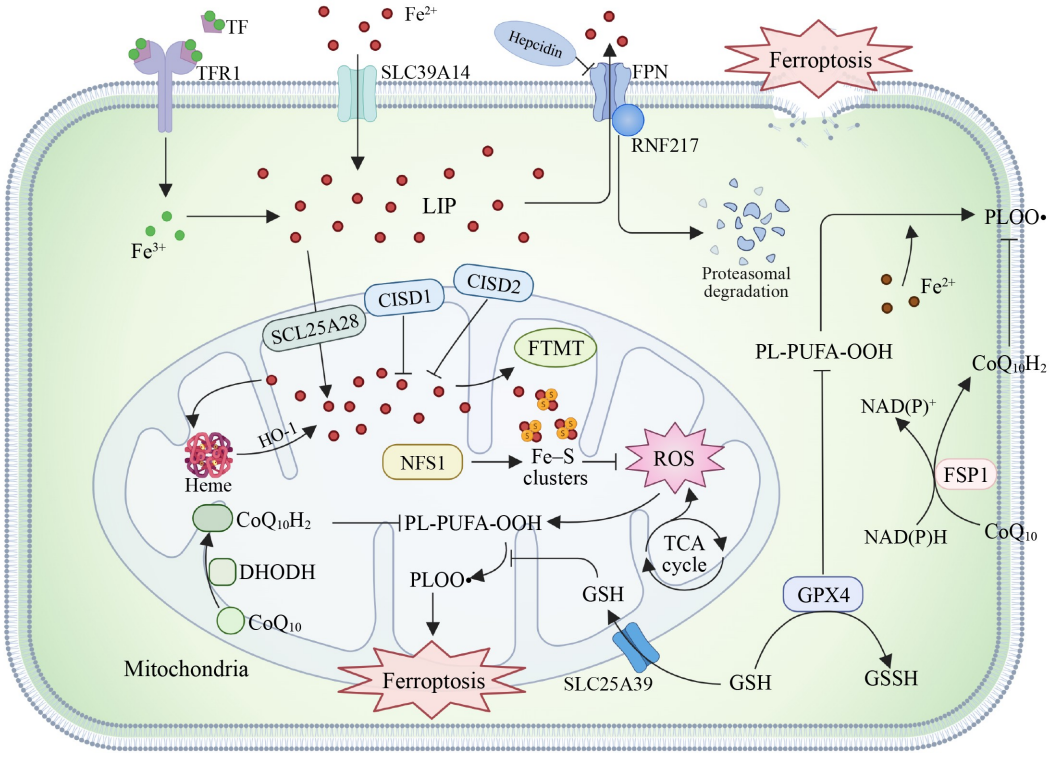

Fig. 3 Mitochondria iron metabolism in ferroptosis. As a major source of cellular ROS, mitochondrial metabolism plays a key role in the execution of ferroptosis. The key mitochondrial iron importer SLC25A28 is engaged in heme and Fe-S biogenesis. HO-1 catalyzes the degradation of heme to produce Fe^{2+}, which leads to mitochondrial iron overload and promotes ferroptosis. Separate mitochondria-localized defense systems have evolved to prevent mitochondrial lipid peroxidation and ferroptosis. For example, either the mitochondrial version of phospholipid hydroperoxide GPX4 or DHODH can specifically detoxify mitochondrial lipid peroxides. Mitochondrial ferritin protects mitochondria from iron overload-induced oxidative injury. In addition, CISD1 and CISD2 suppresses ferroptosis by limiting mitochondrial iron uptake. Abbreviations: ROS, reactive oxygen species; TCA, tricarboxylic acid; DHODH, dihydroorotate dehydrogenase; CoQ_{10}, coenzyme Q_{10}; FSP1, ferroptosis suppressor protein 1; FTMT, mitochondrial ferritin; HO-1, heme oxygenase 1; CISD, CDGSH iron sulfur domain; GPX4, glutathione peroxidase 4; GSH, glutathione; GSSG, glutathione disulfide; LIP, labile iron pool; PL-PUFA-OOH, polyunsaturated fatty acid-containing phospholipid hydroperoxides; PLOO·, phospholipid peroxyl radical; SCL25A28, also known as MFRN2, mitoferrin 2; SLC39A14, solute carrier family 39 member 14; SLC25A39, solute carrier family 25 member 39; NFS1, cysteine desulfurase; TF, transferrin; TFR1, transferrin receptor protein 1; RNF217, E3 ubiquitin protein ligase RNF217; FPN, ferroportin.

iron reservoir for several iron-containing enzymes that have the capability of promoting lipid peroxidation and thus can drive ferroptosis. For example, arachidonate lipoxygenases (ALOXs) initiate the formation of lipid hydroperoxides that are substrates for the Fenton reaction [73]. 15-lipoxygenase (ALOX15) forms a complex with PE-binding protein 1 (PEBP1), switching the substrate specificity of the enzyme from free PUFAs to PUFA tails of PLs [74]. Loss of one 12-lipoxygenase (ALOX12) allele is sufficient to abrogate p53-mediated ferroptosis and accelerates tumorigenesis, indicating that ALOX12 is required for p53-dependent ferroptosis [75]. Another Fe(II)-dependent enzyme, cytochrome P450 oxidoreductase (POR), also contributes to lipid peroxidation during ferroptosis [76].

Ferroptosis in human diseases

Ferroptosis has been increasingly considered to mediate the pathogenesis and development of multiple diseases (Fig. 1), including cancers, neurological diseases, cardiovascular diseases, lung diseases, digestive system diseases, urogenital system diseases, endocrine system diseases, iron overload diseases, musculoskeletal system diseases, and autoimmune system diseases. Here, we summarize the recent advances of ferroptosis in various diseases and also describe the potential targets of ferroptosis in the treatment of these diseases (Table 1).

Ferroptosis in cancer

Ferroptosis in tumor growth

Many studies have shown that ferroptosis plays a crucial role in killing tumor cells and inhibiting tumor growth. At least three mechanisms are involved in tumors evading ferroptosis to promote tumor development and metastasis, including limiting PUFA-PLs synthesis and peroxidation,

Table 1 Key mechanisms and regulators of ferroptosis in different diseases

Organs/systems	Diseases	Key mechanisms	Inhibitors	Inducers
Brain	AD	Decreased GPX4, GSH and increased 4-HNE and MDA protein levels [116,117] Increased lipid peroxidation [116,117] Increased ROS level [118] Iron overload [119]	Lip-1 [116] ALDH2 [121] TSG [122] Eriodictyol [124] FA [123] LA [126] Apolipoprotein E [125]	–
	PD	Increased lipid peroxidation [128] Reduced GPX4 and SLC7A11 expression and GSH depletion [129,130] Increased ROS level [129,130] Deficiency of CoQ_{10} [127] Downregulate FTH1 [131]	TRX-1 [132] Deferiprone [133] CQ [134]	–
	HD	Increased lipid peroxidation [137,138] GSH depletion [139] Iron overload [140]	DFO [142] Fer-1 [143]	–
	Brain trauma	Iron overload [282]	Fer-1 [282]	–
	FRDA	Iron overload [283]	EPI-743 and SFN [287]	–
Heart	IRI	Increased lipid peroxidation [150] Increased the levels of ACSL4, iron and MDA [149] Decreased GPX4 level [149] Iron overload [154] Increased the transcription of FTH and FTL [66]	Fer-1 [66] Lip-1 [158] DFO [161] 2, 2-bipyridyl [162] mTOR [163,164] Dex [160] Baicalin [167] Britanin [168] Xanthohumol and naringenin [169,170] Resveratrol [171] Cyanidin-3-glucoside [172]	–
	HF	Increased ROS level [181] Decreased GPX4 level [178] Downregulate the expression of FTH1 [181] Iron overload [181]	Puerarin [184] DFO [66] Canagliflozin [185]	Doxorubicin [179,180]
	Atherosclerosis	Accumulation of lipid peroxides and reduced GSH synthesis [186] Iron overload [189]	PDSS2 [187] Fer-1 [190]	–
Lung	ALI	Decreased GSH, GPX4 and SLC7A11 [195,196] Iron overload [195] MDA and 4-HNE accumulation [196]	Fer-1 [196] iASPP [197] PX [198] Dimethyl fumarate [199]	–
	COPD	Iron overload [201] Increased phospholipid peroxidation [202] Increased ROS level and decreased GSH and NADPH levels [203]	DFO [201] Fer-1 [201]	–
	PF	Reduced GPX4 expression and increased ROS [206]	Lip-1 [206]	Erastin [207] Paraquat [208]

(*Continued*)

Organs/systems	Diseases	Key mechanisms	Inhibitors	Inducers
	Lung cancer	Upregulate SCD1, FADS2, and FSP1 [45,314,315] Decreased intracellular Fe^{2+} and ROS levels [316,317]	–	Curcumin [91] Orlistat [98] DHA [318] Erianin [319] APAP [320]
Breast	Breast cancer	Not clear	–	27-hydroxycholesterol [80] Metformin [321] Lidocaine [322] Sulfasalazine [323] Curcumin [109] EC330/EC359 [103]
Liver	NAFLD	Increased lipid peroxidation [209] Increased ACSL4 level [213] Increased GPX4 level (early stage) [220] Iron overload [210]	IMA-1 [214] ECH1 [218] Lip-1 [215,216] ENO3 [220] Tβ4 [217] GB [219]	–
	ALD	Increased lipid peroxidation [224] Decreased hepatic GSH levels [225] Iron overload [223]	Fer-1 [222] Frataxin [226]	Lipin-1 [224] Intestinal SIRT1 [225]
	Liver fibrosis	Increased lipid peroxidation [227] Inhibit xCT/SLC7A11 [229] Iron overload [227]	–	Wild bitter melon extract [230] ART [231,232] Artesunate [233]
	HCC	Upregulate ACSL3 and ACSL4 [93] Stabilize SLC7A11 protein, increase intracellular GSH production, reduce lipid peroxidation [100,324]	ABCC5 [100]	IFNγ [325] MicroRNA-214-3p [326] Ceruloplasmin [106] Haloperidol [107]
Gastrointestinal	Gastric cancer	Upregulate SCD1, ELOVL5, and FADS1 [327,328] Decreased GPX4 expression [329]	–	Tanshinone IIA [330] ACP [331] Apatinib [329]
	Colorectal cancer	Upregulate SLC7A11 expression [332] Increased GSH and decreased ROS level [332]	–	Apatinib [92] TalaA [333] miRNA-15a-3p [334] SRSF9 [335] LCN2 [105]
Pancreas	Pancreatic cancer	Increased ROS level [336] Increased GSH synthesis [337]	MGST1 [97] BCAT2 [104]	Cyst(e)inase [337] Piperlongumine [338] Ponicidin [339] DHA [110] Ruscogenin [111]
Kidney	AKI	Increased lipid peroxidation [236] Decreased GPX4 and GSH levels [239] Iron overload [239,241]	Quercetin [245] Nuciferine [246] Vitamin D receptors [247]	Legumain [244] miR-182-5p [240] miR-378a-3p [240]

(*Continued*)

Organs/systems	Diseases	Key mechanisms	Inhibitors	Inducers
	CKD	Increased ACSL4 content [249] Increased lipid peroxidation [249,250] Decreased expression of SLC7A11 and GPX4 protein [250] Iron overload [249]	Rosiglitazone [249] Fenofibrate [252] Tocilizumab mimotopes [254] Fer-1 and DFO [255]	–
	ADPKD	Decreased expression of system Xc^- and GPX4 [256] Increased expression of TFR1, DMT1 and HO-1 [256] Iron overload [256,257]	Fer-1 [256] CPX-O [257]	Erastin [256]
Endocrine	T2DM	Increased whole-body iron status [261]	Cryptochlorogenic acid [262] Resveratrol [263] Polyphenols [264] Quercetin [259]	Acrolein [263]
	Obesity	Upregulate ACSL4 [266] Iron overload [268]	DFO [269]	–
Blood	HH	Iron overload [273]	Fer-1 [273] FGF21 [275]	AUR [274]
	Thalassemia	Iron overload [278]	Deferiprone [280] DFO [280]	–
Orthopedic	OA	Iron overload [290] Decreased expression of SLC7A11 and GPX4 [290]	Fer-1 [290] D-mannose [292]	–
	OP	Iron overload (osteoblast) [294] Increased ROS level (osteoblast) [294]	FTMT [294] Melatonin [295]	2ME2 [296] Artemisinin [297]
Autoimmune	SLE	Reduced GPX4 expression [301]	Lip-1 [301] DFO [301]	–
	RA	Increased expression of FTH1, GPX4, and SLC7A11 [303]	–	IKE [302] Glycine [303]
	IBD	Reduced GPX4 expression [306] Increased lipid peroxidation [306] Iron overload [307]	Fer-1 [307] DFO [307]	–

Abbreviations: IRI, ischemia–reperfusion injury; ACSL4, acyl-CoA synthetase long-chain family member 4; MDA, malondialdehyde; GPX4, glutathione peroxidase 4; FTH, ferritin heavy chain; FTL, ferritin light chain; Fer-1, ferrostatin-1; Lip-1, liproxstatin-1; DFO, deferoxamine; mTOR, rapamycin; Dex, dexmedetomidine; HF, heart failure; ROS, reactive oxygen species; FTH1, ferritin heavy chain 1; GSH, glutathione; PDSS2, prenyldiphosphate synthase subunit 2; NAFLD, nonalcoholic fatty liver disease; ECH1, enoyl coenzyme A hydratase 1; ENO3, enolase 3; Tβ4, thymosin beta 4; GB, ginkgolide B; ALD, alcoholic liver disease; SIRT1, aberrant liver sirtuin 1; SLC7A11, solute carrier family 7 member 11, also known as xCT; ART, artemether; HH, hemochromatosis; AUR, auranofin; HCC, hepatocellular carcinoma; ACSL3, acyl-CoA synthetase long-chain family member 4; ABCC5, ATP binding cassette subfamily C member 5; IFNγ, interferon-γ; AD, Alzheimer's disease; 4-HNE, 4-hydroxynonenal; ALDH2, aldehyde dehydrogenase; TSG, tetrahydroxy stilbene glycoside; FA, forsythoside A; LA, α-lipoic acid; PD, Parkinson's disease; CoQ_{10}, coenzyme Q_{10}; TRX-1, thioredoxin-1; CQ, clioquinol; HD, Huntington's disease; FRDA, Friedreich's ataxia; SFN, sulforaphane; AKI, acute kidney injury; CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; TFR1, transferrin receptor protein 1; DMT1, divalent metal transporter 1; HO-1, heme oxygenase-1; CPX-O, ciclopirox olamine; iASPP, inhibitor of apoptosis stimulating protein of p53; PX, panaxydol; COPD, chronic obstructive pulmonary disease; NADPH, nicotinamide adenine dinucleotide phosphate; PF, pulmonary fibrosis; DHA, dihydroartemisinin; APAP, acetaminophen; SCD1, stearoyl-CoA desaturase 1; FADS2, fatty acid desaturase 2; FSP1, ferroptosis suppressor protein 1; ELOVL5, elongation by very-long-chain fatty acid protein 5; FADS1, fatty acid desaturase 1; ACP, *Actinidia chinensis* Planch; TalaA, Talaroconvolutin A; LCN2, lipocalin 2; T2DM, type 2 diabetes mellitus; MGST1, microsomal glutathione S-transferase 1; BCAT2, branched-chain amino acid aminotransferase 2; FGF21, fibroblast growth factor 21; OA, osteoarthritis; OP, osteoporosis; FTMT, mitochondrial ferritin; 2ME2, 2-methoxyestradiol; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; IKE, imidazole ketone erastin; IBD, inflammatory bowel diseases.

strengthening cellular antioxidant systems, and limiting the availability of unstable iron to counter ferroptosis [77].

Reduced levels of peroxidized PUFA-PLs in cancer cells promote ferroptosis evasion and tumor growth. For example, the expression of the adipokine chemerin is often upregulated in renal cell carcinoma (RCC), and this adipokine downregulates the levels of peroxidized PUFA-PLs and inhibits ferroptosis, sustaining the growth of RCC xenografts [78]. In addition, some human cancers have been found to overexpress iPLA2β, which can remove oxidized PUFA tails from PLs. Recent studies have shown that the depletion of iPLA2β sensitizes cancer cells to ferroptosis and suppresses xenograft tumor growth [28,79]. In addition, the evasion of ferroptosis via regulation of fatty acid metabolism contributes to tumor metastasis. In the presence of hypercholesterolemia, cancer cells exhibit substantially increased tumorigenic and metastatic capacity *in vivo*, possibly due to ferroptosis resistance caused by increased accumulation of lipid droplets and MUFAs in these cells [80].

Most current studies on the antioxidant mechanisms that underly ferroptosis in cancers have focused on SLC7A11, which is found to be overexpressed in a variety of human cancer types [81,82]. The transcription factor NRF2, a master regulator in the antioxidant machinery, regulates the transcription of many genes in the GPX4-GSH-mediated ferroptosis defense pathway, including *SLC7A11*, thereby contributing to the escape of cancer cells from ferroptosis [83,84]. Numerous studies have shown that inactivation of tumor suppressors, such as p53, BAP1, and KEAP1, or activation of the oncogenic factor KRAS upregulates *SLC7A11* expression, which may be dependent or independent of NRF2, leading to ferroptosis evasion and further tumor growth [27,83–87]. Both endogenous [50] and exogenous [15] antioxidants can protect cancer cells from ferroptosis. Moreover, the expression of GCH1 determines the susceptibility of cancer cells to ferroptosis, in accordance with its expression in human tumor samples [49], implying that ferroptosis evasion correlates with increased tumorigenic capacity.

Dysregulation of iron metabolism increases the risk of cancer occurrence [88], which is partially controlled by the occurrence of ferroptosis. Some iron-containing enzymes are involved in this progress. Fe–S clusters are important cofactors in redox maintenance and iron homeostasis, and their associated regulatory pathways help cancer cells escape ferroptosis by reducing the LIP [89]. Both NFS1 and frataxin (FXN, a mitochondrial protein involved in iron-sulfur cluster synthesis and a mediator of iron homeostasis), are involved in ISC biosynthesis. FXN has been shown to attenuate ferroptosis in different types of cancer cells, thereby facilitating the growth of xenogeneic tumors [89]. Taken together, elevated iron uptake and increased intracellular iron levels in rapidly proliferating cancer cells reveal the potential of ferroptosis induction as a target for cancer treatment.

Ferroptosis in tumor therapy

Current oncology treatments are unable to effectively counteract the resistance of tumor cells to existing chemotherapeutic agents. Ferroptosis has been identified as the cause of tumor cell death in lung cancer, colorectal cancer (CRC), hepatocellular carcinoma (HCC), gastric cancer (GC), breast cancer, pancreatic cancer, and many others. Therefore, targeted induction of ferroptosis to reverse chemoresistance may be a new strategy for tumor treatment [90].

Lipid remodeling is closely linked to the vulnerability of cancer cells to ferroptosis. Curcumin is a polyphenol compound derived from the turmeric plant. Both *in vivo* and *in vitro* studies have shown that the curcumin-treated group had higher ACSL4 protein levels than the control group, indicating that curcumin induces ferroptosis and is beneficial for the treatment of non-small cell lung cancer [91]. It was found that the tyrosine kinase inhibitor, apatinib, induces ferroptosis by activating the ELOVL6-ACSL4 signaling pathway in CRC cells, providing new mechanistic support for the use of apatinib in the clinical treatment for this cancer type [92]. In addition, the expression of ACSL3 and ACSL4 was found to be increased in HCC compared with normal liver [93], while ACSL4 was found to be engaged in erastin-induced ferroptosis via 5-hydroxyeicosatetraenoic acid (5-HETE)-mediated lipotoxicity [94]. Indeed, the induction of ferroptosis by inhibition of ADP ribosylation factor 6 (ARF6) to activate ACSL4 has been reported to overcome gemcitabine resistance in pancreatic cancer [95]. The sensitivity of GC to cisplatin-paclitaxel has been enhanced by promoting the expression of ALOX15, which induces ferroptosis [96]. Also, microsomal glutathione S-transferase 1 (MGST1) inhibits ferroptosis in pancreatic ductal adenocarcinoma (PDAC) cells partly by binding to ALOX5, resulting in reduced lipid peroxidation, indicating that targeting the MGST1 redox-sensitive pathway may be a promising strategy for the treatment of PDAC [97].

Studies have reported that some small molecules and anticancer agents can directly or indirectly activate any link in the xCT-GSH-GPX4 system pathway to maintain the redox state of cancer cells and prevent tumor growth [1]. Orlistat facilitates ferroptosis in lung cancer cells by decreasing GPX4 expression and increasing lipid peroxidation levels, which inhibited tumor growth *in vivo* [98]. Disruption of the KIF20A-NUAK1-PP1β-GPX4 pathway induced cellular ferroptosis, thereby overcoming

oxaliplatin resistance in CRC [99]. Downregulating expression of ATP binding cassette subfamily C member 5 (ABCC5), a critical inhibitor of ferroptosis that works by increasing intracellular GSH production and by reducing the accumulation of lipid peroxidation products via stabilization of the SLC7A11 protein, significantly reduces the resistance of hepatoma cells to sorafenib [100]. In contrast, inhibition of NRF2-Keap1-Xc^- signaling induces ferroptosis to resensitize cisplatin-resistant cells in GC [101]. Similarly, targeting the SIRT6-Keap1-NRF2-GPX4 signaling pathway to activate ferroptosis overcomes sorafenib resistance in GC [102]. Our team's latest study found that treatment of breast cancer cells with EC330/EC359 decreased GPX activity and GSH levels [103]. In addition, branched-chain amino acid aminotransferase 2 (BCAT2), an aminotransferase that mediates sulfur amino acid metabolism, specifically antagonizes the inhibitory effects of the system Xc^- and protects PDAC cells from ferroptosis *in vitro* and *in vivo* [104]. Thus, it was speculated that inhibition of BCAT2 to promote ferroptosis may be an avenue to treat PDAC.

Elevated intracellular LIP levels enhance the susceptibility of cancer cells to ferroptosis. A recent study showed that targeting lipocalin 2 (LCN2), a protein that regulates iron homeostasis, reduces the resistance of colon cancer cells to 5-fluorouracil by increasing intracellular iron levels, which in turn results in ferroptosis [105]. Depletion of ceruloplasmin (CP), a glycoprotein that plays an important role in iron homeostasis, leads to the accumulation of Fe^{2+} and ROS in HCC cells and promotes ferroptosis [106]. Similarly, the psychotropic drug haloperidol enhances erastin- and sorafenib-induced ferroptosis in HCC cells by increasing intracellular Fe^{2+} levels and reducing cellular GSH levels [107]. Inhibition of DMT1 has been reported to lead to lysosomal iron overload, ROS production, and cell death with features of ferroptosis, thereby killing breast cancer stem cells and countering multidrug resistance [108]. Curcumin induces ferroptosis in breast cancer cells by increasing the levels of lipid ROS, lipid peroxidation, and free intracellular iron [109]. Moreover, DHA treatment overcomes cisplatin resistance in pancreatic cancer by inducing ferroptosis via acceleration of the accumulation of unstable free iron and lipid peroxidation [110]. Ruscogenin, the main component of Radix *Ophiopogon japonicas*, induces ferroptosis in pancreatic cancer cells by increasing intracellular Fe^{2+} content and ROS production [111].

Taken together, ferroptosis is considered to play an increasingly important role in anti-cancer therapy. Cancer cell ferroptosis not only overcomes resistance to conventional chemotherapies, but also plays a role in reversing resistance to radiotherapy, immunotherapy, and targeted therapies [90,112–115]. However, the possibility of additional toxicity, resistance, and adaptation during combination therapy is an important concern. Therefore, the link between ferroptosis and cancer is an emerging area that needs to be explored further.

Ferroptosis in neurodegenerative diseases

Ferroptosis in Alzheimer's disease

Alzheimer's disease (AD) is the most common type of dementia in clinical practice and is mainly characterized by the accumulation and aggregation of β-amyloid (Aβ) and Tau proteins. Mice with specific cortical and hippocampal neuron *GPX4* knockouts exhibit significant cognitive deficits, as well as degeneration of hippocampal neurons, which can be reversed by feeding the mice the ferroptosis inhibitor liproxstatin-1 (Lip-1), suggesting that ferroptosis may be an important pathomechanism in AD [116]. Elevated NOX4 significantly decreases GSH levels and increases the levels of 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) in human astrocytes, suggesting that NOX4 promotes ferroptosis via oxidative stress-induced lipid peroxidation, which is an important molecular mechanism of astrocyte injury during AD [117]. It has also been suggested that the progressive cytotoxic effects of Aβ in neuronal cells are mediated by cellular ferroptosis, with reduced levels of GSH, significantly increased production of ROS and elevated levels of several oxidized species of AA in MC65 neuronal cells with Aβ aggregation [118].

In addition, new evidence from a large autopsy cohort demonstrates that relatively high iron levels may play an upstream role in the pathogenesis of AD by altering the processing of Aβ precursor proteins through iron-dependent ferroptosis [119]. Our team found that downregulation of FPN and the presence of brain atrophy were observed in the hippocampus of an AD mouse model and in brain tissue of individuals who had AD, implying that the promotion of ferroptosis by an increased iron content may play a role in progressive brain atrophy in AD [120].

Ferroptosis plays an important role in neuronal death during the progression of AD. Inhibition of ferroptosis can reduce neuronal damage in AD in preclinical models. Mitochondrial aldehyde dehydrogenase (ALDH2) was observed to inhibit ACSL4-dependent ferroptosis by abrogating the manifestation of reduced GPX4 and SLC7A11 in an AD mouse model, thereby ameliorating their cognitive deficits [121]. Tetrahydroxy stilbene glycoside (TSG), a primary active substance from *Polygonum multiflorum*, reduces ferroptosis and oxidative stress by promoting the expression of GPX4 and other ferroptosis-related proteins, thereby inhibiting Aβ production and deposition in the brains of APP/PS1 mice, suggesting that TSG could be a possible promising agent

for the treatment of AD [122]. Furthermore, both eriodictyol and forsythoside A (FA), natural products from plants or traditional medicines, inhibited ferroptosis via elevation of GPX4 expression in the brains of APP/PS1 mice, thereby ameliorating cognitive deficits and memory impairment [123,124]. Apolipoprotein E activates the PI3K/AKT pathway, which inhibits ferritinophagy, and thus suppresses ferroptosis by averting iron-dependent lipid peroxidation in AD pathogenesis [125]. Furthermore, α-lipoic acid protects neurons from ferroptosis in P301S mice by regulating intracellular iron concentrations mediated by TFR1 and FPN1 and by acting as a free radical scavenger and antioxidant [126]. In brief, targeting key pathways of ferroptosis to treat AD could be a significant breakthrough for a disease whose treatment has so far been intractable in the clinic.

Ferroptosis in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disease featuring motor deficits, such as resting tremor and myotonia. Many key signatures and triggers of the ferroptosis pathway have been found to be important pathophysiological features in PD, in addition to progressively deteriorating dopaminergic neuronal degeneration and the accumulation of α-synuclein (α-Syn) in the formation of Lewy bodies [127]. In a synaptic nucleopathy model of PD, excess α-synuclein oligomers incorporate into the cell membrane leading to lipid peroxidation, and inhibition of lipid peroxidation can eliminate these effects and prevent oligomer-induced neuronal toxicity, further validating the role of ferroptosis in PD [128]. Quite a few studies have shown that inducing cellular ferroptosis by reducing SLC7A11 expression, depleting GSH, and increasing ROS levels facilitates the degradation of dopaminergic neurons in PD [129,130]. Observed CoQ_{10} deficiency in patients with PD may induce ferroptosis by reducing their antioxidant capacity, thus promoting the development of PD [127]. Furthermore, FTH1 links ferritinophagy and ferroptosis in the 6-hydroxydopamine model of PD, providing a new perspective and potential for a pharmacological target in the disease [131].

Inhibition of ferroptosis may be a prospective strategy to prevent PD progression. Overexpression of thioredoxin-1 (Trx-1), a redox-regulated protein, resulted in upregulated GPX4 levels in an MPTP-induced PD mouse model, while its knockdown decreased GPX4 expression and exacerbated ferroptosis-induced dopaminergic neuronal damage [132], emphasizing the beneficial effect of Trx-1-inhibited ferroptosis on dopaminergic nerves. An early clinical randomized controlled trial suggested that after treatment with the iron chelator deferiprone, the progression of motor dysfunction was slowed in patients with PD [133]. Clioquinol (CQ), an antiparasitic agent, was found to reduce iron content in the substantia nigra and to inhibit oxidative stress *in vivo* and *in vitro*, providing neuronal protective effects in PD [134]. The expression of GPX4 and FTH1 were significantly elevated in a rat model of PD rats that underwent moxibustion (a form of external treatment in traditional Asian medicine), demonstrating that the protective effect of moxibustion treatment on dopaminergic neurons may be related to the effective inhibition of ferroptosis [135,136]. Hence, inhibition of ferroptosis in dopamine neurons may become a strategy to treat PD.

Ferroptosis in Huntington's disease

Huntington's disease (HD) is a genetic-based neurodegenerative disorder with clinical manifestations of choreiform involuntary movements, psychiatric disorders, and progressive dementia. Several features of ferroptosis, such as lipid peroxidation [137,138], GSH depletion [139], and iron accumulation [140] have been noted in HD animal models and in patients, indicating that ferroptosis may be involved in the regulation of HD pathogenesis [141]. The delivery of iron chelators, such as DFO, improved cognitive function of HD mice [142]. In addition, the specific ferroptosis inhibitor Ferrostatin-1 (Fer-1) significantly inhibited oxidative lipid damage and ferroptosis of neuronal cells in isolated brain slices from HD rats [143]. However, studies on ferroptosis and HD are still scarce. More *in vivo* studies are needed to validate the effect of ferroptosis in the development of HD and its disease-specific pathological mechanisms.

In addition to neurodegenerative diseases, ferroptosis is also closely associated with cerebrovascular diseases, such as stroke, cerebral hemorrhage, and traumatic brain injury [144]. Previous studies have found that ferroptosis is engaged in brain ischemia-reperfusion injury (IRI) [145]. Tau knockout mice without iron deposition are resistant to IRI, and ferroptosis inhibitors can restore the protective effect in tau knockout mice [145]. Additionally, selenium supplementation enhances the activity of GPX4, thereby alleviating ferroptotic damage in the brain I/R model [146]. Furthermore, inhibition of ferroptosis through downregulation of the thrombin-ACSL4 axis may be beneficial for I/R and is a potential key therapeutic target for ameliorating ferroptosis-induced neuronal damage during ischemic stroke [147].

Ferroptosis in cardiovascular diseases

Ferroptosis in myocardial IRI

Acute myocardial infarction has become a severe threat to human life and health, and its most effective treatment is

to restore arterial blood flow to the ischemic tissue as quickly as possible. However, reperfusion or hematologic reconstitution and reoxygenation of the ischemic area may lead to further excessive tissue injury and trigger destructive inflammatory responses [148]. Many recent studies have provided evidence of how ferroptosis is involved in IRI and how targeting ferroptosis can be beneficial in I/R-related disorders.

Ferroptosis occurs mainly in the reperfusion phase of the myocardium rather than in the ischemic phase, as ferroptosis indices such as ACSL4, iron, and MDA are gradually increased, while GPX4 levels decrease with the prolongation of reperfusion, but there were no significant changes in ferroptosis indices with the prolongation of ischemic time [149]. Lipid peroxidation was found to be a key factor contributing to I/R oxidative damage [150]. The results of *in vitro* experiments have shown that the presence of PL oxidation products in cardiomyocytes undergoing I/R impairs the activity of cardiomyocytes [151,152]. Moreover, oxidized phosphatidylcholine is responsible for IRI in cardiac myocytes by triggering ferroptosis [153].

Iron overload is an important reason for myocardial cell damage [154]. I/R leads to increased cardiac non-heme iron and transcription of *FTH* and *FTL*, suggesting iron overload in the ischemic myocardium [66]. Overexpression of ATF3 decreased the levels of Fe^{2+}, ROS, MDA, and cell death in erastin- or RSL3-treated cardiomyocytes, which emphasizes an important role of ATF3-mediated iron metabolism in myocardial I/R-induced ferroptosis [155]. A recent study found that inhibition or knockdown of ubiquitin-specific proteinase 7 (USP7) attenuated myocardial IRI due to reduced ferroptosis by inhibiting TfR1 expression, mainly in terms of decreased iron content and lipid peroxidation [156]. During I/R, hypoxia induction upregulates HO-1 which localizes to the ER, leading to heme degradation and the generation of large amounts of Fe^{2+}, thus causing ferroptosis in the myocardium [157].

Strategies to target ferroptosis for the treatment of myocardial IRI primarily include the application of lipophilic radical-trapping antioxidants (e.g., Fer-1 and Lip-1), iron chelators (e.g., deferiprone and DFO) and inactivation of genes that drive lipid peroxidation (e.g., ACSL4). With respect to an antioxidant aspect, our group found that Fer-1 alleviated cardiac injury and hypertrophy caused by acute and chronic I/R in mice [66]. Another study reported that Lip-1 can protect myocardium from ischemia-reperfusion injury in mice by reducing mitochondrial ROS production and maintaining GPX4 activity [158]. Dexmedetomidine (Dex) is an α2-adrenergic receptor agonist that protects cardiomyocytes from ferroptosis by activating the SLC7A11-GPX4 signaling pathway [159]. Furthermore, USP22 deubiquitination could ultimately negatively regulate ferroptosis by inhibiting p53 to increase the expression of SLC7A11 levels and reduce ROS production, which alleviated myocardial IRI [160].

DFO can reduce IRI by inhibiting ferroptosis in an *ex vivo* heart model [161]. Additionally, the use of 2,2-bipyridyl, a mitochondrial permeable iron chelator, can pharmacologically target mitochondrial iron reduction and protect mice from IRI [162]. During I/R, high expression of rapamycin (an inhibitor of mTOR) is accompanied with increased expression of TfR1 and FPN, which may lead to cellular iron reduction due to increased iron export, and protects cardiomyocytes from excess iron and ferroptosis [163,164].

Some traditional Chinese medicines and natural products can also alleviate myocardial IRI by inhibiting ferroptosis [165,166]. For example, baicalin is a natural class of lipophilic flavonoid glycosides with antioxidant effects, which was shown to deactivate ACSL4 and induce resistance to ferroptosis, thereby preventing myocardial IRI [167]. On the other hand, britanin can also inhibit ferroptosis-dependent IRI by promoting GPX4 expression [168]. Likewise, xanthohumol and naringenin, both flavonoids, can regulate GPX4 protein levels and exert a protective effect against I/R-induced ferroptosis in the *ex vivo* heart [169,170].

As for the regulation of iron metabolism, resveratrol was found to downregulate the expression of TFR1 and upregulate the expression of FTH1, confirming its role in reducing intracellular Fe^{2+} content, which inhibits ferroptosis and improves myocardial IRI [171]. Coincidentally, a recent study showed that cyanidin-3-glucoside (CG3, a member of the anthocyanin family) treatment attenuates myocardial IRI by inhibiting ferroptosis through reducing Fe^{2+} content mediated by TFR1 and FTH1 expression [172]. In addition, certain non-coding RNAs have been found to affect myocardial IRI via the regulation of ferroptosis, which also has some therapeutic potential [173–175].

Ferroptosis in heart failure

Heart failure (HF) is a clinical syndrome characterized by cardiac hypertrophy and fibrosis, in which the pumping function of the heart is impaired to the point that cardiac output is unable to meet basic metabolic needs [176]. As the loss of terminally differentiated cardiomyocytes is irreversible in HF, early prevention of cardiomyocyte hypertrophy and death is expected to preserve cardiac function and delay HF. Recent studies have shown that ferroptosis plays an important role in the development of HF [177,178]. Iron overload is one of the important mechanisms of doxorubicin-induced heart failure [179,180]. During HF, the expression of FTH is downregulated, which in turn releases large amounts of

ferrous ions, ultimately leading to ROS accumulation and ferroptosis [181]. Our group has shown that ferritin's iron-storage function is critical for protecting against cardiac ferroptosis and subsequent heart failure, while selective overexpression of SLC7A11 in cardiomyocytes increases cellular glutathione levels and prevents FTH deficiency-mediated cardiac ferroptosis, providing the first evidence that SLC7A11 has an anti-ferroptotic role in the heart [182]. These findings point to the possibility of targeting ferroptosis to regulate HF.

Ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2), a lipid kinase important for the production of lysophosphatidic acid (LPA), has been shown to protect H9c2 cardiomyocytes from erastin-induced ferroptosis when overexpressed by decreasing the expression of ACSL4 and upregulating the expression of GPX4 [183]. Knockdown of Toll-like receptors (TLR4) or NOX4 by lentiviral delivery of siRNA both restored GPX4 and FTH expression to inhibit ferroptosis and alleviate symptoms of HF [178]. Moreover, treatment with the antioxidant puerarin can inhibit ferroptosis by increasing expression of GPX4 and FTH1, decreasing the expression of NOX4 and eliminating ROS, which together retard the development of HF and exert a cardioprotective effect [184]. DFO has been reported to reduce HF or myocardial infarction [66]. A recent study has shown that canagliflozin may ameliorate HF with preserved ejection fraction (HFpEF) by inhibiting ferroptosis through reductions in iron uptake and iron content, increases in GSH production and reductions of lipid peroxidation [185]. Based on these findings, exploring new drugs or other approaches based on the regulation of ferroptosis may represent a new strategy for the treatment of HF.

Ferroptosis in atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arteries characterized by disturbances in lipid metabolism. Its pathogenesis is complex and involves three major cell types, including endothelial cells, smooth muscle cells and macrophages. The development of ferroptosis is related to the accumulation of lipid peroxides, restricted GSH synthesis, and disturbances in iron homeostasis, which are also closely associated with the development of atherosclerosis.

The positive correlation between atherosclerotic severity and ACSL4 expression suggests that ferroptosis regulates the onset and progression of atherosclerosis [186]. Atherosclerosis can be alleviated by inhibiting ferroptosis via activating the antioxidant NRF2, inhibiting ROS release, and iron levels, which are mediated by prenyldiphosphate synthase subunit 2 (PDSS2), a key enzyme in the synthesis of CoQ_{10} [187]. Knockdown of HO-1 in endothelial cells treated with high glucose and high lipids reduced iron overload, ROS production, and lipid peroxidation, thereby inhibiting ferroptosis, indicating that ferroptosis is associated with the occurrence and development of diabetic atherosclerosis [188]. Our previously study showed that iron accumulation in macrophages promotes the formation of foam cells and the development of atherosclerosis [189]. In addition, the progression of atherosclerosis can be inhibited by reducing iron content and lipid peroxidation in mouse aortic endothelial cells [190]. All these findings show that ferroptosis has an important impact on the development of atherosclerosis, although the study of ferroptosis in atherosclerosis is still at a very early stage. What role ferroptosis plays in the pathogenesis of atherosclerosis and what role it plays in other organ damage underlying atherosclerosis remain to be further investigated.

Ferroptosis in lung diseases

Ferroptosis in acute lung injury

Acute lung injury (ALI) is a diffuse interstitial and alveolar edema caused by various direct (intrapulmonary) and indirect (extrapulmonary) factors, resulting in acute hypoxic respiratory insufficiency or even respiratory failure. A large number of studies have shown that ferroptosis is involved in the initiation and development of ALI [191].

Inhibition or knockdown of ACSL4 attenuates ferroptosis by reducing lipid peroxidation and increasing GSH and GPX4 levels in IR-induced pulmonary injury [192]. Ferroptosis-mediated intestinal ischemia reperfusion (IIR)-induced ALI via regulation of SLC7A11 has been well studied [193,194]. Lung tissue of oleic acid (OA)-induced or lipopolysaccharide (LPS)-induced ALI mice showed iron overload, decreased antioxidant capacity (reflected by reductions in GSH, MDA, or 4-HNE) and downregulated expressions of GPX4, SLC7A11, or ferritin, suggesting that ferroptosis plays a role in the pathogenesis of ALI [195,196].

Ferrostatin-1 attenuated LPS-induced ALI by inhibiting ferroptosis, suggesting that ferroptosis inhibitors may have a therapeutic effect in patients with ALI [196]. Inhibitor of apoptosis stimulating protein of p53 (iASPP) inhibits IIR-induced ferroptosis and attenuates ALI by activating the NRF2-HIF-1-TF signaling pathway [197]. Panaxydol (PX) is a polyacetylene compound isolated from the roots of *Panax ginseng*. The results of *in vitro* studies showed that PX dose-dependently increased GPX4 and GSH expression and decreased Fe^{2+} accumulation, and the results of *in vivo* studies showed that PX treatment significantly improved LPS-induced pathological changes of lung tissues, indicating that PX is a promising new therapeutic candidate for ALI by inhibiting ferroptosis [198]. Signal transducer and activator of transcription 3 (STAT3) enhances the

antioxidant capacity of cells by upregulating the level of SLC7A11, thereby attenuating ferroptosis in IIR-ALI [194]. Similarly, in mouse models of IIR-induced ALI it was shown that NRF2 inhibited ferroptosis through upregulation of SLC7A11 and had a protective effect against IIR-ALI [193]. The NRF2 agonist dimethyl fumarate reduced intracellular ROS and lipid ROS levels, prevented GSH depletion and lipid peroxide accumulation, and increased the mRNA expression of FTH1 and GPX4, ultimately inhibiting ferroptosis and increasing the viability of mouse lung epithelial cells, suggesting that NRF2 could be a potential therapeutic target for ALI [199]. Together, these results suggest that targeted inhibition of ferroptosis in lung tissue should be considered as a promising approach for the treatment of ALI.

Ferroptosis in chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a form of chronic bronchitis and/or emphysema featuring restricted airflow and is associated with an abnormal inflammatory response to harmful gases and harmful particles, such as cigarette smoke (CS) and PM2.5 [200]. Preliminary studies have shown the presence of ferroptosis in the lung tissue of COPD mice, although the specific molecular mechanisms of ferroptosis involved in COPD development still need to be further explored. Smoking is the most significant risk factor for the development of COPD, and studies have shown that free radicals in CS cause cellular iron overload, which promotes ferroptosis and facilitates the progression of COPD [201]. In addition, CS promotes PL peroxidation and ferroptosis in human lung epithelial cells through the accumulation of labile iron via NCOA4-mediated ferritinophagy [202]. Inhalation of PM2.5 particles, a major harmful component of airborne pollution, resulted in significant changes in TFRC, FTL, and FTH1 expression in human endothelial cells, leading to increased iron levels and ROS concentrations, as well as decreased GSH and NADPH levels, which in turn led to ferroptosis [203]. Treatment of bronchial epithelial cells exposed to CS with the ferroptosis inhibitors DFO and Fer-1 ameliorated the reduction in GSH and NADPH levels, thereby attenuating the induced ferroptosis [201]. Together, these results suggest that targeting of ferroptosis could be considered as a promising approach for the treatment of COPD.

Ferroptosis in pulmonary fibrosis

Pulmonary fibrosis (PF) is a progressive fibrotic lung disease, the most common of which is idiopathic pulmonary fibrosis (IPF), an interstitial lung disease of unknown cause [204], while secondary pulmonary fibrosis is mainly associated with long-term exposure to certain drugs, radiation exposure, autoimmunity or long-term inhalation of dust and asbestos. Recent studies have shown that ferroptosis in lung tissue promotes the progression of PF. In a mouse model of radiation-induced lung fibrosis (RILF), lung tissue volume is reduced, the outer mitochondrial membrane is disrupted, cristae are reduced, and density is increased, showing typical ferroptosis features [205]. In addition, the lung tissue exposed to radiation was observed to have collagen deposition and showed signs of ferroptosis with reduced GPX4 expression and increased ROS [206]. In an IPF model, erastin inhibits GPX4 expression in human fetal lung fibroblasts, increases lipid peroxidation and ROS levels, and contributes to fibroblast differentiation, thereby inducing PF [207]. The ferroptosis inhibitor Lip-1 inhibits collagen deposition and reduces inflammatory cytokines and ROS by increasing GPX4 levels in RILF mice, suggesting a significant therapeutic effect in this model [206]. Recent studies have shown that ferroptosis is associated with paraquat-induced PF and that ferroptosis inhibitors may become an effective therapy against such poisoning [208]. In conclusion, these findings provide evidence for delaying PF by inhibiting ferroptosis in future clinical practice.

Ferroptosis in liver diseases

Ferroptosis in nonalcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is mainly characterized by an accumulation of lipid droplets, immune/inflammatory cell infiltration, hepatocyte death, and some degree of fibrosis, which can progress to nonalcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and even liver cancer. Oxidative stress-induced lipid peroxidation plays a critical role in the onset and development of NAFLD [209], and iron deposition due to metabolic disorders is also an exacerbating factor in NASH [210]. Indeed, high iron diets exacerbate oxidative stress and inflammatory responses and accelerate the progression of NAFLD to NASH in mouse models [211]. Inhibition of ferroptosis is effective in protecting hepatocytes from necrotizing death [212]. All these findings emphasize a link between ferroptosis and the progression of NAFLD. The key regulator of ferroptosis, ACSL4, was increased in an arsenic-induced rat NASH model, and inhibition of the Mfn2-IRE1α-ACSL4 pathway may become an important mechanism to prevent the onset and progression of NASH [213].

A recent study identified a small molecule, IMA-1, which targets the interaction of ALOX12 with ACC and it was used to treat NASH in mice and macaques [214]. Inhibitors of ferroptosis, such as Lip-1, are able to reduce the severity of NASH [215,216]. GPX4 expression was

reduced in the liver of a methionine-choline deficient diet model of NAFLD that was treated with RSL3, and administration with GPX4 activators dramatically retarded the NASH progression by enhancing GPX4 activity [216]. Thymosin beta 4 (Tβ4) may protect hepatocytes from high-fat diet-induced NAFLD in a rat model by inhibiting the GPX4 depletion-mediated ferroptosis pathway [217]. Enoyl coenzyme A hydratase 1 (ECH1) is a lipid metabolizing enzyme that plays a key role in mitochondrial fatty acid β-oxidation. Research has shown that ECH1 may ameliorate steatohepatitis by elevating GPX4 expression to inhibit ferroptosis, suggesting that pharmacology or gene ECH1 activation may have potential as a future therapy for NASH [218]. Ginkgolide B (GB) is the main component of *Ginkgo biloba* extract. A study showed that GB treatment activates the NRF2 signaling pathway, thereby downregulating the expression of TFR1, upregulating the expressions of FTH1 and GPX4 in HepG2 cells and liver tissues, which eventually affects iron metabolism and inhibits ferroptosis to prevent the progression of NAFLD [219].

In addition to accelerating the development of liver damage in NAFLD, it was found that ferroptosis is gradually suppressed as NASH worsens, implying that ferroptosis may also act as a repair or resistance agent to reduce liver damage in early staged NASH [220], suggesting that ferroptosis may be a specific therapeutic target for NASH [221].

Ferroptosis in alcoholic liver disease

Alcoholic liver disease (ALD) is caused by excessive alcohol consumption and includes alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. The ferroptosis inhibitor Fer-1 has been shown to significantly ameliorate liver damage induced by excessive alcohol consumption [222], indicating ferroptosis plays an important role in the development of ALD. Iron overload promotes alcohol-driven ferroptosis and the development of ALD. A clinical study found that the level of hepcidin was reduced in the liver of patients with ALD, indicating that long-term sustained alcohol consumption may lead to hepatic iron overload and thus cause ferroptosis [223]. Following ethanol administration, hepatic iron overload promotes lipid peroxidation, ferroptosis, and eventually more serious liver injury [224]. Moreover, intestinal SIRT1-mediated hepatic ferroptosis, by disturbing iron metabolism, decreasing hepatic GSH levels and increasing lipid peroxidation damage, plays an important role in the development of ethanol-induced liver inflammation and injury [225]. A deficiency of FXN promotes alcohol-driven ferroptosis by increasing iron content and lipid peroxidation levels, thereby contributing to the development of ALD [226]. All these findings underscore that targeting ferroptosis can be a therapeutic strategy for alcoholic liver disease.

Ferroptosis in liver fibrosis

Liver fibrosis is the result of a pathological repair response of the liver to chronic injury and is a key step in the progression of various chronic liver diseases to cirrhosis. Ferroptosis promotes the development of liver fibrosis and liver damage. Hepatic stellate cells (HSCs), which are key mediators of liver fibrosis, in fibrotic livers have higher levels of iron ions and lipid peroxidation compared to normal livers, suggesting that the process of liver fibrosis may be related to ferroptosis [227]. A recent study showed that ER stress leads to overexpression of the G protein α12 in hepatocytes, which promotes lipid peroxide production by inducing ALOX12, ultimately facilitating hepatocyte ferroptosis and possibly leading to the progression of fibrosis [228]. It was shown that induction of ferroptosis in myofibroblasts through inhibition of xCT-SLC7A11 exacerbates chronic liver injury, which is closely associated with liver fibrosis [229]. Furthermore, our group found that loss of hepatic TRF leads to ferroptosis-induced liver fibrosis. More specifically, under TRF deficiency, SLC39A14 transports significant amounts of non-TRF-bound iron into hepatocytes, thus contributing to ferroptosis-induced liver fibrosis in the presence of high dietary iron and carbon tetrachloride injection [52].

In addition to promoting the development of liver fibrosis and liver damage, the induction of ferroptosis could also be considered as a new strategy to improve liver fibrosis, mainly by inactivating HSCs and inducing HSC death. Wild bitter melon extract downregulated the protein levels of GPX4 and SLC7A11 in lipopolysaccharide-induced HSCs, demonstrating that wild bitter melon extract probably acts as an anti-liver fibrosis agent through the induction of ferroptosis [230]. Artesunate and artemether, both artemisinin derivatives, have been shown to act on ferroptosis-related pathways and to affect the progression of liver fibrosis. Artemether (ART)-mediated upregulation of p53 expression inhibited SLC7A11, which indirectly led to GPX4 inactivation, ultimately promoting HSC ferroptosis and ameliorating liver fibrosis [231]. Another study reported that ART also exerts antifibrotic effects through the induction of HSC ferroptosis by the iron-regulatory protein 2-iron-ROS axis [232]. Artesunate can attenuate liver fibrosis by initiating ferroptosis mediated by ferritin phagocytosis in HSCs [233].

Obviously, ferroptosis has opposite effects on hepatocytes and HSCs in liver fibrosis. The former exacerbates liver injury, while the latter attenuates it. Thus, ferroptosis may have exactly opposite effects in different cell types, and further development of drug

delivery systems for specific cell types may allow side effects to be greatly reduced [234].

Ferroptosis in kidney diseases

Ferroptosis in acute kidney injury

Acute kidney injury (AKI) is a syndrome characterized by rapid loss of renal excretory function within hours and can be caused by reduced blood volume, direct kidney injury and urinary tract obstruction. Recent studies suggest that ferroptosis may be a major driver of AKI [235]. Lipid peroxidation leads to intense vasoconstriction and oxidative damage, which are detrimental factors for AKI. Inhibition of lipid peroxidation can reduce cisplatin-induced kidney injury [236]. Our group has recently demonstrated that YAP mediates ACSL4 upregulation and consequent ferroptosis in skeletal muscle cells, which in turn facilitates the development of rhabdomyolysis after exertional heat stroke [237], and thus targeting ACSL4 and ferroptosis may serve as a new therapeutic strategy to alleviate rhabdomyolysis-induced AKI. Similarly, Wang *et al*. demonstrated a protective effect of ACSL4 deficiency against ferroptosis-mediated AKI [238]. Severe acute pancreatitis (SAP)-induced AKI was followed by iron accumulation, increased lipid peroxidation, and upregulation of ferroptosis, which shows the involvement of ferroptosis in SAP-associated renal damage and suggests ferroptosis as a therapeutic target for the effective treatment of SAP-induced AKI [239]. Similarly, IRI induces the upregulation of miR-182-5p and miR378a-3p, which leads to activation of ferroptosis through downregulation of GPX4 and SLC7A11 in AKI, indicating ferroptosis is involved in IRI-induced AKI [240].

Plasma catalytic iron concentrations were significantly increased and associated with extensive renal injury due to IR, toxic drugs and rhabdomyolysis [241]. Also, both higher plasma catalytic iron levels and lower hepcidin concentrations were related to increased mortality in patients with AKI [241]. Deleting FPN from the whole nephron unit by using Nestin-Cre increased Fth1 expression, leading to reduced serum iron levels and increased ferroptosis, thereby attenuating ischemic AKI [242]. In conclusion, all the above studies support the important role of ferroptosis in AKI directly or indirectly.

In AKI, ferroptosis may enhance renal injury by increasing inflammation and other forms of regulatory necrosis, indicating that inhibition of ferroptosis has the potential to treat AKI disease [243]. Legumain is a conserved asparaginyl endopeptidase that is expressed highly in proximal renal tubular cells, and legumain deficiency has been reported to attenuate renal tubular cell ferroptosis by stabilizing GPX4 in animal models of AKI induced by IRI or nephrotoxic folic acid [244]. Quercetin has been shown to protect against functional acute renal failure and structural organ damage by reducing MDA and lipid ROS levels and increasing GSH levels to inhibit ferroptosis in proximal renal tubular epithelial cells of AKI mice [245]. Nuciferine, a primary bioactive compound isolated from lotus leaves, exhibits a potent protective effect against AKI by directly inhibiting ferroptosis *in vivo* and *in vitro* via limiting iron accumulation and inhibiting oxidative stress and preventing lipid peroxidation in a GPX4-dependent manner [246]. In addition, activation of vitamin D receptors attenuates cisplatin-induced AKI and improves renal function by partially inhibiting ferroptosis through GPX4 trans-regulation [247]. Most of these studies on small-molecule ferroptosis inhibitors were performed in AKI mouse models or *in vitro* experiments, and an in-depth investigation and rational use of ferroptosis in the process of AKI will provide new insights and new strategies for the treatment of AKI.

Ferroptosis in chronic kidney disease

Chronic kidney disease (CKD) is a chronic structural and functional disorder of the kidneys due to various causes over a period of months or years. The two main causes are diabetes and hypertension, while others include nephritis, urinary tract obstruction, recurrent urinary tract infections, and recurrent AKI [248]. Among them, diabetic nephropathy (DN) is the most common cause of CKD, and studies have shown that ferroptosis plays a pathological role in the progression of DN [249]. In kidney biopsy tissue of DN, significantly lower mRNA and protein expressions of SLC7A11 and GPX4 and higher lipid peroxidation levels were observed compared to non-diabetic nephropathy models [250]. A study showed that when DN was induced in mice, increased expression levels of ACSL4, iron content and lipoperoxidation were observed. When the DN-mice were treated with ACSL4 inhibitor (rosiglitazone), the iron content and lipid peroxidation products such as malondialdehyde (MDA) were reduced, which resulted in improved renal function and survival [249]. Furthermore, depletion of high-mobility group box-1 (HMGB1), a transcription factor involved in DNA recombination and repair processes, inhibited ACSL4 and increased GPX4 levels, revealing that inhibition of HMGB1 prevents glucose-induced ferroptosis in mesangial cells [251]. Fenofibrate treatment upregulated NRF2, which inhibited DN-associated ferroptosis by regulating the expression of GPX4, SLC7A11, FTH1 and TFR1, thereby restoring antioxidant capacity and rescuing the disordered iron pool [252].

Renal fibrosis is considered to be an important pathological process in the course of CKD and is closely

associated with ferroptosis [253]. Encouragingly, treatment with tocilizumab mimotopes significantly increased GPX4 and ferritin levels in a unilateral ureter obstruction (UUO) mouse model of renal fibrosis, thereby reducing kidney injury and fibrosis by inhibiting ferroptosis [254]. A new study has shown that treatment with ferroptosis inhibitors, such as Fer-1 and DFO, can largely reduce kidney injury and interstitial fibrosis in mice after UUO or IRI injury [255]. These findings suggest that ferroptosis inhibitors may have protective effects on renal fibrosis in patients with CKD, though clinical studies are needed to explore that possibility.

Ferroptosis in autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is an inherited disease caused by mutations in either polycystic protein 1 or 2 (PKD1 or PKD2). Zhang *et al*. demonstrated for the first time that ferroptosis is involved in the development of ADPKD [256]. They retarded cyst growth with the ferroptosis inhibitor, Fer-1, and promoted cyst growth with the ferroptosis inducer, erastin, both in rapidly and slowly progressing ADPKD mouse models [256]. In PKD1 mutant renal epithelial cells and tissues, they also found changed ferroptosis markers, such as increased lipid peroxidation, decreased GSH and Gpx4 activity, decreased expression of system Xc^- and GPX4 and elevated iron levels [256]. In addition, ferritin was reported to be significantly elevated in the renal cysts of PKD mice [257]. Ciclopirox olamine (CPX-O) is an iron chelator that inhibits ferritin accumulation in the kidney of ADPKD mice and induces ferritinophagy in an iron-independent manner, thereby inhibiting cyst growth in PKD mice [257]. These studies suggest that ferroptosis is one of the key mechanisms to promote the cystic progression of ADPKD, highlighting that targeting ferroptosis may be a novel therapeutic strategy for ADPKD.

Ferroptosis in endocrine metabolic diseases

Ferroptosis in type 2 diabetes mellitus (T2DM)

The main pathological manifestations of diabetes mellitus are islet β-cell failure and/or peripheral insulin resistance. The relationship between ferroptosis and diabetes has been established. Ferroptosis occurs in an arsenic-induced pancreatic dysfunction animal model [258]. It has been reported that ferroptosis may lead to pancreatic β-cell loss and dysfunction, and that erastin or RSL-based compounds that induce ferroptosis worsen insulin secretion [259]. Moreover, islets are vulnerable to ferroptosis *in vitro* and the induction of this mode of cell death results in impaired islet function [260]. Our group obtained genetic evidence from a Mendelian randomization study supporting a causal link between increased whole-body iron status and increased risk of T2DM [261].

Some natural products have potential anti-ferroptosis properties; for example, cryptochlorogenic acid exhibits superior anti-diabetic effects by inhibiting ferroptosis through activation of cystine-xCT-GPX4-NRF2 signaling and inhibition of NCOA4 in diabetes [262]. Furthermore, the antioxidant natural product resveratrol alleviates ER stress and increases PPARγ expression, thus inhibiting acrolein-induced ferroptosis, which provides a new perspective on the protective effect of resveratrol on pancreatic β-cells [263]. Polyphenols, such as curcumin and (–)-epigallocatechin-3-gallate, act as iron chelators and prevent GSH depletion and lipid peroxidation, thereby preventing iron toxicity and ferroptosis in mouse MIN6 pancreatic β-cells [264]. Quercetin may have some beneficial effects on the risk of T2DM by inhibiting iron deposition and ferroptosis in pancreatic β-cells [259].

In conclusion, ferroptosis may be involved in the dysfunction of insulin secretion in pancreatic β-cells. Even before β-cell death, islet function can be impaired by pro-ferroptotic factors [265]. Therefore, monitoring and controlling ferroptosis-related factors may help in the early diagnosis and treatment of diabetes.

Ferroptosis in obesity

Obesity is a nutritional, endocrine and metabolic disease featuring excessive accumulation and storage of fat in the body, leading to various metabolic disorders. Until now, only very few studies have investigated the relationship between ferroptosis and obesity.

Studies have found that ACSL4 expression was observed to be upregulated in mice fed a high-fat diet and that adipocyte-specific ablation of ACSL4 protected mice from high fat diet-induced fat accumulation in adipose and liver, white adipose tissue inflammation and insulin resistance [266]. Iron overload status in adipose tissue has been observed in patients with obesity [267]. Increased iron concentration was found to be correlated with adipose tissue remodeling and increased insulin resistance of adipose tissue in an experimental model of polygenic obese mice [268]. Iron chelators may have the potential to treat obesity. For example, DFO has been reported to reduce the expression of adipogenic genes in adipose tissue, leading to a therapeutic effect on obesity [269]. Therefore, it seems that the inhibition of ferroptosis in adipocytes protected mice from fat accumulation. However, a recent study demonstrated that iron overload protects mice on a normal diet or a high-fat diet from obesity, suggesting a protective effect of iron overload against obesity and emphasizing the critical role of ferroptosis in the regulation of lipid accumulation [270].

The role of ferroptosis in the development of obesity need further experimental researches.

Ferroptosis in iron-overload diseases

Hereditary hemochromatosis

As iron plays a key role in the process of lipid peroxidation, a large number of diseases related to iron overload are almost always associated with ferroptosis [271]. Hereditary hemochromatosis (HH) is a genetic disorder characterized by iron overload due to mutations in iron metabolism genes [272]. To date, there is limited research on how ferroptosis is involved in the pathogenesis of HH. Our team previously found that both *Hjv*$^{-/-}$ (a classic HH mouse model) and *Smad4*$^{Alb/Alb}$ (an HH-like mouse model) mice exhibited systemic iron overload, and when they were treated with Fer-1, their liver MDA and Ptgs2 mRNA levels were significantly reduced and NADPH levels were increased, compared to the untreated mice [273]. However, the low-iron diet completely rescued the above ferroptosis phenotype, indicating that iron overload induces ferroptosis in HH mice [273]. Recently, another of our studies found that the anti-rheumatoid arthritis drug Auranofin (AUR) induces ferroptosis by upregulating hepcidin expression both *in vitro* and *in vivo*, demonstrating that AUR could be a new therapeutic strategy for diseases associated with hepcidin deficiency, such as HH [274]. Fibroblast growth factor 21 (FGF21) is an important stress response hormone that has recently been found to promote ubiquitination and degradation of HO-1, thereby reducing Fe^{2+} production and ultimately inhibiting ferroptosis, thus suggesting that FGF21 may be used to treat iron overload diseases [275]. More research is required to explore the specific functions and underlying mechanisms of ferroptosis in HH.

Thalassemia

Apart from HH, iron overload can also be attributed to secondary causes, such as frequent blood transfusions, exogenous iron intake or certain blood disorders [276]. The iron overload resulting from ineffective erythropoiesis or transfusion can also be caused by myelodysplastic syndromes, leukemia, and so forth [277]. Thalassemia is a blood disorder in which hemoglobin synthesis is impaired and one of its common complications is iron overload [278]. Also, repeated blood transfusions are a common treatment and become another cause of iron overload in thalassemia [279]. Currently, the use of iron chelators such as deferiprone or DFO has become the most effective means of treating thalassemia [280], suggesting the involvement of ferroptosis. In the field of hematology, more research targeting iron metabolic pathways of ferroptosis may be required in the future to develop new iron chelator drugs to ameliorate iron overload and alleviate the diseases [281].

Brain trauma

Brain trauma has been associated with iron overload and can be modeled by the injection of $FeCl_3$ into the somatosensory cortex of rats. Fer-1 rescued the resulting seizures and reduced cognitive functioning in this model and also the effects of iron overload, including GPX activity and protein expression of 4-HNE in hippocampus, suggesting the involvement of excessive lipid peroxidation and possibly ferroptosis [282].

Friedreich's ataxia (FRDA) is another iron overload-associated neurological disorder that is primarily caused by reduced FXN levels [283]. Deletion of FXN leads to mitochondrial iron accumulation, enhanced ROS levels and lipid peroxidation [284–286]. Recent studies have shown that treatment of FRDA fibroblasts with NRF2 inducers (i.e., EPI-743 and SFN) can rescue ferroptosis and redox imbalance, supporting NRF2 activation as a prospective therapeutic approach to prevent ferroptosis-induced neurodegeneration [287].

Ferroptosis in orthopedic diseases

Osteoarthritis

Extensive studies have shown the importance of ferroptosis in the development and progression of orthopedic diseases [288]. Osteoarthritis (OA) is the most common joint disease and its progression is closely associated with chondrocyte death, degradation of the extracellular matrix (ECM) and inflammatory infiltration of the synovium [289]. Yao *et al*. induced inflammation and iron overload in chondrocytes with interleukin-1 beta (IL-1β) and ferric ammonium citrate (FAC), respectively, and found that GPX4 and SLC7A11 expression decreased, while ACSL4 expression increased, which could be rescued by Fer-1 [290]. They first demonstrated that chondrocytes underwent ferroptosis under conditions of inflammation and iron overload [290]. In addition, GPX4 knockdown induces chondrocytes to undergo ferroptosis and ECM degradation, suggesting that GPX4 inducers may have therapeutic potential in OA [291]. D-mannose, a C-2 epimer of glucose, slows the progression of OA in mice by inhibiting HIF-2α-mediated ferroptosis in chondrocytes, which provides a new strategy for the treatment of OA [292].

Osteoporosis

Osteoporosis (OP) is a systemic disease involving pathological loss of bone mineral density and an increase

in poor quality bone, thus increasing the risk of fracture that poses a serious threat to the health of the elderly. Its pathogenesis mainly includes poor bone coupling, resulting in the weakening of osteoblast function and the activation of osteoclasts [293]. Several studies have begun to emerge to determine whether ferroptosis is involved in the pathogenesis of OP and to search for new strategies with therapeutic effects on OP in recent years. In a cell-based model of T2D-related osteoporosis involving a high glucose-treated human fetal osteoblastic cell line, overexpression of FTMT was able to reduce the extent of iron overload and ROS production, and increase the expression of GPX4, indicating that FTMT was able to inhibit the occurrence of ferroptosis and restore osteogenic function [294]. Moreover, melatonin decreased lipid peroxidation levels by activating the NRF2-HO-1 pathway both *in vivo* and *in vitro*, thereby significantly inhibiting ferroptosis and improving osteogenic capacity of osteoblasts [295]. On the other hand, an *in vivo* study demonstrated that the HIF-1α-specific inhibitor, 2-methoxyestradiol (2ME2), was able to facilitate ferroptosis in osteoclasts by promoting the degradation of FTH, thereby preventing bone loss in ovariectomized mice [296]. Artemisinin compounds are considered to significantly increase TFR1-mediated iron uptake during osteoclast differentiation, leading to ferroptosis in osteoclasts, and therefore may be potential agents to treat OP [297]. In conclusion, inhibiting osteoblastic ferroptosis while promoting osteoclastic ferroptosis may both be potential approaches for the treatment of OP.

Ferroptosis in autoimmune diseases

Recently, an increasing number of studies have emerged discussing the involvement of ferroptosis in the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel diseases (IBD) and multiple sclerosis [298–300]. Li *et al*. found that GPX4 expression was reduced in neutrophils from patients with SLE as compared to healthy controls, and ferroptosis inhibitors, such as Lip-1 and DFO, reduced serum neutrophil death in patients with SLE [301].

In contrast, the induction of ferroptosis in synovial fibroblasts reduces the severity of synovitis and prevents arthritis [302]. Studies have shown that FTH1, GPX4 and SLC7A11 are increased in synovium and fibroblast-like synoviocytes of patients with RA [303]. TNF-α is a pro-inflammatory cytokine produced by macrophages and plays a major role in the pathogenesis of RA [304]. Treatment of human synovial fibroblasts with the ferroptosis inducer imidazole ketone erastin (IKE) resulted in GSH depletion, whereas TNF administration was able to reverse this effect and increased GSH levels, perhaps partially explaining the therapeutic benefit of anti-TNF biologics in patients with RA [302]. Glycine was able to promote S-adenosylmethionine (SAM)-mediated *GPX4* promoter methylation to reduce the expression of GPX4 and ferritin, ultimately enhancing ferroptosis in RA [303]. Taken together, the promotion of ferroptosis in proliferating synovial fibroblasts may be therapeutic in patients with RA.

Inflammatory bowel diseases includes Crohn's disease (CD) and ulcerative colitis (UC), which manifest as increased cell death in the intestine and colon due to a prolonged state of chronic inflammation [305]. Small intestinal epithelial cells (IECs) in CD exhibit impaired GPX4 activity and signs of lipid peroxidation [306]. Additionally, it was found that higher levels of MDA, and Fe^{2+} significantly increased expressions of FTH and FTL, and decreased GPX4 in colonic samples from patients with UC and in a mouse model of dextran sulfate sodium (DSS)-induced colitis [307]. However, both Fer-1 and DFO rescued necrotic cell death in DSS-induced colonic IECs and prolonged the survival of a mouse model of colitis [307]. These data strongly suggest that ferroptosis plays an important role in the progression of IBD.

Multiple sclerosis (MS) is an autoimmune demyelinating and neurodegenerative disease [308]. Ferroptosis suppression or knockdown of ACSL4 improves the behavioral phenotype of MS, resulting in reduced neuroinflammation and neuronal death in the experimental autoimmune encephalitis (EAE) mouse model of MS [300,309,310]. In addition, the decreased levels of xCT and GPX4 were found in the spinal cord from EAE mouse model [311]. Mechanistically, TFR1 and ferritinophagy could induce ferroptosis in the oligodendrocytes and result in demyelination through catalyzing the generation of lipid ROS at the peak of EAE disease [311]. In contrast, deferiprone protected against axonal damage and the loss of retinal ganglion cells, implying that inhibition of ferroptosis represents a promising therapeutic target for patients with MS [312]. Microglia are more sensitive to ferroptosis than other glial cells, so targeting microglia may provide a new treatment for neurological disorders with inflammation and immune deficiencies, such as MS [313].

Conclusions and perspectives

In summary, ferroptosis is the result of an imbalance of lipid peroxidation and antioxidant systems in the body, mediated by iron overload. However, iron accumulation is not equivalent to ferroptosis, and attention needs to be paid to the redox state of iron, which is important for the capacity to promote ferroptosis. Moreover, different types of oxidized lipids have different effects on ferroptosis. Although a large number of previous research articles and reviews have elaborated and summarized the regulatory

and molecular metabolic mechanisms of ferroptosis, there are still some outstanding questions and unavoidable challenges.

For basic research, the most important question is what is the ultimate executor that enables ferroptosis to occur after lipid peroxidation, which might also contribute to the discovery of additional hallmarks of ferroptosis and significantly differentiate ferroptosis from other forms of regulated cell death. As the research is explored in depth, the molecular mechanisms and signaling pathways involved in ferroptosis will become clearer and provide new ideas for the treatment of human diseases. The development of ferroptosis modulators is expected to provide new opportunities for the treatment of related diseases.

For clinical applications, there is a lack of information on potential biomarkers that can be used to specifically diagnose ferroptosis in the clinical setting. Specific non-invasive biomarkers are essential not only in identifying ferroptosis involved in pathological states, but also in evaluating the pharmacodynamics of novel anti-ferroptosis therapies, as well as monitoring the progress of drug treatment. It would be more meaningful to find ferroptosis biomarkers that indicate the severity of the disease. To better apply ferroptosis to the treatment of clinical diseases, transcriptomic or metabolomic approaches should be used in the future to probe for specific markers of ferroptosis. Moreover, the conditions of application, time point of initiation, dose, form of administration and duration of application of ferroptosis inducers or inhibitors have yet to be explored. Most of the available studies on the pathological effects of ferroptosis have been conducted in animals and in certain types of cells, and there has been little evaluation of its clinical safety and efficacy. More preclinical and clinical trials are needed in the future to validate the role of ferroptosis in the human body and to lay the foundation for the development of drugs to treat human diseases.

It is worth noting that the occurrence of ferroptosis in useful or functional cells can exacerbate the onset and progression of diseases, resulting in some pathological states. Therefore, it is particularly important to selectively control the targeting of ferroptosis in different cells and tissues, depending on the disease. Breakthroughs in this aspect may lead to more effective treatments for clinical diseases and also alleviate the side effects associated with ferroptosis-related drugs.

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Compliance with ethics guidelines

Xue Wang, Ye Zhou, Junxia Min, and Fudi Wang declare that they have no conflict of interest. This manuscript is a review article, and it does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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