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REVIEW

The Emerging Roles of Ferroptosis in Pathophysiology and Treatment of Acute Lung Injury

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Abstract: Ferroptosis, a programmed cell death discovered in recent years, is an iron-dependent lipid peroxidation accumulation. Unlike other modes of cell death (autophagy, necroptosis, pyroptosis, cuproptosis, etc.), ferroptosis has unique morphological characteristics and plays an important role in a variety of diseases. In recent years, there has been great progress in the study of ferroptosis. Studies have found that ferroptosis is associated with acute lung injury (ALI), a condition with a high mortality rate and limited treatment options. This paper summarizes the mechanism of ferroptosis from the perspectives of iron metabolism, lipid metabolism, amino acid metabolism, and glutathione metabolism. It also discusses the research progress of ferroptosis in ALI in order to find new directions for the prevention and treatment of this condition.

Keywords: ferroptosis, acute lung injury, ischemia, sepsis, targeted therapy

Introduction

Cell death plays an important role in promoting organ development and maintaining tissue and cell homeostasis. Cell death is divided into accidental cell death and programmed cell death.[1] Programmed cell death is mainly divided into apoptotic and non-apoptotic forms. Ferroptosis is a programmed cell death different from necroptosis and autophagy discovered in recent years and is characterized by iron-dependent lipid peroxides (LPO) accumulation.[2,3] ALI refers to alveolar epithelial cells and capillary endothelial cells damage caused by various intrapulmonary and extrapulmonary pathogenic factors, resulting in diffuse pulmonary interstitial and alveolar edema, leading to acute hypoxic respiratory insufficiency. Rapidly developing respiratory failure characterizes the acute, exudative phase of ALI (0–7 days). Within the first 12 to 24 hours following the onset of the disease, tachypnea, tachycardia, and respiratory alkalosis may occur. These symptoms may precede the discovery of diffuse bilateral infiltrates on an X-ray. These findings point to diffuse alveolar damage caused by the breakdown of the epithelial-endothelial barrier, which led to an excessive leakage of blood cells and protein-rich fluid into the interstitium and alveoli. Active neutrophils migrate in reaction to tissue damage, working with platelets, alveolar macrophages, other inflammatory and fixed lung cells to produce a number of substances that exacerbate inflammation but can also serve as biomarkers of the acute stage of the disease.[4] ALI has a mortality rate of up to 40% and is a major disease endangering human life and health. The pathogenesis of ALI is very complex and is currently considered to be associated with cytotoxic mechanisms such as inflammation and oxidative stress, but there are no effective targeted therapeutic measures.[5] As research has deepened, more evidence suggests that ferroptosis is involved in the pathogenesis of ALI. In recent years, Scientists have confirmed that ferroptosis is associated with ALI caused by ischemia-reperfusion,[6–8] sepsis,[9,10] radiation,[11] drowning[12] and oleic acid[13] through animal and cell

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model experiments. However, their specific mechanisms, and potential treatment options remain to be further investigated. In this paper, the mechanism of ferroptosis and its research results in the pathogenesis and treatment of ALI are summarized. It is considered that ferroptosis can be used as a target for the prevention, diagnosis of ALI and shows great prospects in the treatment of ALI.

Materials and Methods

The following databases were searched for articles focusing on ferroptosis and ALI: EMBASE, PubMed, and Google Scholar. The retrieval period spanned from 2012, when ferroptosis was introduced, to January 2023. The papers were extracted using search keywords such as "acute lung injury" with "ischemia", or "sepsis", or "radiation", or "drowning", or "oleic acid", and "ferroptosis"; studies written in English were extracted. We considered the manuscript suitable for further analysis if two of the three authors agreed that it met the eligibility criteria.

Mechanism of Ferroptosis

In 2012, Dixon et al[13] found that the cause of death in some cells was related to iron ion concentration and named this novel mode of non-apoptotic cell death "ferroptosis" for the first time. Since then, the concept of ferroptosis has been gradually known by international scholars. In 2018, the Cell Death Nomenclature Committee defined ferroptosis as one of the programmed cell death patterns.[1]

Abnormal Iron Metabolism (Iron Overload)

Iron overload has been found to be one of the key links in ferroptosis. As an essential micronutrient for maintaining the health of the body, iron is mainly present in various cellular activities in the form of Fe^{2+} or Fe^{3+}. In normal human body, iron requires the help of transferrin (TF) and TF receptor (TFR) 1 to complete the process of operation, that is, one molecule of TF binds two molecules of Fe^{3+} to form a complex.[14] When extracellular material enters the cell, Fe^{3+} released from the complex is reduced to Fe^{2+}, which is then stored in a variable iron pool by divalentmetal-iontransporter-1 (DMT1), and the remaining Fe^{2+} is oxidized out of the cell and circulates in the body to maintain iron homeostasis.[15] When the imbalance of iron in the body initiates, the supply exceeds the demand for iron in the human body, and the excess active iron accumulates in the vital organs and tissue cells of the human body, resulting in iron overload. It produces a large number of cytotoxic hydroxyl radicals and a large number of reactive oxygen species (ROS) under the action of the Fenton reaction, which in turn breaks the molecular structure of genes and destroys vascular endothelial cell membranes, lipids and DNA. Superoxide radicals ($O_2^{\bullet-}$), hydrogen peroxide ((H_2O_2), hydroxyl radicals ($OH^{\bullet}$), and singlet oxygen ($^1O_2$) are examples of non-free radical oxygen intermediates (peroxides) that are included in ROS. These compounds are produced by diverse cytosolic enzymes, including cyclooxygenases, lipid metabolism inside peroxisomes, and plasma membrane proteins, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Despite the fact that all of these sources add to the overall oxidative burden, the majority of cellular ROS (about 90%) are produced in the mitochondria through oxidative phosphorylation.[16,17] At the same time, iron also plays a non-negligible role in lipid peroxidation or ferroptosis.[18,19] Therefore, ferroptosis is more likely to occur in response to stimulation by iron overload, and abnormal iron metabolism is an important manifestation of the cellular ferroptosis process.

Lipid Peroxidation

One of the most striking features of ferroptosis is plasma membrane damage mediated by lipid peroxide accumulation. Lipidomics have shown that long chain acyl-coenzyme A synthetase 4 (ACSL4) and lysophosphatidylcholine acyl transfer 3 (LPCAT3) play key roles in regulating lipid peroxidation.[20,21] ACSL4 catalyzes the combination of acetyl-CoA and polyunsaturated fatty acids (PUFAs) such as arachidonic acid (AA) and adrenic acid (Adrenoyl, AdA) to generate AA-coenzyme A and AdA-coenzyme A, which are esterified to phosphatidylethanolamine (PE) to form AA-PE and AdA-PE under the action of LPCAT3, and LPO under the action of lipoxygenase. LPO is eventually metabolized into the toxic aldehydes 4-hydroxynonenal and malondialdehyde (MDA), causing irreversible damage to the cell membrane and plasma membrane, leading to cell death.[22] Therefore, high expression of ACSL4 and LPCAT3 is considered as one of the

important hallmarks of ferroptosis. Notably, Doll et al[23] and Bersuker et al[24] named ferroptosis suppressor protein 1 (FSP1), which uses NAD (P) H to catalyze coenzyme Q10 to promote the expression of lipophilic free radicals, inhibits the membrane lipid peroxidation cascade in the absence of GPX4 content, and prevents the occurrence of ferroptosis. In addition, ferroptosis inducer 56 (FIN56), a novel ferroptosis inducer, can inactivate GPX4 through the mevalonate pathway and inhibit the synthesis of lipophilic antioxidants and promote ferroptosis.[25] Interestingly, autophagic degradation of lipid droplets promotes ferroptosis in hepatocytes induced by the ferroptosis activator RSL3, while RSL3-induced LPO with ferroptosis is prevented by promoting lipid storage or inhibiting lipid droplet degradation, suggesting that lipid droplets may play an antioxidant role during ferroptosis.[26] The above studies showed that ferroptosis can be regulated by regulating enzymes related to PUFA membrane phospholipid biosynthesis.

Glutamate-Cystine Transport Dysfunction

Cystine/glutamate reverse transporter (systemXc-), which is blocked in glutamate-cystine transport as an important amino acid transporter, plays an important role in maintaining glutamate homeostasis, cystine transport, and glutathione (GSH) synthesis.[27] Through this transporter, extracellular cystine can be transported into the intracellular space in healthy organisms to promote GSH synthesis. GSH acts as an antioxidant and detoxifying agent by transforming toxic substances in the body into nontoxic and harmless substances that eventually excrete them from the body. Substantial accumulation of ROS in the body is removed by GSH. GSH can assist GPX4 to complete the antioxidant effect.[28,29] When cystine/glutamate reverse transporter is accidentally blocked, the influx of cystine is limited, the production of GSH decreases correspondingly with the decrease of cysteine, then GPX4 reactivity weakens, which further promotes the accumulation of ROS, and increases the probability of ferroptosis[30] (Figure 1).

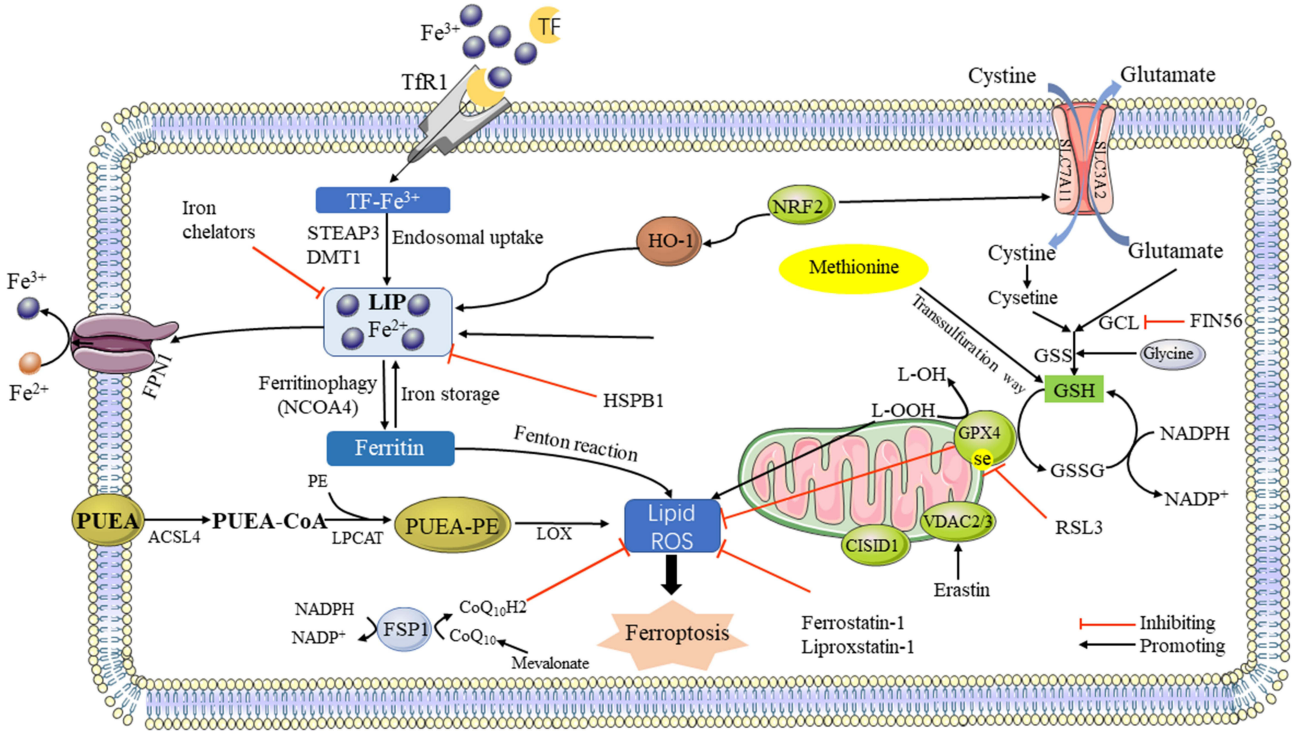

Figure 1 The mechanisms of ferroptosis. Iron accumulation, excessive ROS production and overwhelming lipid peroxidation are hallmarks of ferroptosis. There are three main metabolic pathways that initiate and execute ferroptosis, amino-acid/GSH, lipid, and iron pathways. Moreover, ferroptosis sensitivity is also controlled by additional signaling pathways and regulators. Ferroptosis is illustrated here, demonstrating the key molecules and targets involved in regulating the peroxidation of iron and lipids.
Abbreviations: TF, transferrin; TFR1, transferrin receptor 1; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT, lysophosphatidylcholine acyltransferase; FIN 56, Ferroptosis-Inducer-56; DMT1, divalent metal transporter 1; FPN1, ferroportin 1; GSH, glutathione; GSSG, oxidized glutathione; GSS, glutathione synthetase; GCL, glutamate-cysteine ligase; GPX4, glutathione peroxidase 4; HO-1, haem oxygenase 1; HSPB1, heat shock protein beta-1; LOX, lipoxygenase; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor E2-related factor 2; PUFA, polyunsaturated fatty acid; PE, phosphatidylethanolamine; ROS, reactive oxygen species; RSL3, Ras-selective lethal 3; STEAP3, six-transmembrane epithelial antigen of prostate 3 metalloreductase; SLC7A11, solute carrier family 7 member 11; SLC3A2, solute carrier family 3 member 2; VDAC2/3, voltage dependent-anion channel 2/3.

Regulatory Mechanism of Ferroptosis

In recent years, scientists have made rapid progress in the study of ferroptosis regulation mechanism. Glutathione peroxidase 4 (GPX4), nuclear factor E2 related factor 2 (Nrf2), and Xc-system have been validated as important regulators of ferroptosis. GPX4 converts intracellular lipid hydrogen peroxide into lipid alcohols, promotes the breakdown of hydrogen peroxide (H_2O_2), repairs oxidative damage in lipid cells, and protects cell membranes from oxidative damage, and its inactivation will lead to the accumulation of intracellular lipid peroxides and ferroptosis.[31] Nrf2 plays a very important role in ferroptosis by regulating anti-inflammatory, iron homeostasis, and lipid peroxidation.[32] The Xc − system synthesizes GSH by transporting intracellular glutamate in exchange with extracellular cystine, scavenging intracellular free radicals, and inhibiting system Xc-can lead to a rapid decrease in intracellular GSH levels causing ferroptosis.[33] Scientists have confirmed that a variety of compounds can induce and inhibit ferroptosis (Table 1). The above studies reveal that the occurrence and development of ferroptosis are regulated by a variety of cellular components and intracellular signaling pathways. It would be helpful to gain a deeper understanding of ferroptosis, as well as verify the agonists and antagonists that contribute to its onset and development, so that we can work towards developing effective treatment to ALI.

ALI/ARDS and Its Clinically Relevant Biomarkers

ALI/acute respiratory distress syndrome (ARDS) is a common cause of respiratory failure in critically ill patients and often presents clinically with respiratory distress and progressive hypoxemia. The final severe stage of ALI is defined as ARDS. There are many risk factors inducing ALI/ARDS, common direct factors are severe pulmonary infection, gastric content aspiration, pulmonary contusion, etc., and indirect factors are severe extrapulmonary infection, severe non-chest trauma, severe acute pancreatitis, and massive blood transfusion, etc.[57] At present, there is no specific clinical treatment for this disease. Therefore, how to effectively prevent the occurrence of ALI in the early stage and prevent ALI from further developing into ARDS is an important issue that urgently needs to be solved.[58] Researchers have investigated blood, pulmonary edema fluid, and bronchoalveolar lavage fluid (BALF), exhaled air for biomarkers of the exudative and proliferative phases of ARDS. Despite their insufficient reliability if considered alone, combinations of biomarkers are recommended. The following table provides a list of the most important biomarkers associated with the exudative and fibroproliferative phases of ARDS[4,59–61] (Table 2).

Ferroptosis and ALI

Normally, iron homeostasis is maintained by phagocytosis of macrophages, transferrin secretion, antioxidant molecules on the epithelial surface of the respiratory tract, and the respiratory ciliary expectoration system in lung tissue. Once the protective mechanism is disrupted by endogenous or exogenous factors, deposition after disturbance of iron metabolism affects the normal function of cells. Iron deposition can be found in the lower respiratory tract of ALI patients, and iron accumulation can lead to inflammatory response, oxidative stress and mitochondrial dysfunction, further aggravating the degree of lung injury.[62] Recent studies have shown that ferroptosis is associated with ALI caused by ischemia-reperfusion, sepsis, radiation, drowning, and oleic acid, etc. (Figure 2).

Table 1 Common Ferroptosis Agonists, Antagonists and Their Regulatory Mechanisms

	Regulatory Mechanism	Representative Compound
Agonist	Inhibiting Xc-System	Sorafenib;[34] erastin;[35] HO-1;[36] glutamate;[37] deubiquitylase otub1;[38] dihydroorotate dehydrogenase;[39] etc.
	Inhibition/degradation of GPX 4	RSL3;[40] acetaminophen;[41] naringenin;[42] etc.
	Others	FINO (2);[43] statin;[44] ammonium ferric citrate;[45] artesunate;[46] cyst(e)inase;[47] etc.
Antagonists	Inhibits iron accumulation	Ciclopirox olamine;[48] Fty720,[49] dynasore;[50] baicalein;[51] etc.
	Inhibition of lipid peroxidation	Hspb1;[52] Fsp1;[23] Fer-1;[53] cycloheximide;[54] rapamycin;[55] etc.
	Others	Sevoflurane;[56] ginsenoside rd;[56] etc.

Table 2 Biomarkers of Acute (Exudative) and (Fibroproliferative) Phase of ARDS.[4,59]

	Marker	Biological Source of Biomarker	Change in ARDS
Alveolar cells type I	sRAGE	Plasma, BALF	↑
Alveolar cells type II	SP-A, SP-B, SP-D	Plasma, BALF	↓ BALF, ↑ plasma
	KL-6	Plasma, BALF	↑
Non-ciliary bronchial cells	CC16	Plasma, BALF	↑
Extracellular matrix	Laminin	Plasma, BALF	↑
	Elastin/Desmosin	Urine	↑
	MMPs	Plasma, BALF	↑
Endothelial cells	Angiopoietin-2	Plasma	↑
	sP-selectin	Plasma	↑
	sICAM- 1	Plasma	↑
	vWF	Plasma	↑
	Thrombomodulin	Plasma	↑
Coagulation	PAI- 1	Plasma	↑
	Protein C	Plasma	↓
	vWF	Plasma	↑
Inflammation	IL- 1β, IL-6, IL-8,	Plasma, BALF	↑
	IL- 10	Plasma, BALF	↑
	TNFα	Plasma, BALF	↑
	CRP	Plasma	↑
	KGF	BALF	↑
Proliferation of epithelium	HGF	BALF	↑
	VEGF	Plasma, BALF	↑ Plasma, ↓ BALF
	Angiopoietin-2	Plasma	↑
Apoptosis of epithelial cells	Fas/FasL	BALF	↑
Proliferation of fibroblasts	N-PCP-III	BALF	↑

Abbreviations: BALF, bronchoalveolar lavage fluid; CC16, Club cell protein; CRP, C-reactive protein; IL, interleukin; KL, Krebs von den Lungen protein; PAI, plasminogen activator inhibitor; sICAM, soluble intercellular adhesion molecule; SP, specific surfactant protein; sRAGE, soluble receptor for advanced glycation end products; vWF, von Willebrand factor; TNF, tumor necrosis factor; MMPs, matrix metalloproteinases; KGF, keratinocyte growth factor; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; N-PCP-III, N-terminal procollagen peptide-III; sP-selectin, soluble P-selectin.

Ferroptosis Antagonists and ALI

The regulatory mechanism of ferroptosis in ALI is far more complex than previously understood, and although there have been many recent research advances and new findings, the detailed regulatory mechanism of ferroptosis remains unclear. Future studies should focus on the diagnostic and prognostic value of ferroptosis-related genes, and more in-depth studies on their regulatory mechanisms are also needed in order to improve our understanding of the pathogenesis and treatment of ALI. We believe that in the near future, the regulatory mechanisms of ferroptosis will become more and more thoroughly investigated, and ferroptosis will become a new therapeutic strategy for ALI (Table 3). Ferroptosis is expected to be an important target for the treatment of ALI, and its key is to inhibit iron metabolism and lipid peroxidation. Mechanism of various ALI and treatment of ferroptosis antagonists in typical ALI models were representatively elucidated (Table 4 and Figure 3).

Ischemia-Reperfusion Related ALI (IRRALI) and Ferroptosis

Recent studies have shown that ferroptosis is a major cause of ischemic injury. Ferroptosis has been demonstrated in animal models or cellular models of ischemia-reperfusion injury of the myocardium, kidney, liver, intestine, and brain.[69–71] Damage away from lung tissue such as abdominal injury, infection, and surgery-induced intestinal ischemia-reperfusion (IR) can cause ALI.[72] Li et al[6] found that inhibitor of apoptosis stimulating p53 protein (iASPP), a p53 inhibitor, exerted a protective effect against ferroptosis by mediating Nrf2/HIF-1/TF and reduced lung tissue edema, atelectasis, necrosis, alveolar and interstitial inflammation in IR- ALI. p53 plays a critical role in ferroptosis in other disease models, while it is unknown whether iASPP acts by regulating p53 remains to be further investigated. Xu et al[63] noticed iron content and lipid peroxidation accumulation in

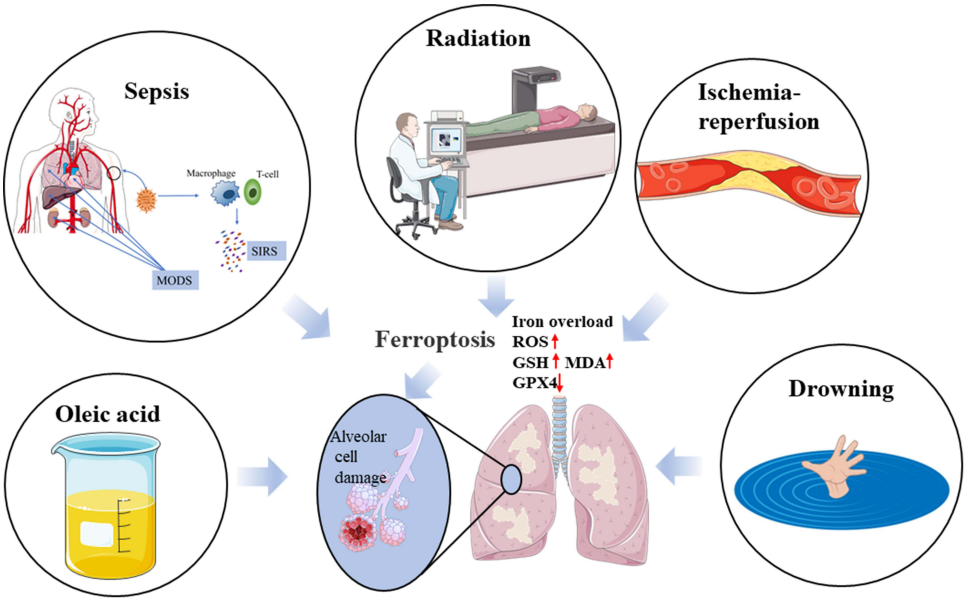

Figure 2 Ferroptosis is associated with ALI caused by ischemia-reperfusion, sepsis, radiation, drowning, and oleic acid.

lung tissue and altered expression of key proteins (GPX4 and ACSL4) during reperfusion in a mouse model of IR-ALI. In addition, rosiglitazone, an ACSL4 inhibitor, administered before ischemia alleviated ferroptosis injury in lung tissue, which is consistent with the protective effect of ACSL4 gene knockout on lung epithelial cells. As a result, ACSL4 is an important ferroptosis regulatory gene. However, Nrf2, an antioxidant molecule, regulates downstream HO-1 and signal transducer and activator of transcription 3 (STAT3) phosphorylation expression and inhibits ferroptosis in IR- ALI thereby reducing tissue injury. In a recent study, possible mechanisms of IRRALI were clarified, and its effects on IR-induced ALI were explored. The study demonstrates that isoliquiritin apioside could protect against intestinal IR-induced ALI by reducing lung epithelial ferroptosis in a Hif-1α-dependent manner.[7] But so far, the pathogenesis of IR-induced ALI has not been fully elucidated, and there are no specific drugs.[32,73] In a study conducted by Dong et al,[8] in their results, IR-ALI significantly reduced telomerase reverse transcriptase (TERT) in lung tissue of Nrf2-/-mice. Furthermore, MDA levels increased significantly in ALI models, while GSH and GPX4 levels decreased significantly. Additionally, type II alveolar epithelial cells in IR-ALI model showed typical structural changes. To examine Fe^{2+} levels and distribution within cells, they used scanning transmission X-ray microscopy (STXM). Their data suggest that Nrf2 can negatively regulate ferroptosis via modulation of TERT and solute carrier family 7, membrane 11 (SLC7A11) levels. As a result of this study, new candidates have been identified for IR-ALI treatment in the future.

Table 3 Ferroptosis Antagonists and ALI

Drug	Pathway	ALI Category	Reference
iASPP	Nrf2 / HIF - 1 / TF	Ischemia related ALI	[6]
Rosiglitazone	ACSL4	Ischemia related ALI	[63]
Liproxstatin - 1	Lipid peroxidation	Ischemia related ALI	[11,63]
Ferrostatin - 1	GPX4, SLC7A11	Ischemia related ALI, sepsis related ALI, drowning related ALI	[6,12,53]
GSMTX4	Piezo1	Radiation related ALI	[64]
Sevoflurane	HO - 1	Sepsis related ALI	[65]
Panaxydol	KEAP1 - Nrf2 - HO - 1	Sepsis related ALI	[66]
Mucin 1	GSK3 β/Keap1-Nrf2-GPX4	Sepsis related ALI	[67]
Ferulic acid	Nrf2/HO-1	Sepsis related ALI	[68]

Table 4 Treatment of Ferroptosis Antagonists in Typical ALI Models

ALL Model	Study Type	Cell type	Ferroptosis Antagonist	Target	Signal Pathway	Detected Biomarkers	Results	Reference
IRRALI	In vivo	MLECs (BALF)	iASPP	Nrf2/	Nrf2 / HIF - 1 / TF	IL-1β↓, IL-6↓, and TNF-α↓	Relieved ALI	[6]
RRALI	In vitro and in vivo	HULEC-5a/MLECs (BALF)	GSMTX4	Piezo1/ GPX4	Ca2+/calpain signaling	IL-1β↓, IL-6↓, IL- 10↓, VEGF↓	Relieved ALI	[64]
SRALI	In vitro and in vivo	BEAS-2B cells /MLECs (BALF)	Panaxydol	Nrf2	Keap1-Nrf2/HO-1	TNF-α↓, IL-1β↓, and IL-6↓, SP-A↓, SP-B↓, SP-D↓	Relieved ALI	[66]
DRALI	In vitro	MLECs-12	Ferrostatin-1	Nrf2/ GPX4	Nrf2 pathway	IL- 1β↓, IL-6↓, IL-8↓, IL- 10↓	Relieved ALI	[12]
OARALI	In vivo	MLECs (BALF)	-	-	-	-	-	[13]

Abbreviations: ALI, acute lung injury; MLECs, mice lung epithelia cells; BALF, bronchoalveolar lavage fluid; HULEC, Human pulmonary microvascular endothelial cells; IRRALI, Ischemia-reperfusion related ALI; RRALI, radiation related acute lung injury; SRALI, sepsis related acute lung injury; DRALI, drowning related acute lung injury; OARALI, oleic acid related acute lung injury; IL, interleukin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; SP, specific surfactant protein.

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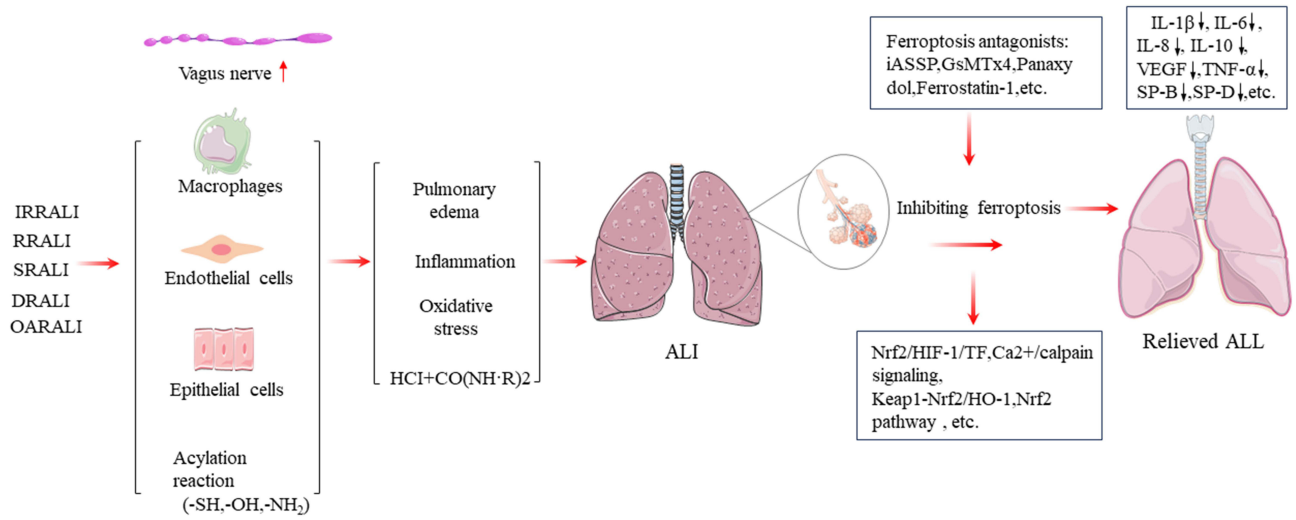

Figure 3 Mechanism of various ALI and treatment of ferroptosis antagonists in typical ALI models.
Abbreviations: ALI, acute lung injury; IRRALI, Ischemia-reperfusion related ALI; RRALI, radiation related acute lung injury; SRALI, sepsis related acute lung injury; DRALI, drowning related acute lung injury; OARALI, oleic acid related acute lung injury. IL, interleukin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; SP, specific surfactant protein.

Radiation Related ALI (RRALI) and Ferroptosis

RRALI is an important complication after radiotherapy for thoracic tumors, and its incidence is 16.7% ~ 50.3%, which increases the mortality and morbidity of cancer patients.[74] Radiation induced a large amount of ROS production and is considered to be an important mechanism causing RRALI, and ferroptosis in lung tissue of mice is aggravated after radiation treatment. In addition, ferroptosis in alveolar endothelial cells in RRALI affects their barrier function, with increased expression of the mechanosensitive calcium channel. Piezo1 increased calcium influx, and increased calpain activity, and the degree of ferroptosis is relieved after the use of its specific inhibitor GsMTx4. Piezo1 regulates ferroptosis through the Ca^{2+}/calpain/VE- Cadherin pathway, and ferroptosis is associated with Ca^{2+} overload, but the mechanism remains to be further studied.[64] It provides a new target for future mitigation of RRALI by revealing the previously unknown role of Piezo1 in modulating ferroptosis. Superoxide dismutase (SOD) is a typical endogenous antioxidant enzyme that directly inactivates ROS, and the clinical use of SOD and its analogues has been shown to protect the lung from radiation injury.[75] Due to the characteristics of poor stability, low cellular uptake, high immunogenicity, and less circulation in the body, the clinical application of natural SOD as a therapeutic drug is extremely limited. Genetic engineering technology encapsulated SOD into a biomimetic nanoreactor composed of linear peptide ARA290-HBc to improve the stability and lung retention of ARA290 peptide, and further studies confirmed that it prevented radiation-induced alveolar epithelial cell apoptosis, ferroptosis, and oxidative stress.[74] Although the feasibility of SOD@ ARA29- HBc in clinical application needs to be more widely and experimentally verified, it is undeniable that bio-nanotechnology has great therapeutic prospects.

Sepsis Related ALI (SRALI) and Ferroptosis

Sepsis is secondary to severe trauma, infection and surgery, and may develop into shock and multiple organ dysfunction syndrome after progression, and the lung is one of the organs easily involved. Lipopolysaccharide (LPS), a major component in Gram-negative bacteria, has been used to induce ALI. Liu et al[53] further illustrated that ferroptosis is involved in LPS-ALI progression. By using ferrostatin- 1, an inhibitor of ferroptosis, they found that Nrf2/ARE signaling pathway may regulate ferroptosis to participate in LPS-induced ALI.[76] An analysis of ferroptosis found that F-box and WD repeat domain containing 7 (FBXW7) mediates ubiquitination and degradation of AUF1. AUF1 inhibits ferroptosis through opposite regulation of NRF2 and activating transcription factor 3 (ATF3). Activating AUF1 pathway may be beneficial to the treatment of SRALI.[9] Sevoflurane, a commonly used anesthetic, has a protective effect on ALI, and recent studies have found that its protective

effect is partially achieved by inhibiting ferroptosis, but the specific mechanism remains to be further studied, and the practical feasibility for clinical use remains to be studied;[65] another study elucidated that the Mucin 1 mechanism inhibits ferroptosis and sensitizes Vitamin E to ameliorate SRALI through GSK3 β/Keap1-Nrf2-GPX4 pathway.[67] Tang et al found that ferulic acid may alleviate SRALI by activating the Nrf2/HO-1 pathway and inhibiting ferroptosis, suggesting a new approach for treating sepsis.[68] While in terms of traditional Chinese medicine, Li et al[66] isolated ginseng epoxyethynol from the roots of ginseng and found that it significantly inhibited ferroptosis and improved lung injury by up-regulating the level of the KEAP1-Nrf2-HO-1 pathway. In a study aiming to explore the regulatory role of itaconate on ferroptosis in SRALI, the researchers found that itaconate inhibits ferroptosis of macrophages via Nrf2 pathways in response to SRALI8.[10] In summary, ferroptosis may be a potential therapeutic target for SRALI, and ferroptosis inhibitors have therapeutic potential.

Drowning Related ALI (DRALI) and Ferroptosis

Drowning is one of the main causes of accidental injury death, and ALI is one of the most common complications of drowning. Seawater has a chemical irritating effect on the respiratory tract and alveoli, and a large amount of protein and water exudate into the pulmonary interstitium and alveolar space after alveolar epithelial cells and pulmonary capillary endothelial cells are injured by seawater, causing non-cardiogenic pulmonary edema. Hypoxemia of varying degrees developed, resulting in heart failure and death.[77] Because fluid enters the alveoli from the blood vessels, hemoconcentration, hypovolemia, hypoproteinemia, hypernatremia, hypercalcemia, and hypermagnesemia may occur. Hypermagnesemia can cause bradycardia, arrhythmias, conduction block, and even asystole.[78] It also depresses central and peripheral nerves, dilates blood vessels, and lowers blood pressure. Using Nrf2-specific agonist (dimethyl fumarate), Nrf2 inhibitor (ML385), Nrf2-knockout mice and ferroptosis inhibitor (Ferrostatin-1), Qiu et al investigated the potential roles of Nrf2 on seawater DRALI and the underlying mechanisms. They found that Nrf2 inhibits ferroptosis, thus alleviating seawater DRALI. The effectiveness of ferroptosis inhibition by Nrf2 provides a novel therapeutic target for seawater DRALI.[12]

Oleic Acid Related ALI (OARALI) and Ferroptosis

Oleic acid, also called cis-9-octadecenoic acid, is an unsaturated fatty acid containing a double bond in natural oils and is present in natural animal and vegetable oils in the form of glycerides. Oleic acid, especially high purity oleic acid, is an important fine chemical product and can be widely used in paint inks, coatings, mineral flotation agents, thin film antistatic agents, smooth agents, textile additives, explosive emulsifiers and so on. Metal salts of oleic acid are widely used as surfactants and corrosion inhibitors. Oleic acid is modified by functional groups and can be used in lubricating oil, chemical analysis, pharmaceuticals and other industries. Recent study found that oleic acid could cause ALI, and there are three main mechanisms of oleic acid-induced respiratory failure: 1. Oleic acid is a highly toxic fatty acid, which strongly constricts pulmonary micro-vessels after intravenous injection, resulting in fat emboli blocking pulmonary capillaries and causing pulmonary microcirculatory disturbances. 2. Oleic acid can directly stimulate blood vessels to damage the vascular endothelium, increase vascular permeability, pulmonary interstitial edema, and thus causing dyspnea. 3. Oleic acid decreases alveolar surfactant, resulting in pulmonary edema.[79,80] Ferroptosis has distinct morphological characteristics that differ from other cell death types. Existing studies have identified that ferroptosis is morphologically characterized by reduced mitochondria, ruptured mitochondrial membrane, reduced mitochondrial ridges, and reduced mitochondrial size. In the model of OARALI in mice, lipid peroxidation, iron overload, GSH depletion and MDA accumulation in lung tissue were observed, the protein expression levels of GPX4 and ferritin in lung tissue were down-regulated, mitochondrial atrophy in lung cells and the occurrence of ferroptosis were found suggesting that ferroptosis plays a potential role in the pathogenesis of OARALI.[13,81] The above study attempts to investigate the mechanism of ferroptosis in ALI model induced by oleic acid, and expounds the typical changes of ferroptosis in OARALI model.

The importance of ferroptosis in the onset and development of ALI has been shown by an increasing amount of in vitro and in vivo research in recent years (Table 5). There were also review studies that mainly focused on the mechanism of ferroptosis in a general way, and briefly discussed the emerging role of ferroptosis in ALI,[82,83] whereas we not only analyzed the mechanism of ferroptosis in a deeper way, but we also put much more time and effort specifically in better demonstrating the emerging roles of ferroptosis in pathophysiology and treatment of ALI. In summary, recent

Table 5 Ferroptosis and ALI

Category of ALI	Main Manifestations	Signaling Pathway
IRRALI and ferroptosis	GPX4 expression and GSH content were decreased, and MDA levels and lipid peroxidation were increased.	iASPP: Nrf2 / HIF - 1 / TF;[6] Nrf2 / HO - 1;[32] Nrf2 / STAT3;[73] Hif-1α-dependent manner;[7] TERT and SLC7A11.[8]
RRALI and ferroptosis	Substantial ROS production, disruption of alveolar endothelial function barrier function, and increased Ca2 + influx.	Piezo: Ca2 + / calpain/ VE – Cadherin.[64]
SRALI and ferroptosis	SLC7A11 and GPX4 expression was decreased, and MDA and total iron contents were increased.	Nrf2 / ARE;[76] NRF2 and ATF3;[9] GSK3 β/Keap1-Nrf2-GPX4 Pathway;[67] Nrf2/HO-1;[68] KEAP1- Nrf2-HO-1;[66] Nrf2 pathways.[10]
DRALI and ferroptosis	GSH expression and SOD activity were decreased, intracellular ROS and MDA levels were increased, and lipid peroxidation was increased.	Nrf2[12]
OARALI and ferroptosis	Changes such as lipid peroxidation, iron overload, GSH depletion, and MDA accumulation in lung tissue, and protein expression levels of GPX4 and ferritin were down-regulated in lung tissue.	Ferroptosis.[13]

Abbreviations: ALI, acute lung injury; IRRALI, Ischemia-reperfusion related ALI; RRALI, radiation related acute lung injury; SRALI, sepsis related acute lung injury; DRALI, drowning related acute lung injury; OARALI, oleic acid related acute lung injury.

studies indicate that iron metabolism, oxidative stress, and glutathione potentially contribute to the pathogenesis of ALI. Ferroptosis antagonists are expected to be an important option for the treatment of ALI.

Limitation

There are still many limitations in ferroptosis-related studies. First, the specific mechanism of ferroptosis in ALI has not been fully elucidated, more detailed signal transduction pathways are still being further explored; second, many studies still stay in the experimental stage at the cellular and animal levels, there is still a lack of large-sample, multicenter clinical randomized controlled studies and evidence; Lastly, more comprehensive, in-depth studies are needed to further investigate the relationship between ferroptosis and ALI, and intervention for ALI according to different signal transduction pathways is the direction of future exploration.

Conclusion

As novel programmed cell death, ferroptosis has been demonstrated to play an important role in a variety of systemic diseases. In recent years, scientists have demonstrated that ferroptosis plays an indispensable role in the pathogenesis of ALI from cellular or animal model studies such as IRRALI, SRALI, RRALI, DRALI and OARALI. GPX4 and Nrf2 are the key points in the occurrence and development of ferroptosis in ALI. Ferroptosis antagonists are expected to be an important option for the treatment of ALI. Relying on the latest technology to carry out a large number of basic and clinical research is helpful to further understand the occurrence and development of ALI, provide more reliable means for the prevention, and treatment of ALI.

Data Sharing Statement

All data analyzed were included in this paper; further requests can be consulted and data can be obtained from the correspondent author.

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Disclosure

The authors declare no competing interests in this work.

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