REVIEW

Molecular mechanisms of ferroptosis and relevance to inflammation

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Abstract

Introduction Inflammation is a defensive response of the organism to irritation which is manifested by redness, swelling, heat, pain and dysfunction. The inflammatory response underlies the role of various diseases. Ferroptosis, a unique modality of cell death, driven by iron-dependent lipid peroxidation, is regulated by multifarious cellular metabolic pathways, including redox homeostasis, iron processing and metabolism of lipids, as well as various signaling pathways associated with diseases. A growing body of evidence suggests that ferroptosis is involved in inflammatory response, and targeting ferroptosis has great prospects in preventing and treating inflammatory diseases.

Materials and methods Relevant literatures on ferroptosis, inflammation, inflammatory factors and inflammatory diseases published from January 1, 2010 to now were searched in PubMed database.

Conclusion In this review, we summarize the regulatory mechanisms associated with ferroptosis, discuss the interaction between ferroptosis and inflammation, the role of mitochondria in inflammatory ferroptosis, and the role of targeting ferroptosis in inflammatory diseases. As more and more studies have confirmed the relationship between ferroptosis and inflammation in a wide range of organ damage and degeneration, drug induction and inhibition of ferroptosis has great potential in the treatment of immune and inflammatory diseases.

Keywords Ferroptosis · Inflammation · Iron metabolism · Lipid peroxidation · Mitochondria

Introduction

Ferroptosis, a relatively new form of cell death first discovered in 2012, is induced by small molecule compound erastin (an inducer of ferroptosis) and dependent on iron and lipid peroxidation, which is different from autophagy, pyrosis and other forms of cell death [1]. The morphological features are observed as cell swelling, dense electron of mitochondria, rupture of outer membrane, reduction or disappearance of mitochondrial cristae. Three fundamental hallmarks define ferroptosis: the dysfunction of lipid peroxide scavenging, the existence of redox active iron and the oxidation of phospholipids containing polyunsaturated fatty acids (PUFA) [1–3]. The molecular basis of ferroptosis includes glutamate/cystine anti-transporter, antioxidant system (glutathione peroxidase 4, GPX4), iron metabolism, unsaturated fatty acid metabolism, and ferroptosis suppressor protein 1 (FSP1)-ubiquinone system. As a kind of stress response, ferroptosis has pathological roles in a wide variety of diseases, including neurodegenerative diseases, cancer, inflammatory diseases of various organs, ischemia–reperfusion injury (IRI), and brain injury, among others.

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Inflammation is the activation of innate immune cells by damage and microbe-associated molecular patterns, manifested as the recruitment of macrophages and neutrophils, as well as the appearance of five major signs: rubor (redness), calor (heat), tumor (swelling), dolor (pain), and functio laesa (loss of function) [4]. On the one hand, inflammation is beneficial to the body. Inflammation benefits the host by promoting the removal of invading pathogens and removing cell debris after tissue damage. Inflammation also stimulates tissue repair and regeneration to restore homeostasis and body health [5, 6]. On the other hand, immune cells activated by inflammatory responses are usually accompanied by further inevitable damages to the host through the release of cytokines such as reactive oxygen species (ROS). It is the basis of a variety of physiological and pathological processes, which can cause serious damage to the body.

The complexity of the known regulatory pathways of ferroptosis makes it inevitably play an important pathological role in a variety of diseases, such as inflammatory diseases. Ferroptosis is accompanied by the release of pro-inflammatory molecules, such as interleukin (IL)-1β and IL-18 [7]. Elucidating the relationship between ferroptosis and inflammation may provide valuable insights into developing novel targets for inflammatory diseases. In recent years, more and more studies have shown that ferroptosis inhibitors are of great benefit in the treatment of inflammation [2, 8, 9]. Mitochondria are important organelles in inflammatory response. Here, we also discussed the relationship among mitochondria, inflammation and ferroptosis. This article reviews the molecular mechanisms of ferroptosis, describes the role of ferroptosis in inflammation, and summarizes the role of ferroptosis inhibitors in the treatment of inflammatory diseases.

Methodology

A systematic literature review of PubMed database was conducted with "ferroptosis" and "inflammation" as keywords. Inflammation, Ferroptosis, Lipid Metabolism, Iron Metabolism, IL-6, TNF-α, IL-1β, PUFA, arachidonic acid (AA), COX2, Mitochondria, NF-κB, Liposome, acute kidney injury (AKI), acute lung injury (ALI), inflammatory bowel disease (IBD), Neurodegenerative Diseases, IRI, etc. are the keywords to collect and summarize the articles published so far in 2010 to understand the role of Ferroptosis in inflammatory diseases (Fig. 1).

Mechanism of ferroptosis

Regulation of intracellular iron homeostasis

Iron is a transition metal that is a basic component of almost all living cells and organisms. It is a component of a variety
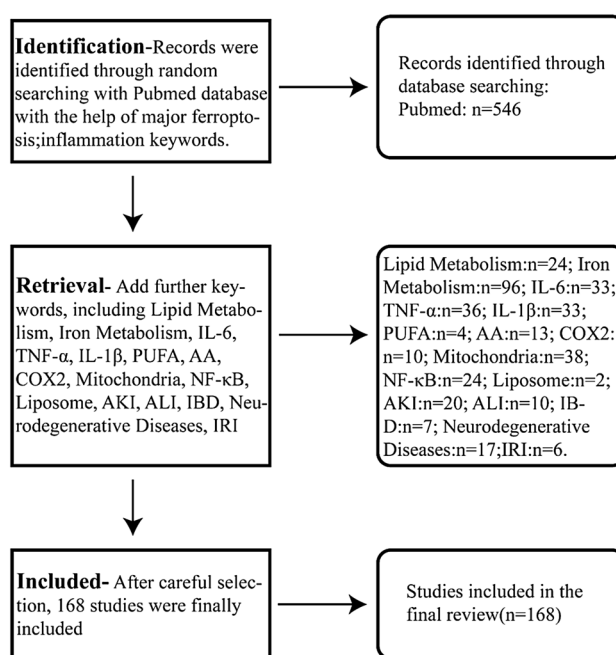

Fig. 1 Flowchart of the methodology

of metal proteins, involved in tissue oxygen transport, mitochondrial respiratory electron transfer reaction, DNA synthesis and repair, metabolism of exogenous substances and other key biochemical process. Overload of iron content can cause multiple organ damage (e.g., liver, kidney, spleen, etc.) and cell death. Therefore, maintaining the homeostasis of iron is crucial to human body.

Iron metabolism is the dynamic process of absorption, storage, utilization and excretion. Many mRNAs involved in iron metabolism include iron-responsive elements (IREs): stem-loop structures located in the 5′- or 3′-untranslated regions (UTRs) on the flanking of coding sequence (CDS) [10]. Intracellular iron homeostasis is associated with iron regulatory proteins 1 and 2 (IRP1, IRP2) and the IRE system. IRP is a protein that can bind to the 5′ or 3′ UTRs of IRE mRNAs. These key mRNAs are involved in iron regulation, including iron uptake (e.g., DMT1, TFR1), iron retention (e.g., ferritin subunits: FTH1, FTL) and iron export [e.g., ferroportin (FPN)]. Upon cellular iron deficiency, IRP not only binds to the 5′ IRE of ferritin and FPN to inhibit their translation, but also binds to the 3′ IRE of TFR1 to inhibit their degradation. When iron meets the demand, IRP degrades and these bindings stop [11]. Therefore, in response to the cell demands for iron, IRE/IRP interaction promotes the stability of TFR1 mRNA and inhibits FTH translation, thereby regulating the uptake and storage of cell iron [12]. Furthermore, hepcidin the main regulator of iron homeostasis, involves in iron metabolism through the internalization and degradation of FPN [13].

Ferroptosis is a new type of cell death that is distinct from other cell deaths. Excessive iron accumulation is easy to induce fenton reaction, resulting in a large amount of ROS along with membrane lipid peroxidation and further inducing ferroptosis. The signaling pathways affecting iron metabolism have been proved to regulate ferroptosis [14]. PPARα activation attenuates iron overload-induced ferroptosis in mouse liver by promoting GPX4 expression and decreasing TRF expression [15]. One of the markers of liver injury after liver transplantation is the high level of serum ferritin. Yamada et al. found that the iron chelation of deferoxamine (DFO) can significantly inhibit liver ischemia–reperfusion (I/R) ferroptosis and reduce liver I/R injury [16]. In culture and xenotransplantation models, downregulation of HSPB1 or HSF1 gene increases the sensitivity of cancer cells to ferroptosis through intracellular iron accumulation and related lipid peroxidation, while overexpression of HSPB1 inhibits ferroptosis [17].

The sensitivity of cancer cells to ferroptosis is affected by regulating intracellular iron homeostasis, and the effect of cancer treatment is achieved. A recent report shows that artemisinin compounds can sensitize cancer cells to ferroptosis by regulating iron homeostasis [18]. The specific mechanism is the ability of dihydroartemisinin

(DAT) to induce lysosomal degradation of ferritin in a non-autophagic manner, increasing free iron levels and making cells more sensitive to ferroptosis [18]. In addition, by binding to free iron in cells, the binding of IRPs to mRNA molecules containing IRE sequence is stimulated. Cells contain a small amount of incompatible and redox active Fe^{2+}, the so-called "labile iron pool" (LIP). Ferroptosis inhibitors and iron chelators (such as deferiprone (DFP)) can inhibit the fenton reaction by reducing the availability of iron in the LIP and inhibiting the production of free radicals [19]. Therefore, iron homeostasis is closely related to ferroptosis, and iron accumulation is a necessary condition for ferroptosis (Fig. 2).

DMT1 and TFR1 mediate the transfer of Fe^{2+} into cells, and Heme in the cytoplasm can release Fe^{2+}, which is stored in LIP and FTH1 in the cytoplasm. FPN mediates the release of Fe^{2+} from the cytoplasm into the blood. Hepcidin can combine with FPN to promote its internalization and degradation. When intracellular Fe^{2+} is absent, IRP binds with ferritin and FPN to inhibit their translations, as well as inhibiting the degradation of TFR1, ultimately increasing the content of Fe^{2+} in cells. Fe^{2+} in the cytoplasm generates ROS through fenton reaction, resulting in ferroptosis.

Fig. 2 The link between ferroptosis and iron metabolism
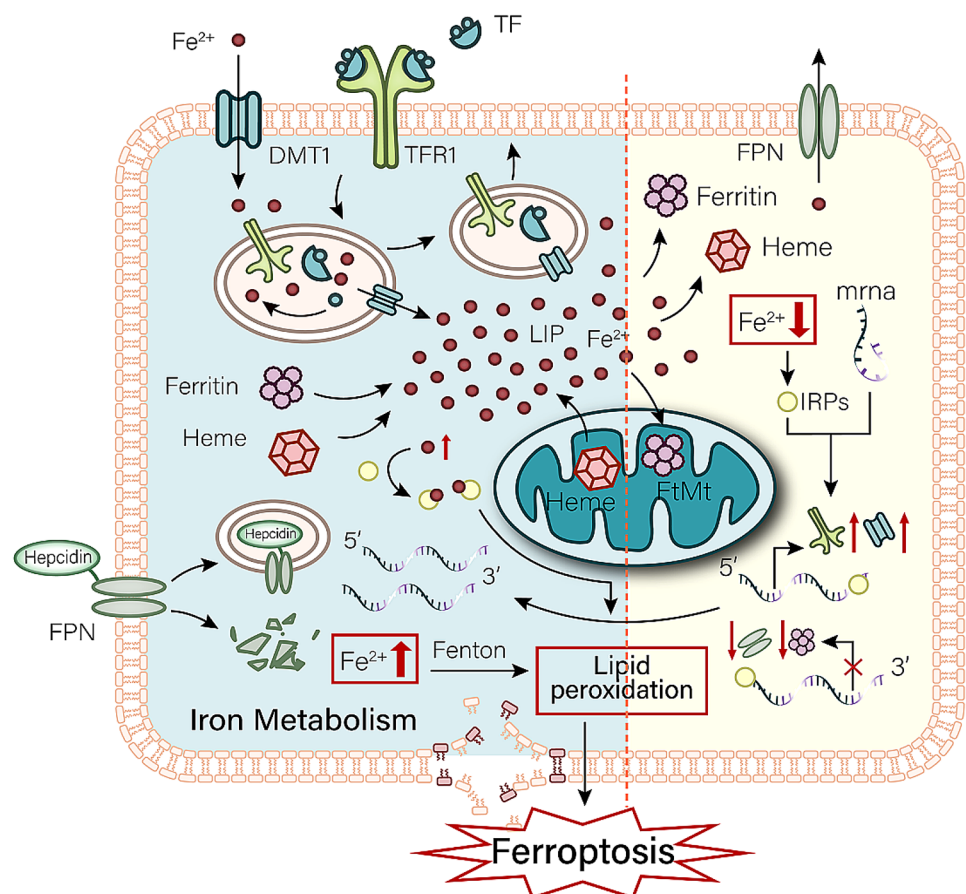
Lipid peroxidation

Lipid peroxidation is a free radical-driven reaction that primarily affects PUFAs in cell membranes. PUFAs undergo enzymatic or non-enzymatic oxidation reactions to form lipid hydroperoxides. Lipid hydroperoxides can react with Fe^{2+} to generate toxic lipid free radicals though fenton reaction. Lipid free radicals can attack major components of cells and cause cell damage, resulting to ferroptosis. In addition, lipid free radicals can also transfer protons from adjacent PUFAs, restarting the lipid peroxidation process. Lipid peroxidation products include initial lipid peroxides (LOOHs) and subsequent reactive aldehydes (such as malondialdehyde (MDA) and 4-hydroxynonenal (4HNE)), which increase during ferroptosis and are also among the markers of ferroptosis [1]. Lipid peroxidation directly damages phospholipids, and oxidized phospholipids can also play an important role in many inflammatory diseases and mediate pro-inflammatory changes [20].

The GPX4, together with glutathione (GSH) as an essential cofactor, is an antioxidant enzyme that neutralise LOOHs and protect the fluidity of membranes, thus protecting cells and membranes from peroxidation. GSH can be recycled by GSH reductase and nicotinamide adenine dinucleotide phosphate (NADPH)/H^+ reduction oxidation of glutathione disulfide (GSSG) to inhibit ROS production [21]. Transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) is a key regulator of cellular antioxidant response, which controls the expression of genes involved in antioxidant and electrophilic stress. Due to gene mutation, endogenous stress-induced modification, competitive binding of other interacting partners or exogenous pharmacological inhibition, NRF2 can be translocated to the nucleus to initiate the transcription of genes containing antioxidant response elements (ARE). NRF2 targets can be divided into three categories: iron/metal metabolism, intermediate metabolism and GSH synthesis/metabolism, all of which have validated ARE. NRF2 has been proved to regulate the activities of several ferroptosis and lipid peroxidation-related proteins [22].

Mammalian arachidonic acid lipoxygenases (ALOXs) family (arachidonic acid lipoxygenase) can mediate PUFA peroxidation to produce AA/AdA-PE-OOHs, which play a tissue or cell dependent role, leading to ferroptosis [1]. ALOX is not the only regulator of lipid peroxidation in ferroptosis. In fact, cytochrome P450 oxidoreductase (POR) combines with two cofactors [lutein mononucleotide (FMN) and lutein adenine dinucleotide (FAD)] to directly provide electrons to P450 enzymes from NADPH, the basic electron donor of all organisms, thereby promoting the peroxidation of PUFA in cancer cells in a manner independent of ALOX [23]. However, it is unclear whether

other oxygenase, such as cyclooxygenase (COX) and peroxidase, play a similar role in lipid peroxidation.

At present, studies have shown that peroxisomes promote ferroptosis by synthesizing polyunsaturated ether phospholipids (PUFA-ePL), which acts as a substrate for lipid peroxidation and resulting in the induction of ferroptosis [24]. Therefore, peroxisome-driven synthesis of ether phospholipids, rather than other lipids, plays an important role in regulating susceptibility to ferroptosis. The prevailing view has long been that ferroptosis is mainly caused by peroxidation of long-chain PUFAs through non-enzymatic oxidation of free radicals or enzymatic stimulation of lipoxygenases (LOXs). There is emerging evidence revealing that long-chain saturated fatty acids (SFA) may be related to ferroptosis, and FAR1 is a key factor in ferroptosis mediated by SFA. FAR1 catalyzes the reduction of C16 or C18 SFA to fatty alcohols, which has been identified as a critical role for the synthesis of alkyl ether lipids and acetal phospholipids. FAR1 inactivation reduces SFA-dependent ferroptosis [25]. Therefore, FAR1-mediated ferroptosis depends on peroxisome-driven ether phospholipid biosynthesis (Fig. 3).

PUFA is oxidized under the action of ACSL4 and other factors, while NRF2 pathway can inhibit the oxidation of PUFA, thereby reducing the degree of lipid peroxidation and ultimately inhibiting ferroptosis. Cystine is transferred into cells mediated by System Xc-, and promotes the expression of GPX4 through GSH-GSSG pathway, thereby inhibiting lipid peroxidation and ferroptosis.

Regulatory pathway of ferroptosis

Ferroptosis occurs through iron-catalyzed lipid peroxidation, which is triggered by non-enzymatic (fenton reaction) and enzymatic mechanism (LOX). The accumulation of LOOHs, mainly phosphatidylethanolamine-OOH (PE-OOH), eventually leads to ferroptosis, while iron acts as a catalyst or a key regulator of ferroptosis [26]. PUFAs are the main targets of membrane lipid peroxidation [27]. It is currently believed that the initial signal of ferroptosis induction is the production of ROS from various sources, especially iron metabolism, mitochondrial electron transport chain and NADPH oxidase (NOX) protein family [28].

The system Xc⁻-GSH-GPX4 axis

System xc⁻ consists of a regulatory subunit solute carrier family 3 member 2 (SLC3A2) and a catalytic subunit solute carrier family 7 member 11 (SLC7A11) [29], which promotes the exchange of extracellular cystine and intracellular glutamate on the plasma membrane. SLC7A11 is a major functional subunit that can transport cystine into cells for GSH synthesis. SLC7A11 knockout mice appear healthy and fertile, and fibroblasts isolated from these mice

Fig. 3 The link between ferroptosis and lipid peroxidation
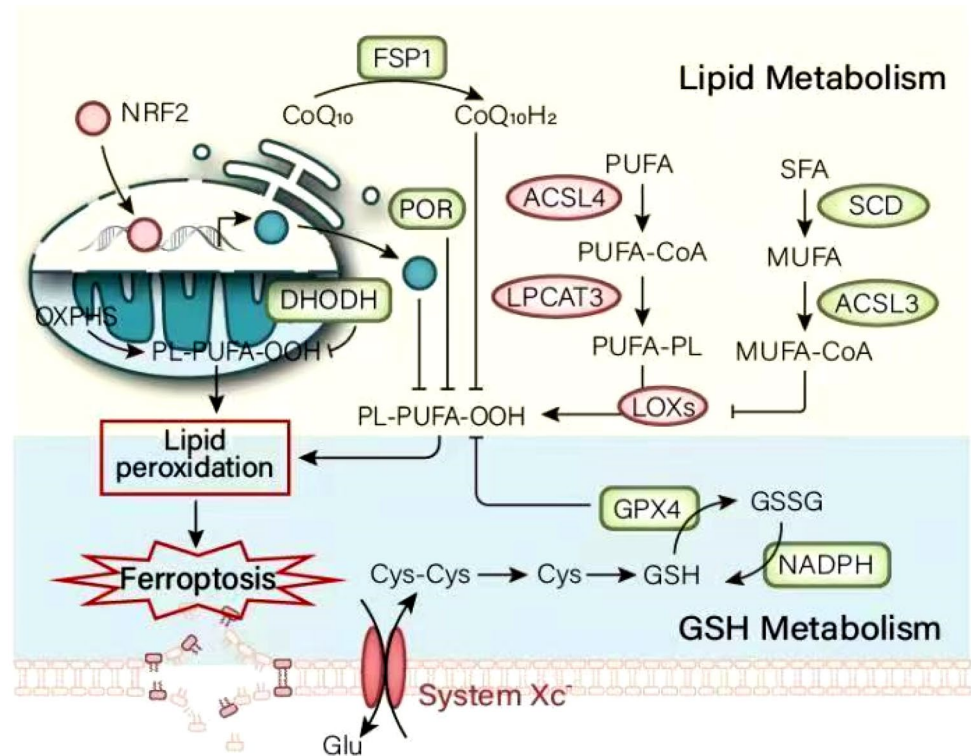
undergo cell death, which can be rescued by the presence of β-mercaptoethanol (β-ME), *N*-acetylcysteine (NAC) or vitamin E [30]. Badgley MA et al. found that the deletion of the system X_C^- subunit SLC7A11 can induce tumor-selective ferroptosis and inhibit the growth of pancreatic ductal adenocarcinoma (PDAC) [31]. Therefore, when the cystine/glutamate transporter is disrupted, GSH is depleted, thus causing inactivation of GPX4, ultimately resulting in lipid peroxidation accumulation and ferroptosis. Other than that, GPX4 can use tripeptide GSH as a cofactor to detoxify the lipid peroxidation formed during oxidative stress, thereby inhibiting the occurrence of ferroptosis.

Non GPX4 dependent pathways

Recently, an antioxidant pathway independent of GPX4 has been found, which relies on AIFM2-mediated coenzyme Q (CoQ) production [32, 33]. CoQ, also known as panquinone, is an endogenously generated isoprenoid benzoquinone compound, which is ubiquitous in nature. In addition, ubiquinol-10 (CoQ10H2), the reduction form of CoQ10, was used as an effective lipophilic antioxidant involved in the recovery of other antioxidants, such as tocopherol and ascorbic acid. CoQ10 is a key component of mitochondrial electron transport chain, which can inhibit lipid peroxidation by capturing free radical intermediates in this process [34]. AIFM2 (now renamed FSP1) was screened by gene screening, which can block lipid peroxidation and inhibit

ferroptosis by regenerating reduced CoQ, independently of any demand for GPX4 or GSH [32, 33]. In addition, recent studies have reported DHODH inactivation induces extensive mitochondrial lipid peroxidation and ferroptosis in GPX4^{low} cancer cells, whereas DHODH inactivation synergizes with ferroptosis inducers to induce mitochondrial lipid peroxidation and ferroptosis in GPX4^{high} cancer cells. Mechanistically, DHODH operates in parallel to mitochondrial GPX4 (but independent of cytosolic GPX4 or FSP1) to inhibit ferroptosis in the mitochondrial inner membrane, through reducing ubiquinone (CoQ) to ubiquinol (CoQH2), a radical-trapping antioxidant with anti-ferroptosis activity [33]. In addition to mediating the reduction of CoQ10 production, AIFM2 supports the anti-injury effect of membrane AIFM2 by activating the inner sorting complex required for plasma membrane transport (ESCRT) -III dependent membrane repair, which is related to ferroptosis resistance [35]. In addition, another pathway independent of GPX4 has been reported. The metabolic derivative tetrahydrobiopterin/dihydrobiopterin (BH4/BH2) synthesized by GCH1 (GTP hydrolase 1) may also antagonize ferroptosis by controlling the production of CoQ10 [30].

The NRF2-HO-1 signaling pathway

NRF2 is a transcription factor and phosphorylated NRF2 translocate into the nucleus to transactivate its target genes, including heme oxygenase-1(HO-1), as well as NRF2 itself

[36]. HO-1 is an enzyme that exerts anti-inflammatory and antioxidant stress effects [37]. NRF2 is a critical modulator of the expression of HO-1. HO-1 mediates heme decomposition into carbon monoxide, iron and biliverdin [38]. Among them, biliverdin and its reduced bilirubin have an effective ROS scavenging activity to resist peroxides, peroxynitrite, hydroxyl and superoxide radicals. It's proved that tagitinin C induces ferroptosis through ER stress-mediated activation of PERK-NRF2-HO-1 signaling pathway [36]. So how does the NRF2-HO-1 axis regulate ferroptosis? As a matter of common knowledge that NRF2 is a key regulator of endogenous antioxidant pathways. NRF2 targets play a key role in the regulation of iron metabolism. The light and heavy chains of ferritin (FTL/FTH1), which is a key iron storage protein, and also the FPN responsible for iron flowing out of cells, are controlled by NRF2 [39]. In addition to iron metabolism, NRF2 is also involved in the regulation of GSH antioxidant system. The expression of enzymes involved in GSH synthesis was controlled by NRF2, including glutamate cysteine ligase (GCLC/GCLM), glutathione synthase (GSS), and SLC7A11 [22]. Iron metabolism and GSH synthesis are important regulatory processes of ferroptosis, and NRF2/HO-1 is the main signal pathway regulating ferroptosis. Moreover, activation of NRF2-HO-1 antioxidant element signaling pathway is the main mechanism of cellular defense against oxidative stress. For example, zinc increased the expression of NRF2/HO-1, thereby increasing the contents of GPX4, SOD, and GHS and reducing the levels of LOOHs, MDA, and ROS [40], ultimately thereby inhibiting the onset of ferroptosis.

# Correlation between ferroptosis and inflammation

The inducing factors of inflammation are generally divided into three types: loss or damage of tissue structure, temporary or permanent loss of tissue function, and destruction of body regulation function [41]. As we all know, controlling inflammatory response can play a protective role by enabling the body adapt to stimulation, while improper regulation may cause harmful stimulus, such as aggravating collateral tissue damage [41, 42].

It is reported that as a new form of cell death, ferroptosis is closely related to inflammation. Through the mediums of some ferroptosis regulators, such as GPX4, ROS, LOXs, and inflammatory mediators produced in the process of ferroptosis, ferroptosis can aggravate inflammatory response to varying degrees. Here, we describe the relevance of several inflammatory mediators and metabolic pathways that mediate inflammation and ferroptosis (Fig. 4; Table 1).

Proinflammatory cytokines

The expression of pro-inflammatory cytokines can be regulated by a variety of factors, including cytokines themselves or LPS [43]. Previous studies have shown that circulating inflammatory mediators, such as IL-1β, IL-6 and tumor necrosis factor-α (TNF-α), play a considerable role in the induction of endocrine disorder during inflammation [43]. In the process of immune response to infection, the activation of coagulation pathways leads to the excessive production of

Fig. 4 The link between ferroptosis and inflammation
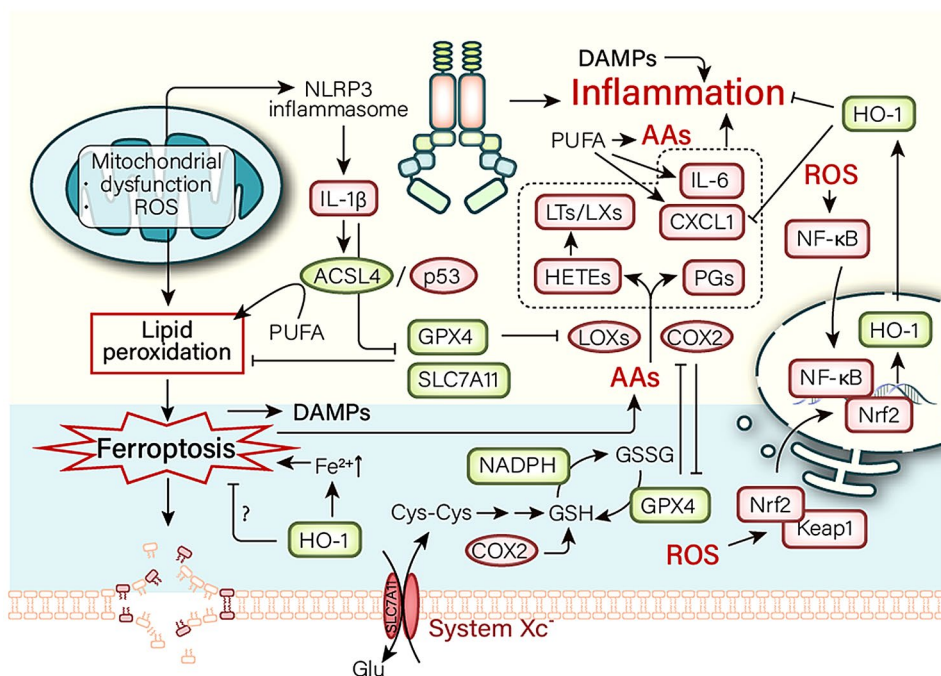
Table 1 Regulation of inflammatory factors in ferroptosis-related inflammation. List inflammatory factors that are tightly linked to inflammation and ferroptosis (IL-6, IL-1β et al.), providing a brief overview of the ferroptosis-associated inflammatory diseases and the specific regulatory mechanisms involved

Regulatory factors	Diseases	Regulatory mechanism	References
IL-6	Intervertebral disc degeneration (IDD)	Interferes with iron homeostasis of macrophages and results in iron accumulation	[48]
IL-6	Asthma	Induces lipid peroxidation	[101]
IL-6	Cardiac ferroptosis and inflammation	Via IL-6/STAT3/GPX4 axis	[44]
IL-6	Iron-related diseases	Via NF-κB/IL-6/hepcidin	[49]
IL-6	Intervertebral disc lesions	Via IL-6/miR-10a-5p/IL-6R	[48]
IL-1β	OA	Induces ROS, lipid ROS accumulation and MDA in chondrocytes	[66, 102]
IL-1β	Diabetic endothelial dysfunction	Via p53-xCT-GSH axis	[67]
TNF-α	Neurodegenerative disease	Activates NLRP3 inflammasome and LMP	[103]
TNF-α	Inflammation	Via TNF/IKK/NF-κB axis	[104]
PUFA	Atherosclerotic lesions	triggers endothelial ROS increase and nitric oxide (NO) decrease	[105]
PUFA	Asthma and AKI	15-LOX/PEBP1 complex increase in oxidized PEs	[106]
PUFA	CD	Via GPX4-LPO-PUFA axis	[3]
AA	Inflammation	Produces AA-OOH-PE by Oxygenation and Esterification	[107]
COX-2	Brain I/R	Inhibition of COX-2 / PGE2 pathway and reduction of PGE2 production	[80]
COX-2	Renal I/R	COX/PGE2 pathway mediates oxidative stress-induced ferroptosis and renal I/R	[108]
NF-κB	Neuroinflammation	Resist ferroptosis and inflammation via NRF2/ARE/NF-κB pathway	[109]
NF-κB	Sepsis-induced cardiac dysfunction	Via TLR4/NF-κB pathway	[57]
Liposomes	Corneal alkali burn	Inhibits accompanying ferroptosis and inflammation	[100]

proinflammatory cytokines, which ultimately leads to multiple organ injury.

IL-6

Iron calmodulin participates in the intestinal absorption and release of iron, thus maintaining iron homeostasis, and plays a pivotal role in a variety of ferroptosis-related diseases [44, 45]. Some studies have shown that IL-6 participates in iron metabolism by mediating the expression of ferritin, and iron overload in turn promotes the expression of pro-inflammatory cytokines, such as IL-6 and IL-1β, via regulating the redox balance [46]. IL-6 has been documented in a variety of chronic inflammation, such as IBD, multiple sclerosis (MS), rheumatoid arthritis (RA) and inflammatory lung disease [47]. IL-6, highly expressed in degenerative chondrocytes, induces lipid peroxidation and iron imbalance through the IL-6/miR-10a-5p/IL-6R axis, which promotes the occurrence of ferroptosis and aggravates the inflammatory response of intervertebral disc lesions [48]. Some chronic diseases are along with the activation of NF-κB pathway and IL-6, the downstream factor, while IL-6 further plays the role of anti-ferritin through JAK1/STAT3 pathway. IL-6 and sIL-6R α synergism can promote inflammation and the transformation of inflammatory types through leukocyte recruitment [44, 49]. Similarly, IL-6–IL-2 axis can regulate

and maintain the homeostasis of T17/Treg cells, and then regulate the process of inflammation [50].

TNF-α

The content of serum TNF-α in tissues was significantly increased when ferroptosis occurs. Studies have shown that ferroptosis inhibitors can inhibit TNF-α [51]. TNF-α has complex pathophysiological functions: it participates in the formation of vasodilation and edema, as well as the adhesion between leukocytes and epithelial cells via the expression of adhesion molecules, regulates blood coagulation, and indirectly induces fever [52]. Under the action of pro-inflammatory factors (such as virus, infection, etc.), M1 macrophages polarize and secrete TNF-α and iNOS [53]. TNF-α, inducing the production of iNOS, prostaglandins (PGE2, PGF2α, PGI2) and ROS, participates in and promotes inflammatory response such as aggravating the oxidative stress at the inflammatory site and participating in the formation of edema, which leads to the vicious circle of inflammation. The phenomenon of high expression of systemic TNF-α is manifested in RA, IBD and sepsis, and is associated with the high incidence rate of CVD, as well as atherothrombotic events, indicating that TNF-α is closely related to pathophysiology [54].

In addition, LPS induced sepsis and systemic inflammation are closely related to ferroptosis. Ferrostatin-1 (Fer-1, a ferroptosis inhibitor) and lipoxstatin-1 (a kind of ferroptosis inhibitors) have been shown to inhibit elevated levels of TNF- α and IL-6 in sepsis [55–57]. In addition, TNF treatment of cells can result in sustained downregulation of GPX4 expression, which is critical for the production of lipid mediators [58]. ROS, one of the markers of ferroptosis, activates NF-κB/NOX pathway, which inducing the production of inflammatory mediators (including TNF-α).

IL-1β

IL-1β is one of the IL-1 family members with the most pro-inflammatory characteristics [59]. As an upstream signal of NLRP3 inflammasome assembly, mitochondrial dysfunction, ROS and lysosomal destruction activate NLRP3 inflammasome, leading to subsequent IL-1β maturation [60]. The pro-inflammatory pattern of IL-1β indicates that it can participate in the occurrence of a variety of inflammatory diseases. It has been reported that IL-1β can induce liver injury and inflammation in mice, and participate in the formation of systemic inflammation, RA, periodontitis and secondary inflammatory injury in the brain caused by asthma [61–65].

It is worthy of note that in osteoarthritis (OA), IL-1β can inhibit the expression of SLC7A11 and GPX4, the markers of ferroptosis, and increase the expression of P53 and ACSL4, indicating that IL-1β is one of the bridges between inflammation and ferroptosis [66]. In addition, the existing research results show that IL-1β induces the activation of P53-XCT-GSH axis in endothelial cells and inhibits the expression of xCT and the uptake of cystine, which leads to ferroptosis and endothelial dysfunction. There is no doubt that the occurrence of endothelial dysfunction often increases the incidence of vasculitis and other symptoms [66, 67]. IL-1β and TNF can strongly induce highly active COX2 with low GPX4 activity, indicating that IL-1β is expected to become a vital target for the treatment of ferroptosis-related inflammation.

PUFA

Under oxidative stress, phospholipids and cholesterol esters containing PUFA in cell membranes and lipoproteins are easily oxidized by free radical-induced lipid peroxidation to form complex mixtures of oxidation products. A large body of evidence suggests that these oxidized lipids actively participate in the inflammatory response of atherosclerosis by interacting with immune cells (such as macrophages) and endothelial cells [68]. PUFA rich in Western diet plays an important role in the induction of inflammation, especially intestinal inflammation [3], PUFA-induced metabolic

enteritis as a fuel for Crohn's Disease (CD) [69]. PUFA, such as AA, can be metabolized into bioactive lipid mediators through COX, LOX and cytochrome P450 enzymes, mediating the production of inflammatory cytokines in IECs and the balance of intestinal microbiota [3, 70]. Moreover, PUFA derived lipid mediators, such as AA and docosahexaenoic acid (DHA), are synthesized under stress and play a role as inflammatory activators [71]. However, studies have shown that increasing Omega-3 PUFA intake may reduce the risk of inflammatory storms [72].

In the process of lipid peroxidation, oxidants (such as ROS) attack lipid carbon double bonds (especially PUFA), indicating the importance of PUFA as a substrate of lipid peroxidation in ferroptosis [30]. ACSL4 is the key factor of sensitivity to ferroptosis, which can catalyze coenzyme A to promote the esterification of PUFA to phospholipids. This may also reveal a new combined therapeutic strategy, blocking ferroptosis by inhibiting ACSL4 and PUFA-ePL biosynthesis enzymes [24, 30].

Metabolites of AA

AA, a 20-carbon fatty acid, is the main precursor of AA and an integral part of all cells [73]. The oxidation of PUFA to AA mediated by ALOX accelerates the occurrence of ferroptosis. COX, a bifunctional enzyme in line with dioxygenase and peroxidase, carries out complex free radical reactions and participates in the catalytic oxidation and cyclization of AA. Under the action of inflammatory stimulation, COX-2 is rapidly induced and acts at the inflammatory site to accelerate the inflammatory process [73, 74]. The state of these enzymes is directly affected by the redox state and peroxide tone in the cells. Peroxide hue refers to the steady-state level of cellular lipid hydroperoxide required for the final activation of LOX and COX. Therefore, this metabolic process is related to the regulation of GSH/GPX4 metabolism [73, 74]. Consistent with the production of PGs and leukotrienes during AA metabolism, PGs is expressed in a variety of cells and tissues, and widely regulates life activities. The formation of bioactive prostaglandins from PGH2 occurs through the action of a group of synthases expressed in a selective manner of tissue and cell type. These synthase include prostaglandin D synthase (PGDs), prostaglandin E synthase (PGEs), prostaglandin F synthase (PGFs), prostaglandin I synthase (PGIS) and thromboxane A synthase (txas), which form PGD2, PGE2 and PGF2 α, PGI2 (also known as prostacyclin) and TXA2. PGE2 and PGI2 are involved in many studies, including but not limited to enhancing vasodilation and edema formation. Furthermore, PGE2 is related to neuroinflammation and participates in allergic inflammation by regulating lymphocyte function. Patients with IBD also show elevated levels of PG and other AA derived eicosanoids in the inflammatory mucosa. In addition, leukotriene

produced through PPAR γ-dependent mechanism up regulates the expression of COX-2, leading to the production of PGD2, thus forming a vicious circle of enhancing inflammatory response in a positive feedback way [74].

An important feature of ferroptosis-sensitive cells or ferroptosis-related cancer cells is the synthesis of a large number of oxidative lipid mediators. It was previously described that AA anchored in phosphatidylethanolamine is a target of LOX and can be enriched by ACSL4, thus being one of the major components of ferroptosis [75]. Relevant studies in gastric and colorectal cancer cells have shown that AA supplementation increases their susceptibility to ferroptosis [75]. Not hard to find, AA provides a mediator of the association between ferroptosis and inflammatory diseases. For example, GPX4, a key regulator of ferroptosis, helps promote resolution of inflammation by eliminating the oxide species produced by the AA metabolic network [76].

COX-2

I/R is the main cause of many inflammatory diseases and cell damage. At present, ferroptosis has been regarded as a new target for the treatment of I/R injury. COX-2/prostaglandin E2 (PGE2) pathway is closely related to I/R. COX-2 is regarded as a marker gene of ferroptosis, and the increase of its expression is considered to be an important sign of ferroptosis [77]. It has been reported that BMP4/ROS/COX-2 pathway is involved in cerebral ischemia/reperfusion injury (IRI), and the activation and recovery of this pathway can mediate the combination of ischemic preconditioning (IPC) and resveratrol (RES) to provide brain protection after I/R [78].

A study on SH-SY5Y cells showed that the activation of COX2/PGE2 pathway could reverse the reduction of iron accumulation and lipid peroxidation caused by EXS$^{mir-137}$ co-incubation, and reduce the expression of GSH and GPX4 which represent the reverse of the inhibition of ferroptosis [79]. In addition, in brain I/R, the inhibition of ferroptosis by DFO can completely inactivate the synthase and degrading enzyme in COX-2/PGE2 pathway, and ultimately lead to the reduction of PGE2 [80]. Fer-1 reduced the increase of pro-inflammatory factors, including COX-2, while inhibiting ferroptosis in astrocytes [81].

Mitochondria

Mitochondria are important organelles involved in the regulation of energy metabolism, cell signal transduction and cell death pathways (including ferroptosis). Studies have shown that mitochondrial fatty acid metabolism genes, including citrate synthase (CS) and acyl CoA synthase family member 2 (ACSF2), may be necessary for ferroptosis induced by erastin [82]. Mitochondrial voltage dependent anion channel (VDAC) has been proved to be a potential target of erastin. The opening of VDAC leads to the production of mitochondrial ROS, the increase of mitochondrial potential, and then oxidative stress induces cell death [83].

Inhibition of mitochondrial TCA cycle or electron transfer chain (ETC) can reduce mitochondrial membrane potential hyperpolarization, lipid peroxidation accumulation and thus ferroptosis. The blocking of glutamine dissolution has the same inhibitory effect and can be offset by the provision of intermediates through the downstream TCA cycle. Similarly, the loss of function of fumarate hydratase (a tumor suppressor and TCA cycle component) makes people resistant to ferroptosis induced by cysteine deprivation [84].

The increase of mitochondrial ROS can induce the accumulation of lipid peroxidation. There is experimental evidence that activation of NRF2 can protect mitochondria, avoid mitochondrial damage and inflammation induced ROS accumulation, and regulate the occurrence of ferroptosis. The increase of active iron in mitochondria can lead to the accumulation of ROS during ferroptosis, so increasing mitochondrial iron storage may inhibit ferroptosis [83]. Consistent with this, mitochondrial ferritin (FTMT) is an iron storage protein. It is reported that FTMT regulates iron metabolism by regulating the redistribution of iron from mitochondria to cytoplasm and inhibits oxidative stress-dependent injury, especially in some high oxygen consuming tissues. FTMT can significantly inhibit the level of LIP, ROS and subsequent ferroptosis induced by erastin [85].

There are at least three mechanisms by which mitochondria damage or kill the host: ROS generation, pro-inflammatory signal or mitochondrial membrane permeability [86]. Some mitochondrial components may participate in the activation of PRRS by playing the role of PRR ligands to further stimulate the process of inflammatory response. In addition, four mitochondrial components, SMAC, N-formyl peptides, cardiolipin and cytochrome c, have been shown to promote inflammatory response [87]. Mitochondrial dysfunction and ROS production are closely related to the assembly and activation of inflammatory body NLRP3, and then affect the inflammatory process of intestinal inflammation and obesity induced inflammation [88–91]. In addition, the change of mitochondrial membrane permeability has become an important pro-inflammatory signal leading to inflammation through the release of mitochondrial DNA (mtDNA) and the down-regulation of apoptosis protein inhibitors (IAPS) [91]. It can't be ignored that the transfer of mitochondria and mtDNA between cells can promote the spread of inflammation [92].

NF-κB

The transcription factor NF-κB is a nuclear factor that binds to an enhancer element of the activated B-cell

immunoglobulin Kappa light chain (hence the abbreviation for NF-κB) [93]. It is a protein with specific DNA-binding activity that is expressed in almost all cell types and regulates many target genes with a wide variety of functions. Because NF-κB plays a key role in the expression of proinflammatory genes, including cytokines, chemokines, and adhesion molecules. NF-κB signaling is considered to be a typical proinflammatory signaling pathway. More and more evidence indicate that genes/drugs regulate the inflammatory response and reduce inflammatory damage by regulating NF-κB signaling pathway. In addition, NF-κB is involved in the regulation of iron metabolism pathway during inflammation. Transcription factor Spic in macrophages downregulates pro-inflammatory cytokines and promotes iron efflux by regulating FPN expression in activated macrophages [94]. Iron metabolism is an indispensable process in cell energy cycle, and the disturbance of its homeostasis may lead to inflammation. Targeting iron metabolism regulates NF-κB to regulate inflammatory response and plays a role in the prevention and treatment of inflammatory diseases [95]. Since iron metabolism is an important physiological process in ferroptosis, we hypothesized that ferroptosis links NF-κB with inflammation. In AKI, curcumin inhibits ferroptosis by inhibiting TLR4/NF-κB axis and activating HO-1, which further reduces inflammation and oxidative stress and plays a therapeutic role [96]. Therefore, NF-κB signaling pathway checkpoints may be important targets in the regulation of inflammatory diseases by targeting ferroptosis.

Liposomes

Liposomes, vesicles with an aqueous core entrapped in one or more lipid bilayers, are widely used as drug delivery systems. Liposomes can be used as delivery vehicles for a variety of drugs and biological agents, including small molecules, peptides, proteins, nucleic acids and vaccine antigens. Previous studies show that nanoliposomes can effectively target infected and inflamed tissue [97]. Sea cucumber saponin liposomes could effectively alleviate adipose tissue inflammation by reducing pro-inflammatory cytokine releases and macrophage infiltration [98]. In addition, folic acid and PEG conjugated Pae-loaded liposomes (PAE-LS) inhibited STAT1 phosphorylation, decreased the levels of proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and iNOS expression, and significantly increased the levels of anti-inflammatory cytokines (IL-10) and CD206 by increasing p-STAT6, reduce the inflammatory response in RA [99]. Recently, it has been reported that Fer-1 liposomes can treat corneal injury caused by alkali burn by inhibiting ferroptosis, inflammation and neovascularization [100]. Based on the close relationship between ferroptosis and inflammation, Fer-1 liposomes are expected to become a therapeutic strategy for more inflammatory diseases. Because liposomes

can be produced in large quantities with good production practices and stored for long periods at high antigen/vesicle mass ratios, there is great promise for future development of more liposomes to treat inflammatory diseases by targeting ferroptosis checkpoints.

The occurrence of ferroptosis promotes the generation of AAs, which is metabolized to generate PGs and so on under the action of LOX, COX2, and further promotes inflammatory responses. Mitochondrial ROS stimulates NLRP3 inflammatory corpuscles to promote inflammatory factor IL-1β, and inhibits the expression of anti-oxidation factor GPX4 at the same time, thus weakening the inflammatory reaction mediated by the activation of LOX and COX2 though GPX4. ROS stimulates the NRF2-Keap1 pathway, which in turn causes HO-1 to transfer from the nucleus to the cytoplasm and inhibits the inflammatory response.

Ferroptosis and inflammatory disease

AKI

AKI, formerly known as acute renal failure (ARF), is a common and critical disease caused by ischemia, nephrotoxic drugs, and urinary tract obstruction. An important feature of AKI is a rapid decline in renal function. However, the pathogenesis of AKI remains unclear, but it has long been recognized that one of the key factors is prolonged or excessive inflammation [110]. A large number of studies have shown that renal impairment can be slowed by suppressing inflammation in AKI, such as hydrogen sulfide [111], Gasdermin E [112] and Gypenoside XLIX [113]. In addition, early studies have shown that certain inflammatory cytokines can be used as therapeutic targets to reduce renal injury in AKI by inhibiting inflammation.

Significant advances have been made in the treatment of AKI in recent years, yet there are still no specific drugs developed to prevent and treat AKI. The underlying role of ferroptosis in AKI has attracted widespread attention, and recent findings suggest that ferroptosis is a potential avenue for the treatment of AKI. Changes in various ferroptosis metabolic sensors were observed in cisplatin-induced AKI models, including lipid peroxidation, GPX4 activity, NADPH and reduced GSH levels, and ferritinophagy [114]. Ferroptosis inhibitors have anti-inflammatory effects in AKI. In a mouse model of oxalate-induced AKI, Fer-1 alleviates neutrophil infiltration and pro-inflammatory cytokine release [115]. Irisin attenuated renal injury in AKI by upregulating GPX4 downregulated the inflammatory response and inhibited ferroptosis [116]. In addition, it has been shown that curcumin can reduce renal injury in AKI by inhibiting ferroptosis in renal tubular epithelial cells [116]. How ferroptosis participates in the pathogenesis of AKI is still a

mystery. Studies have reported that cells with ferroptosis can recruit macrophages and stimulate macrophages to recruit neutrophils, thereby causing an inflammatory cascade of AKI [117]. Future exploration by targeting ferroptosis in AKI may be a major breakthrough in the treatment of AKI.

ALI

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a common and critical disease caused by infection, trauma, radiotherapy, ischemia reperfusion and other factors. The pathogenesis of ALI was previously thought to be related to oxidative stress, apoptosis, inflammation and hypoxia. Recent studies suggest that ferroptosis may be involved in the development and progression of ALI, and targeting the ferroptosis pathway has become an important approach for the treatment of ALI. AUF1 inhibits ferroptosis and attenuates sepsis-induced ALI by regulating NRF2 and ATF3 [118]. Panaxydol inhibits ferroptosis and inflammatory response through the Keap1-NRF2/HO-1 pathway that attenuated LPS-induced ALI in mice [119]. Astaxanthin attenuates ferroptosis via Keap1-NRF2/HO-1 signaling pathways in LPS-induced ALI [120]. In addition, it has also been shown that isoliquiritin apioside attenuates ALI induced by intestinal I/R by blocking HIF-1α mediated ferroptosis [121]. All these studies suggest that ferroptosis is involved in the development of ALI disease pathology. Ferroptosis may regulate ALI through neutrophil extracellular traps mediate m^6A modification [122]. The future development of additional drugs or potential targets is essential for the treatment of ALI by targeting ferroptosis.

IBD

IBD is a family of chronic autoimmune diseases of the gastrointestinal tract that includes CD and ulcerative colitis (UC). Symptoms can manifest as intermittent relapses and quiescent inflammatory remissions. It is well known that inflammation caused by an abnormal immune system response in the intestinal mucosa plays an important role in the pathogenesis of IBD. Ferroptosis has been reported to be associated with intestinal epithelial cell death, research shows that STAT3-mediated ferroptosis is involved in the pathogenesis of UC [123]. Moreover, ferroptosis is involved in intestinal epithelial cell death in UC via endoplasmic reticulum stress [124]. Pharmacological inhibition of MELK significantly alleviates the inflammatory response and reduces intestinal injury in mice with colitis. Among them, the MELK inhibitor OTSSP167 significantly inhibited ferroptosis in intestinal tissues, suppressed macrophage infiltration and M1 polarization, and reduced the secretion of pro-inflammatory factors [125]. A study has shown that intestinal epithelial cells in CD showed impaired GPX4

activity and ferroptosis. The diet is rich in ω-6-PUFA-AA, which increases the risk of IBD [3]. In the future, finding more biomarkers of IBD ferroptosis has great prospects for the treatment of IBD.

Brain and neurodegenerative diseases

Neurodegenerative diseases are a kind of chronic progressive degeneration and loss of neurons in the brain and spinal cord. Major diseases include Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), etc. Iron is essential to the physiology of all tissues in the body. However, in some cases, it can be harmful, especially to the brain. Although cellular metabolism in the central nervous system requires iron as a REDOX metal for energy production and primary ATP production, neural tissue is vulnerable to oxidative damage from excess iron and the reduction of antioxidant systems. Due to the lack of specific biomarkers, several factors that may be involved in the ferroptosis process and prevent the unambiguous recognition of iron in the body. However, there is substantial evidence that ferroptosis is associated with the pathophysiology of neurodegenerative changes. Ferroptosis involves the accumulation of iron in the brain, consumption of GSH, and lipid peroxidation, while triggering a series of events including inflammatory activation, neurotransmitter oxidation, neuronal communication failure, myelin degeneration, astrocyte dysplasia, dementia, and cell death. Iron or free iron overload can trigger lipid peroxidation in neurons, astrocytes, oligodendrocytes, microglias, and Schwann cells [126]. In addition, low activity of the GPX4 and GSH systems has been shown to be associated with ferroptosis in motor neurodegeneration. The level of endogenous α-synuclein can determine the sensitivity of dopaminergic neurons to ferroptosis, by regulating the composition of ether phospholipid membrane [127]. In AD, ferroptosis may induce iron homeostasis disorder by downregulating FPN, and excess iron exacerbates oxidative damage and cognitive defects [128]. This suggests that the use of iron chelators (DFO) and ferroptosis inhibitors may be an alternative approach to the treatment of neurodegenerative diseases.

IRI

I/R is a pathological process that occurs in numerous organs throughout the human body, and it is frequently associated with severe cellular damage and death. Recently it has emerged that ferroptosis plays a significant detrimental role in many I/R models. Myocardial reperfusion injury, also known as lethal reperfusion injury, results in the death of cardiac myocytes, which are viable before reperfusion. The destruction of viable cardiac myocytes upon reperfusion ensures that the rate of death or cardiac failure is still

high, even with optimally controlled myocardial reperfusion. Clinical studies indicate that residual myocardial iron is a risk factor for inadequate left ventricular remodeling after reperfusion [129]. Notably, evidence indicates that the mitochondria-specific overexpression of GPX4 in mitochondria alleviates cardiac dysfunction following I/R [130]. Inhibition of glutaminolysis, a component of the GSH generation pathway, can also attenuate I/R-associated heart injury by blocking ferroptosis. The cardiac mechanistic target of rapamycin (mTOR) protects the heart against IRI and was found to exert protective effects against excess iron and ferroptosis. Fer-1 and iron chelation can also ameliorate heart failure induced by both acute and chronic I/R [131], consistent with the notion that targeting ferroptosis can serve as a potential strategy to prevent cardiomyopathy. A recent study found that inhibition of ferroptosis reduced endoplasmic reticulum damage and myocardial damage. At the same time, inhibition of endoplasmic reticulum can reduce ferroptosis and cell damage [132]. Tissue pigment (HC), with an effective antioxidant component and iron chelating capacity, is now used in clinical practice. However, data on HC's protective effect on ferroptosis in myocardial I/R injury are limited. A recent study found that early myocardial intervention prior to reperfusion can salvage myocardial I/R injury by preventing ferroptosis. Therefore, HC is a promising treatment option to provide secondary cardiac protection for patients undergoing coronary reperfusion therapy [133].

Indeed, there are many gaps in the specific mechanisms of ferroptosis involved in inflammatory diseases. The future development of more drugs, targets or mechanisms that target ferroptosis in inflammatory diseases could help in the treatment of inflammatory diseases, and targeting ferroptosis could be the dawn of treatment for inflammatory diseases (Table 2).

Conclusions and perspectives

The susceptibility to ferroptosis is closely linked to cellular metabolism (especially lipids, iron and amino acids), which involves a complex network structure. This also provides a possible and involvement of ferroptosis in the development of various diseases. As inflammation is present in various human diseases, further studies on the interaction between ferroptosis and the immune system are needed in the future. Regulation of ferroptosis is considered to be an effective intervention strategy for the prevention and treatment of inflammatory diseases. Damage-associated molecular patterns (DAMPs) are immune mediators of various types of regulatory cell death (RCD) [30]. HMGB1 (high mobility group box 1) is a typical DAMP that is released by ferroptosis cells and drives inflammation by activating macrophages to produce pro-inflammatory cytokines [167]. This suggests

that pharmacological induction of ferroptosis is a promising means of treating inflammatory diseases. However, the establishment of drug targets, active ingredients, potential side effects, pharmacokinetic studies, and preclinical toxicology studies are all urgent problems to be solved. In addition, how to control the side effects of ferroptosis regulation in preclinical studies and patient clinical trials is also a potential problem.

There is increasing evidence of cross-talk between various cell death modes, such as ferroptosis, apoptosis and autophagy. Studies have shown that hesperidin can alleviate cisplatin-induced AKI by reducing oxidative stress, inflammation and apoptosis [168]. This suggests that ferroptosis and apoptosis play a synergistic role in AKI, and inhibition of ferroptosis and apoptosis can exert the greatest protective effect. Some factors are involved in both apoptosis and ferroptosis control, such as P53. P53 is a tumor suppressor that can be stimulated by apoptosis stimulating proteins to induce apoptosis. In addition, P53 can also regulate ferroptosis by regulating SLC7A11. Autophagy is a protective physiological process that phagocytoses metabolites produced by cells under pressure such as starvation and hypoxia, and protects cells from the effects of these harmful metabolites. However, NCOA4-mediated ferritinophagy can induce ferroptosis by promoting ferritin degradation. This suggests that autophagy plays an essential role in the regulation of cell ferroptosis. Therefore, therapy combining ferroptosis inhibitors and autophagy or apoptosis inhibitors may provide a potential therapeutic strategy for treating inflammatory diseases, but the mechanisms underlying the interaction between ferroptosis and other cell death modes require further investigation.

In this review, we summarize the molecular mechanisms of ferroptosis and the possible mechanisms of ferroptosis involved in inflammation and inflammatory diseases. Ferroptosis is considered as a target for the treatment of inflammatory diseases. The development of more ferroptosis inhibitors or drugs targeting ferroptosis will greatly improve the therapeutic effect of inflammatory diseases. However, practical applications still face many difficulties. First, it is difficult to determine whether the effects of ferroptosis inhibitors or drugs that target ferroptosis are specific to a particular class of inflammatory diseases with unique characteristics or are generally applicable to most inflammatory diseases. Since the specific mechanisms by which ferroptosis is involved in various inflammatory diseases have not been fully elucidated, a deeper understanding of the mechanisms associated with ferroptosis and inflammation will help to achieve this goal. Second, besides inflammatory diseases, ferroptosis is associated with pathological cell death associated with a variety of diseases, such as cancer. While avoiding systemic adverse reactions, it is particularly important to develop specific treatments that inhibit ferroptosis in inflammatory diseases. Third, there is still a lack of ferroptosis biomarkers

Table 2 About ferroptosis inhibitors for the treatment of inflammatory diseases. List four typical ferroptosis-associated inflammatory diseases (AKI, ALI, UC and PD) as well as the ferroptosis inhibitors treating them and the specific mechanisms

Inflammatory diseases	Ferroptosis inhibitors	Functional mechanisms	References
AKI	Nec-1f (a solid inhibitor of RIPK1 and weak inhibitor of ferroptosis)	NA	[133]
AKI	Quercetin (a selective ferroptosis inhibitor)	By reducing the levels of MDA and lipid ROS and increasing the levels of GSH	[134]
AKI	VDR agonist paricalcitol	By decreasing lipid peroxidation, 4HNE, MDA and reversing GPX4 downregulation	[135]
AKI	Pachymic acid (PA)	The inhibition of ferroptosis in the kidneys through direct or indirect activation of NRF2	[136]
AKI	XJB-5-131	NA	[137]
AKI	Irisin	By upregulating GPX4; via the SIRT1/NRF2	[116, 138]
AKI	HO-1	NA	[139]
AKI	Rheb1	Via maintaining mitochondrial homeostasis	[140]
AKI	Maresin conjugates in tissue regeneration 1 (MCTR1)	Through the NRF2 signaling	[141]
AKI	Dexmedetomidine	By inhibiting ACSL4 via α2-AR	[142]
AKI	A-lipoic acid	NA	[143]
AKI	Polydatin	Via maintenance of the system Xc^--GSH-GPX4 axis and iron metabolism	[144]
AKI	Entacapone	By enhancing antioxidant capacity	[145]
AKI	Farnesoid X receptor	By regulating the transcription of genes involved in ferroptosis	[146]
AKI	Human urine-derived stem cells (USCs)-derived exosomes (USC-Exo)	LncRNA TUG1 carried by USC-Exo regulated ASCL4-mediated ferroptosis by interacting with SRSF1	[147]
ALI	iASPP	Depends on NRF2 signaling	[148]
ALI	NRF2	By modulating TERT and SLC7A11; via regulating SLC7A11 and HO-1	[149, 150]
ALI	Panaxydol	By Keap1-NRF2/HO-1 pathway	[119]
ALI	STAT3	By regulating SLC7A11	[151]
ALI	STAT6	Via regulating P53/SLC7A11 pathway	[152]
ALI	Itaconate	Via NRF2 pathways	[153]
ALI	AUF1	By regulating NRF2 and ATF3	[118]
ALI	Sevoflurane	By up-regulating HO-1 expression	[154]
ALI	Obacunone	By upregulating Nrf2-dependent antioxidant responses	[155]
ALI	Isoliquiritin	By blocking Hif-1α signaling	[121]
UC	miR-137	By targeting glutamine transporter SLC1A5 in melanoma	[156]
UC	MELK inhibitor	By inhibiting AKT/IKK/P65 and ERK/IKK/P65 signaling cascades	[125]
UC	Curculigoside	Through the induction of GPX4	[157]
UC	Astragalus polysaccharide	Via inhibiting NRF2/HO-1 pathway	[158]
UC	Furin	By activating the NRF2-GPX4 signaling pathway	[159]
UC	STAT3	NA	[123]
PD	FTH1	Through ferritinophagy	[160]
PD	PKC inhibitors	NA	[161]
PD	Clioquinol	Through AKT/mTOR pathway	[162]
PD	Thioredoxin-1	Through regulating GPX4 and GSH	[163]
PD	DL-3-n-butylphthalide	NA	[164]
PD	Cu^{II} (atsm)	NA	[165]
PD	Keap1-NRF2 PPI inhibitors	NA	[166]

for specific inflammatory diseases. Exploring appropriate biomarkers will further promote the development of research and treatment of various inflammatory diseases in vivo and in vitro. Fourth, even though targeting ferroptosis is considered a promising approach for the treatment of inflammatory diseases, the crosstalk between ferroptosis and other forms of cell deaths makes the treatment of ferroptosis-specific inhibitors targeting inflammatory diseases limited and resistant. Can combination of ferroptosis inhibitors with other cell death inhibitors improve the efficacy of inflammatory diseases? To address this issue, further exploration of the link between ferroptosis, inflammatory diseases, and other types of cell death will be necessary in the future. Last but not least, although selective inhibition of ferroptosis has been shown to significantly improve inflammatory diseases in a variety of animal models, no clinical trials using specific inhibitors of ferroptosis have been conducted to date. More population-based data are urgently needed to determine whether selective blocking of ferroptosis can improve the prognosis of inflammatory diseases in clinical settings.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare that they have no competing interests.

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