The role of ferroptosis in acute lung injury

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Abstract
Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a common disease with high morbidity and mortality, and its pathogenesis is believed to be related to oxidative stress, apoptosis, inflammation, and hypoxia. Ferroptosis is a type of nonapoptotic cell death characterized by iron-dependent lipid peroxide accumulation and is involved in many cellular physiological processes. Recent studies have confirmed that ferroptosis may be involved in the development of ALI. This review summarizes the most recent discoveries on the role of ferroptosis in ALI to provide new strategies for its prevention and treatment.

Keywords Ferroptosis · Glutathione peroxidase 4 · Lipid peroxidation · Acute lung injury

Acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is a common and critical disease caused by several factors, including infection, trauma, radiation, and ischemia-reperfusion [1–4]. Although significant advancements have been achieved, such as mechanical ventilation and corticosteroid administration, the annual mortality of ALI remains 40% [5]. Thus, efforts to develop new targets that interrupt the progression of ALI to ARDS are an attractive endeavor. The pathogenesis of ALI was previously believed to involve oxidative stress, apoptosis, inflammation, and hypoxia [6–8]. Recent studies have demonstrated that ferroptosis might be involved in the development of ALI [9]. In this review, the most recent discoveries regarding the role of ferroptosis in ALI are reviewed to provide new strategies for its prevention and treatment.

Ferroptosis
Ferroptosis was first found in RAS mutant tumor cells treated with erastin [10]. The morphology of cells undergoing ferroptosis is different from that of cells undergoing apoptosis, pyroptosis, and other cell death mechanisms. Ferroptosis is mainly characterized by the shrinkage of mitochondria, a decrease or disappearance of mitochondrial cristae, atrophy of the mitochondrial membrane and a lack of chromatin condensation [11]. Because the cell death mode depends on iron, accompanied by the accumulation of peroxide in cells, and can be inhibited by iron-chelating agents, it is called ferroptosis [12].

Mechanism and regulation of ferroptosis
Iron overload and ferroptosis
Intracellular free iron plays an important role in ferroptosis and reacts with H₂O₂ to generate free radicals through the Fenton reaction [13]. The fatty acid hydroperoxide produced by lipoxygenase also requires Fe²⁺ to generate free radicals. These free radicals constantly destroy the structures of cell biofilms and disrupt their function, thereby inducing ferroptosis [14]. Additionally, glutathione (GSH), an important antioxidant, can regulate the production of reactive oxygen species (ROS) by the key enzyme glutathione peroxidase.

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Iron overload caused by iron metabolism disorder is closely related to ferroptosis. The application of iron-chelating agents and the upregulation of ferritin levels can inhibit ferroptosis [16], suggesting that iron metabolism plays an important role in the phenomenon. The body maintains the balance of iron input and output under normal conditions; most of the iron used in the body every day derives from the release of iron from aged red blood cells after phagocytosis, and a small part is obtained from the diet [17]. In the intestinal tract, Fe³⁺ is transformed into Fe²⁺ under the action of duodenal cytochrome b (Dcytb) and is then absorbed into intestinal epithelial cells through a divalent metal transporter 1 (DMT1) [18, 19]. After entering the cells, the majority of Fe²⁺ is oxidized to Fe³⁺ and forms ferritin, while a small amount of nonoxidized Fe²⁺ can enter the plasma through the basement membranes of intestinal epithelial cells via ferroportin (Fpn) [20]. After entering the plasma, nonoxidized Fe²⁺ is oxidized into Fe³⁺ again and combines with transferrin (Tf) to form Tf-Fe³⁺. When Tf-Fe³⁺ binds to cellular transferrin receptor 1 (TFR1), Fe³⁺ is reduced to Fe²⁺ via a six-transmembrane epithelial antigen of prostate 3 (Steap3) and then enters the cytoplasm via DMT1 [21]. Some Fe²⁺ forms ferritin, while some forms a labile iron pool (LIP) [22], and cytoplastic iron can also be exported to cells via the membrane iron transporter Fpn [23].

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The iron metabolism balance depends on several regulators, such as Tf and hepcidin [24, 25]. Hepcidin binds to Fpn to promote the degradation of these transporters, thus inhibiting the absorption and release of iron [26]. Under inflammatory conditions, human lactoferrin (hLf) inhibits the expression of interleukin-6 (IL-6) and Fpn to alleviate intracellular iron overload [27]. In addition, lipocalin 2, a key factor involved in iron regulation, prevents bacterial siderophores from obtaining iron during infection, stabilizes the LIP, and isolates iron in the mucosa and cavity during inflammation to ensure low iron levels [28].

The stability of the intracellular iron content depends on iron regulatory protein/iron-responsive elements (IRPs/IREs), including IRP1 and IRP2. IREs are highly conserved RNA stem-loops found in the mRNAs encoding proteins involved in iron metabolism. IREs combine with the 5’ iron-reactive elements of ferritin and iron transporters to prevent their synthesis, and IREs bind to the 3’ iron-reactive elements of transferrin receptor 1 and DMT1 to prevent their degradation, thus increasing the intracellular iron level. When the iron level in cells is high, IRE1 is converted into cis-aconitase, and IRE2 is degraded and reduces the iron storage capacity and iron output, thus reducing the intracellular level of free iron [29]. The iron chelators deferoxamine (DFO) and ciclopirox (CPX) inhibit ferroptosis by reducing the utilization of iron and reducing the oxidative stress level in cells [30, 31].

### Lipid peroxidation and ferroptosis

Fatty acids, including saturated fatty acids, monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFAs), play several roles in cells, including blocking cell membranes, providing energy and even acting as signaling molecules [32]. Interestingly, PUFAs (especially arachidonic acid and adrenal acid) promote ferroptosis through lipid peroxidation [33]. Lipid peroxidation can be achieved via enzymatic and nonenzymatic methods, which require iron. Iron not only promotes lipid peroxidation through a nonenzymatic mechanism but also increases arachidonic acid lipooxygenase (ALOX) activity through endocrine signaling [34]. Additionally, lipid peroxide scavengers such as vitamin E, ferrostatin-1 and lipoxygenase-1 can capture lipid peroxide through lipophilic free radicals and inhibit ferroptosis [35, 36]. Undeniably, additional work is needed to understand the roles of ALOX and lipid peroxide scavengers in mediating different types of ferroptosis.

### GSH depletion and ferroptosis

GSH, a tripeptide that contains cysteine, is often considered the main antioxidant in the human body [37]. System XC, composed of two protein subunits, solute carrier family 7 member 11 (SLC7A11) and solute carrier 3A2 (SLC3A2), is an amino acid transporter that imports cystine and exports glutamic acid, and it exchanges intracellular glutamate with extracellular cysteine to produce GSH [38]. Erastin, a small molecule that induces ferroptosis, can inhibit the transmembrane protein SLC7A11, thus inhibiting the amino acid antiporter system Xc⁻, reducing the amount of cystine taken in by cells and decreasing the level of GSH to promote ferroptosis [39]. Buthionine sulfoximine (BSO) inhibits glutamate-cysteine ligase (GCL) and directly inhibits GSH synthesis, causing ferroptosis [40]. The utilization of GSH depends on the key enzyme GPX4, and GPX4 knockout can promote ferroptosis [41]. RSL3 can covalently bind to the active site Sec of GPX4 and directly inhibit the activity of GPX4, thus inducing ferroptosis [42]. Statins inhibit the formation of selenocysteine-tRNA (tRNA(Sec)) and inhibit the synthesis of GPX4 to induce ferroptosis [43].

### Antioxidant and ferroptosis

Coenzyme Q 10 (CoQ10) is an endogenous fat-soluble antioxidant, and exhaustion of CoQ10 produced by GPX4 and the mevalonate pathway by a ferroptosis inducer derived from CIL56 (FIN56) induces ferroptosis [44]. In addition, inhibiting the lipid metabolism pathway, decreasing the
sources of lipid peroxides, such as modulating/inhibiting acyl-CoA synthase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), and inhibiting lipid peroxidation involving Lox can also inhibit ferroptosis [45]. In addition, ferroptosis suppressor protein 1 (FSP1) can use nicotinamide adenine dinucleotide phosphate (NADPH) to catalyze the regeneration of CoQ10 to thereby inhibit ferroptosis [46]. Nuclear factor E2-related factor 2 (NRF2) and heat shock protein B1 were recently shown to affect the sensitivity of cells to ferroptosis inducers by regulating cellular iron metabolism [47, 48] (Fig. 1).

**Ferroptosis and ALI**

ALI/ARDS is a serious illness with high morbidity and mortality. Increased ROS, epithelial cell apoptosis, and inflammation are important pathogenic mechanisms of ALI [49]. Recent studies have shown that ferroptosis plays a critical role in the development of ALI (Fig. 1).

**Infection-related ALI**

Infection and sepsis are the main pathogenic factors of ALI/ARDS [50]. Recent studies have demonstrated that ferroptosis plays an important role in the occurrence and development of ALI caused by infection. The expression of GPX4 in the lung tissues of mice infected with *Mycobacterium tuberculosis* (MTB) was shown to be significantly decreased, and the production of lipid peroxide in lung parenchyma cells was increased [51]. In an ALI mouse model induced by lipopolysaccharide (LPS), the concentration of free iron in the bronchial epithelial cells of ALI mice was significantly increased, while the expression of SLC7A11 and GPX4, ferroptosis markers, was dramatically decreased [52]. However, the degree of lung injury in mice pretreated with the ferroptosis inhibitor ferrostatin-1 was significantly improved, suggesting that ferroptosis plays an important role in the occurrence and development of ALI caused by MTB and LPS [51, 52]. In addition, panaxydol can inhibit ferroptosis in ALI induced by LPS, and its effect is due to the upregulation of the Kelch-like ECH-associated protein 1 (Keap1)-Nrf2/heme oxygenase-1 (HO-1) pathway [53, 54].

![Diagram](image-url)

**Fig. 1** Mechanism and regulation of ferroptosis in alveolar epithelial cells in ALI. In alveolar epithelial cells, pathogenic factors can increase the levels of Fe$^{3+}$ and H$_2$O$_2$. Increased Fe$^{3+}$ can be reduced to Fe$^{2+}$ by Steap3 and then enter the cytoplasm via DMT1 to generate free radicals through the Fenton reaction. These free radicals can oxidize membrane lipids, such as PUFAs, into lipid peroxides, constantly disrupting the structure and function of cell biofilms, thus inducing ferroptosis and leading to ALI. This process can be inhibited by regulating key proteins of the ferroptosis pathway, such as GPX4 and System XC, as well as the labile iron pool. *System XC* cysite/glutamate antporter system; *PUFA* polyunsaturated fatty acid; *GSH* glutathione; *GSSG* glutathione disulfide; *GPX4* glutathione peroxidase 4; *Fpn* ferroportin; *TFR1* transferrin receptor 1; *STEAP3* six-transmembrane epithelial antigen of the prostate 3; *LIP* labile iron pool; *ROS* reactive oxygen species; *DFO* deferoxamine; *CPX* ciclopirox; *HMOX1* heme oxygenase 1; *BSO* buthionine sulfoximine; *DAMPS* damage-associated molecular patterns; *ALI* acute lung injury.
Pseudomonas aeruginosa is an important pathogen that causes nosocomial infection. The ΔwspF mutant of P. aeruginosa can enhance the activity of lipoxygenase (pLOXA) to oxidize arachidonic acid-phosphatidylethanolamines (AA-PE) into 15-hydroperoxy-AA-PE (15-HOOAA-PE) to thereby induce ferroptosis, suggesting that ferroptosis mediates the occurrence of pneumonia caused by P. aeruginosa [55, 56].

Furthermore, ferroptosis was shown to be involved in the development of viral pneumonia. Banchini et al. found that SARS-CoV-2 could activate the hepcidin-Fpn pathway and promote ferroptosis by mobilizing iron in the vascular space, leading to acute lung inflammation [57]. Further analysis revealed that the levels of peroxide in the myocardial and renal tissues of patients with viral myocarditis of unknown cause were not significantly increased, while its levels in the myocardial cells of patients with COVID-19 were significantly increased, indicating that SARS-CoV-2-induced acute pneumonia may induce intracellular peroxide accumulation and cause ferroptosis in lung parenchyma cells to thereby induce an inflammatory reaction [58]. Regarding the important role of ferroptosis in the pathogenesis of COVID-19, iron chelators, such as lactoferrin (Lf), may have high therapeutic value [59].

Radiation-related ALI

Radiotherapy is a method used to treat malignant chest tumors, and radiation-induced lung injury (RILI) is the most common complication of chest radiotherapy [60]. Because of the heterogeneity of individuals and the high cumulative radiotherapy dose, radiation-induced lung fibrosis (RILF) often develops in the late stage of radiotherapy and seriously affects the prognosis of patients. A strategy for preventing RILI in patients undergoing chest tumor radiotherapy urgently needs to be developed [61]. Recent studies suggest that ferroptosis is a target for the prevention and treatment of RILI and pulmonary fibrosis. In an acute RILI mouse model, the expression of GPX4, a ferroptosis marker, was decreased, and mitochondria in lung tissue developed a ferroptosis phenotype, as evidenced by electron microscopy. Treatment with the ferroptosis inhibitor lipostatin-1 was shown to significantly downregulate the levels of ROS in the lung and the levels of inflammatory cytokines [tumor necrosis factor-alpha (TNF-α), IL-6, interleukin-10 (IL-10), and transforming growth factor-beta1 (TGF-β1)] in serum, indicating that ferroptosis plays a key role in RILI [62, 63].

ALI associated with ischemia–reperfusion

Ischemia–reperfusion injury is an important pathophysiological phenomenon associated with severe trauma, infection, and major surgery, and the main mediator of injury is the systemic inflammatory response [64, 65]. Ischemia–reperfusion injury in a single organ can spread to adjacent or distant tissues and organs through the transmission of inflammatory factors [66]. The lung, one of the most vulnerable organs, is often impacted by ischemia–reperfusion injury, which can lead to ALI [67]. P53, a tumor suppressor, regulates the occurrence and development of ALI by inhibiting apoptosis and ferroptosis. Recent studies have demonstrated that an inhibitor of the apoptosis-stimulating protein of p53 (iASPP) can inhibit ferroptosis and alleviate ALI caused by intestinal ischemia–reperfusion in mice. Additionally, the protective effect of the iASPP inhibitor was reduced in Nfr2-knockout mice, suggesting that the protective effect mediated by iASPP partly depends on Nfr2 signaling. In addition, ACSL4, a key enzyme involved in ferroptosis, can significantly improve ischemia–reperfusion injury [45]. A recent study showed that Nrf2 can inhibit ferroptosis by regulating SLC7A11 and HO-1 to thereby improve ALI caused by intestinal ischemia–reperfusion [68]. Thus, ferroptosis is involved in ALI induced by ischemia/reperfusion [69].

ALI caused by physical and chemical factors

In addition, physical and chemical factors commonly cause ALI. Recent experiments have proven that the levels of ROS and lipid ROS are decreased, that the mRNA expression of GPX4 is increased, and the mitochondrial membrane potential of cells is maintained in lung epithelial cells treated with seawater after treatment with the Nrf2 activator dimethyl fumarate. Additionally, the degree of lung injury observed in Nrf2-knockout mice was more serious than that observed in wild-type mice after drowning in seawater. The above results showed that Nrf2 can reduce drowning-induced ALI caused by inhibiting ferroptosis [70]. In a lung injury mouse model induced by oleic acid (OA), the content of GSH was decreased, and the level of malondialdehyde (MDA) was increased in the lung tissue. In addition, the expression of GPX4 and ferritin was decreased in the lung tissues of the OA-induced lung injury group, which indicated that ferroptosis was also involved [71]. These results suggest that ferroptosis is related to lung injury, but there is still a lack of large-scale clinical research to provide evidence for the optimal treatment plan and treatment safety.

Treatment of ALI based on ferroptosis

Increasing studies have shown that ferroptosis may play a key role in the development of ALI, indicating that the interruption of ferroptosis may be a new target for ALI treatment. In recent studies, several ferroptosis regulators, include iron steady-state regulators and lipid peroxidation.
inhibitors, have been shown to have therapeutic effects on ALI (Table 1).

**Iron homeostasis regulator**

In ALI, the levels of free iron in lung tissues are significantly increased, and the iron homeostasis of cells is out of balance, leading to ferroptosis. The iron chelators DFO and CPX can remove excessive iron from lung tissue to maintain iron homeostasis in cells and inhibit ferroptosis. In the mechanical ventilation-induced ALI model, the high-volume ventilated rats exhibited typical lung edema and histological lung injury, and the level of ROS was increased in alveolar macrophages and mitochondria. However, the level of ROS was reduced in rats preconditioned with DFO, suggesting that DFO ameliorates lung injury in the mechanically ventilated SD rat model [72]. Similarly, DFO inhibited inflammation and improved lung injury by reducing oxidative stress and mitochondrial instability in an LPS-induced ALI model [73]. Heparicin, an iron export protein, can inhibit ferroptosis by regulating iron export mediated by iron transporters and by regulating the level of Fpn in cells. The promoter of the hepcidin gene contains the binding site of the phosphorylated signal transducer and activator of transcription 3 (STAT3) dimer. Furthermore, IL-6 can induce STAT3, and the JAK-STAT signaling pathway acts on the promoter of the hepcidin gene to regulate gene expression, thereby regulating iron homeostasis [74]. Studies have shown that early application of hepcidin downregulates the renal levels of cyclooxygenase-2 (Cox-2) and the serum levels of TNF-α in mice with LPS-induced acute kidney injury, indicating that hepcidin can alleviate acute renal failure and acute tubular necrosis in acute kidney injury induced by ischemia–reperfusion; however, no studies have confirmed its positive effect on ALI [75].

**Small-molecule inhibitor of ferroptosis**

Ferrostatin-1 is an important small-molecule inhibitor of ferroptosis that prevents lipid membrane damage via an iron reduction mechanism [76]. Ferrostatin-1 alleviates inflammation caused by angiotensin II (Ang II) by decreasing ROS levels and activating the Nrf2/HO-1 signaling pathway [77]. In an LPS-induced ALI model, cell viability and the levels of the ferroptosis markers SLC7A11 and GPX4 were downregulated in the LPS group, while the levels of MDA, 4-hydroxynonenal (4-HNE), and total iron were increased by LPS treatment. In contrast, the cell viability in the LPS+ferrostatin-1 group was higher than that in the LPS group. In addition, the amounts of MDA, 4-HNE and total iron in the LPS+Fe-1 group were lower than those in the LPS group. These results indicated that Fer-1 exerts a therapeutic effect on LPS-induced ALI and downregulates the ferroptosis level in lung tissues [52].

**Lipid peroxidation inhibitor**

GPX4 is an important antioxidant enzyme, and a decrease in the level of GPX4 increases lipid peroxidation and promotes lung tissue necrosis in mice with ALI caused by MTB [51]. Nrf2 is also a key regulator of oxidative stability in cells. The target genes of Nrf2 include intracellular redox balance proteins. For example, HO-1, GPX4, and SLC7A11 are activated under high oxidative stress and play antioxidant roles [78]. In recent research, the Nrf2/HO-1 pathway was proven to be involved in ferroptosis. In this study, compared with the LPS-induced ALI group, the PX (panaxydol) + LPS group showed decreased cell viability and increased cell death and Fe²⁺ accumulation. Interestingly, the expression of Keap1 was significantly decreased and the expression of Nrf2 and HO-1 was increased after treatment with PX, which suggested that PX alleviates ALI by upregulating the Keap1-Nrf2/HO-1 pathway [53]. In addition, lipostatin-1 (Lip-1), a ferroptosis-specific inhibitor, is an important lipid peroxidation inhibitor. In the ALI model after lung ischemia–reperfusion, the levels of tissue iron and lipid peroxidation were decreased after the application of Lip-1, thereby alleviating lung injury induced by ischemia–reperfusion by reducing lipid peroxidation and increasing the levels of GSH and GPX4 [45].

**Conclusion**

Ferroptosis is a unique form of regulated cell death, and the ferroptosis process has been observed in the context of several types of acute lung injury. However, most studies on the relationship between acute lung injury and ferroptosis are qualitative, and the extent to which ferroptosis is involved in ALI remains largely unknown. Intervening with the ferroptosis process may contribute to the prevention and treatment of ALI, but the exact dose and side effects of ferroptosis inhibitors remain largely unknown, and whether respiratory-specific ferroptosis regulators exist remains unknown. Therefore, more comprehensive and in-depth studies on the

**Table 1 Ferroptosis inhibitor**

| Ferroptosis inhibitor | Mechanism of action                                    |
|-----------------------|--------------------------------------------------------|
| DFO, CPX, lactoferrin (HLF), curcumin | Chelate iron                                    |
| Thiazolidinedione     | Suppresses ACSL4                                      |
| Vit E, α-tocopherol   | Inhibit lipid peroxidation                            |
| Ferrostatin-1, liproxastin-1 | Inhibit lipid peroxidation                        |
| Zileuton              | Inhibit lipoxygenase                                  |
| Panaxynol, baicalein  | Inhibit lipid peroxidation                            |
relationship between acute lung injury and ferroptosis are needed to expand our understanding of acute lung injury and to regulate ferroptosis to thereby protect the lungs from damage caused by acute lung injury.

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Author contributions WX and JZ developed the idea for the study, and XL wrote the paper.

Data availability Data sharing was not applicable to this article, as no datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All authors are familiar with the contents of the final draft and take responsibility for the authenticity of the data used in the paper. This manuscript is original and has not been previously published, nor has it been simultaneously submitted to any other journal. The manuscript has been approved by all authors for publication.

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