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REVIEW

Role of Ferroptosis in Alveolar Epithelial Cells in Acute Respiratory Distress Syndrome

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Abstract: Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by the rapid onset of respiratory failure resulting from extensive inflammation and damage to the alveolar–capillary barrier. ARDS can be triggered by various factors, including pneumonia, sepsis, trauma, and aspiration, emphasizing its relevance in the field of critical care medicine. Ferroptosis is a novel form of regulated cell death that plays a crucial role in the pathophysiology of ARDS. Unlike apoptosis and necrosis, ferroptosis is characterized by the lethal accumulation of lipid peroxides (LPOs), which is driven primarily by dysregulated iron metabolism and oxidative stress. Alveolar epithelial cells (AECs), pivotal in maintaining pulmonary homeostasis and gas exchange, exhibit heightened vulnerability to ferroptosis in ARDS. The inflammatory microenvironment associated with this syndrome further highlights the potential impact of ferroptosis on lung injury and repair processes. This review elucidates the multifaceted relationships among ferroptosis, inflammation, and oxidative stress in AECs, providing insights into the pathological mechanisms through which ferroptosis contributes to lung injury and the disruption of the alveolar–capillary barrier. Furthermore, the therapeutic implications of targeting ferroptosis in ARDS management, including the roles of antioxidants and intracellular nutrients in mitigating oxidative damage and preserving lung function, are discussed. These mechanistic insights underscore ferroptosis as a tractable therapeutic node in ARDS pathobiology.

Keywords: acute respiratory distress syndrome, ferroptosis, alveolar epithelial cells, oxidative stress, inflammation, immune cells, antioxidants

Introduction

Acute respiratory distress syndrome (ARDS) is a severe clinical condition characterized by the rapid onset of respiratory failure due to widespread inflammation and damage to the alveolar–capillary barrier.[1] This syndrome manifests as severe hypoxemia, diminished lung compliance, and laboured breathing, which collectively result in substantial morbidity and mortality in affected individuals[2.] ARDS develops secondary to heterogeneous etiologies, including pneumonia, sepsis, trauma, and aspiration, and remains a critical clinical challenge in critical care medicine. According to global studies, ARDS accounts for approximately 10% of hospitalized patients and has a mortality rate ranging from 30% to 50%.[3]

Ferroptosis, an emerging non-apoptotic, iron-dependent cell death pathway distinct from necrosis, has emerged as a critical pathogenic mechanism in ARDS.[4] This form of cell death is characterized by the accumulation of lethal levels of lipid peroxides (LPOs), driven by dysregulated iron homeostasis and redox imbalance.[5] In ARDS, ferroptosis is strongly associated with the injury of alveolar epithelial cells (AECs),[6] structural cells central to pulmonary homeostasis and gas exchange.[7] The unique properties of ferroptosis make it a potential contributor to the pathophysiology of ARDS, particularly given the inflammatory microenvironment associated with this condition.[8] As the understanding of the intricate relationships among cell death, inflammation, and oxidative stress deepens,[9] new evidences suggest that ferroptosis may play dual roles—both as a facilitator of lung injury and as a target for therapeutic intervention. By examining the current research on ferroptosis in AECs within the context of ARDS, this review aims to elucidate its potential implications for diagnosis and treatment.

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Pathophysiology of ARDS

ARDS is a complex and multifactorial condition that arising from diverse direct or indirect pulmonary insults, culminating in profound derangements of alveolar-capillary barrier function.[10] Direct lung injuries refer to primary damage to the pulmonary parenchyma itself, exemplified by pneumonia,[11] foreign body inhalation,[12] inhalation of toxic smoke,[13] and lung contusion caused by blunt chest trauma[14]. In contrast, indirect lung injuries originate from systemic processes that affect the lungs without initially damaging them directly. Examples of such indirect injuries include major trauma and sepsis, which can occur as a consequence of various infections.[15] These systemic conditions can lead to inflammatory responses and changes in pulmonary vascular permeability, ultimately contributing to the development of ARDS.

ARDS is pathologically defined by an exaggerated inflammatory response within the lungs, which occurs in response to initial injury. Following an insult, such as bacterial infection, pneumonia, or trauma, a cascade of inflammatory events is triggered.[16] Immune cells, such as alveolar macrophages, release proinflammatory cytokines, including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), which recruit neutrophils and other immune effector cells to the site of injury. As neutrophils infiltrate the lung tissue, they subsequently degranulate and release enzymes, reactive oxygen species (ROS), and additional proinflammatory mediators, thereby escalating the inflammatory response.[17] This recruitment and activation results in damage to both epithelial and endothelial cells, compromising the integrity of the alveolar–capillary membrane. Disruption of this barrier leads to increased permeability, allowing protein-rich fluid to escape into the alveoli. This fluid causes pulmonary oedema, which is a defining characteristic of ARDS.[18] Moreover, this inflammatory milieu activates the coagulation cascade, contributing to microvascular thrombosis and further impairing gas exchange due to venous stasis and clot formation. The balance between proinflammatory and anti-inflammatory signals becomes dysregulated, resulting in a cycle of ongoing inflammation and lung injury.[19]

Mechanisms of Ferroptosis

Ferroptosis is a form of regulated cell death characterized by the accumulation of toxic levels of LPOs, which is primarily driven by iron metabolism and an imbalance between oxidative stress and antioxidant defences[20] (Figure 1).

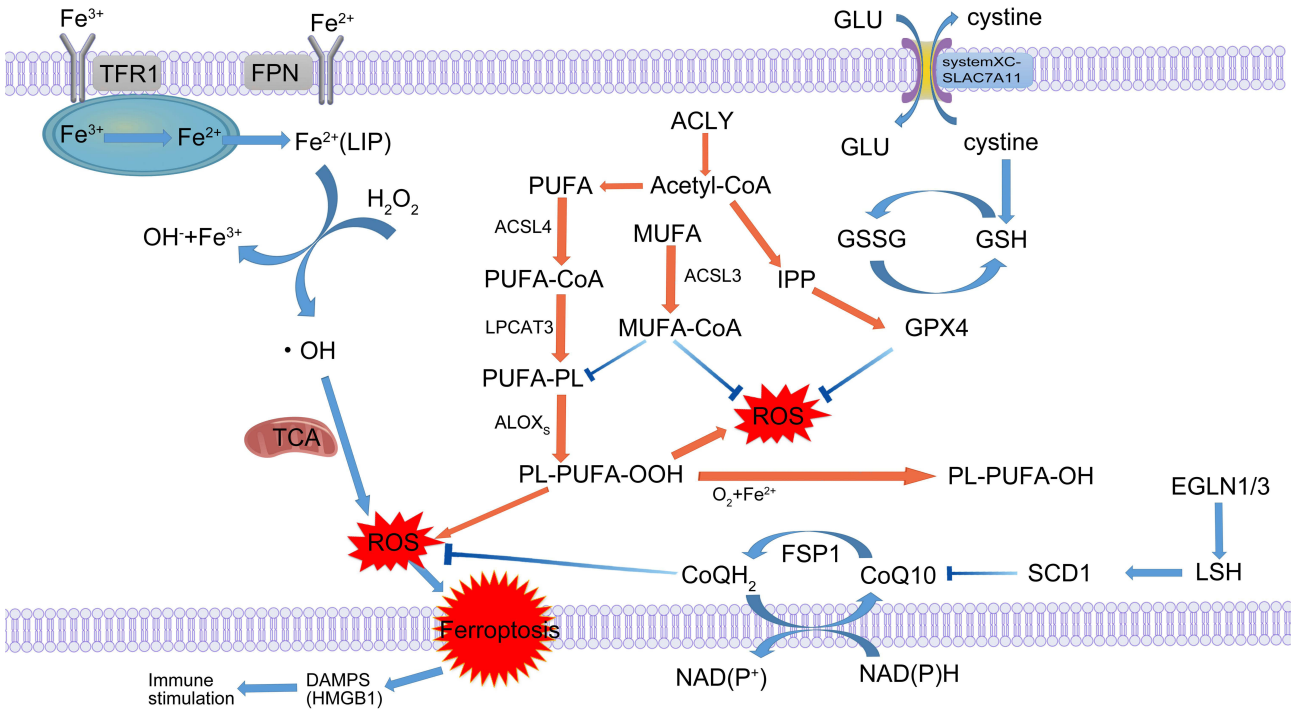

Figure 1 Mechanisms of Ferroptosis.

Key Characteristics of Ferroptosis

Ferroptosis is an iron-dependent regulated cell death pathway, which plays a crucial role in generating ROS.[21] Elevated intracellular iron levels promote the Fenton reaction, where ferrous iron reacts with hydrogen peroxide to produce hydroxyl radicals. These radicals initiate lipid peroxidation, contributing to cellular damage.[22] Additionally, central to ferroptosis is the accumulation of LPOs, generated through degradation of polyunsaturated fatty acids in cellular membranes. Unlike other forms of cell death, lipid peroxidation in ferroptosis reaches lethal levels, leading to membrane rupture and ultimately cell death. This process is influenced primarily by specific lipoxygenase enzymes that oxidize polyunsaturated fatty acids.[23]

Molecular Pathways Involved in Ferroptosis

Role of Glutathione and GPX4

Glutathione (GSH), a tripeptide composed of glutamic acid, cysteine, and glycine, serves as a central redox buffer in mammalian cells. It plays an essential role in protecting cells from oxidative stress by neutralizing ROS and detoxifying free radicals. High levels of GSH are necessary to maintain the cellular redox status and prevent excessive lipid peroxidation.[24] In ferroptotic processes, GSH levels are critically altered. The depletion of intracellular glutathione (GSH) critically compromises cellular antioxidant defenses, significantly increasing susceptibility to ferroptotic cell death. When cellular GSH levels decrease, either because of increased ROS or inadequate synthesis, the capacity to detoxify LPOs is insufficient. The resulting failure in redox homeostasis leads to pathological accumulation of toxic lipid aldehydes, ultimately initiating the execution phase of ferroptotic cell death through iron-dependent phospholipid peroxidation.[25]

Glutathione peroxidase 4 (GPX4) is a key enzyme that uses GSH to reduce lipid hydroperoxides to their corresponding alcohols, effectively suppressing lipid peroxidation.[26] When *GPX4* activity is inhibited or its expression is downregulated, lethal LPOs accumulation results. Various regulatory factors influence *GPX4* expression, including transcriptional regulators[27] and posttranslational modifications, such as phosphorylation and ubiquitination.[28] Furthermore, several studies have shown that lipids themselves regulate *GPX4* activity through pathways such as cell membrane composition, LPOs production, and the regulation of bioactive lipids, linking lipid metabolism to the regulation of ferroptosis.[29] Therefore, GPX4 not only mitigates lipid peroxidation but also serves as a critical checkpoint in the ferroptotic signalling pathway.[30]

System Xc− and the Cystine/Glutamate Antiporter

System Xc− is a vital cystine/glutamate antiporter that plays a crucial role in maintaining cellular redox homeostasis and influencing ferroptosis by regulating the levels of GSH.[31] This cystine-glutamate antiporter, composed of two distinct subunits, mediates cystine uptake through solute carrier family 7 member 11 (SLC7A11) while utilizing solute carrier 3A2 (SLC3A2) to stabilize membrane expression and coordinate glutamate efflux. The transporter's heteromeric structure enables simultaneous transmembrane movement of extracellular cystine into cellular compartments and cytosolic glutamate extrusion into the extracellular space.[32] The entry of cystine is critical because it is converted into cysteine, a key precursor for GSH synthesis, which helps neutralize ROS and prevents oxidative damage. During oxidative stress or inflammatory episodes, cellular cysteine demand escalates;[33] however, system Xc− dysfunction impairs cystine transport capacity, leading to diminished GSH biosynthesis. This depletion impedes the cell's antioxidant capacity, increasing susceptibility to lipid peroxidation that ultimately triggers ferroptosis execution.[34] Furthermore, the activity of system Xc− is influenced by various regulatory factors. Proinflammatory cytokines including TNF-α[35] and IL-1β[36] promote System Xc− expression, whereas anti-inflammatory cytokines such as IL-10 suppress the activity of System Xc−. Under oxidative stress, cytokines can regulate System Xc− by activating transcription factors such as nuclear factor E2 related factor 2 (Nrf2),[37,38] highlighting their critical role not only in maintaining redox balance but also in modulating cell fate in response to stressors.

Interaction with Oxidative Stress

The interplay between ferroptosis and oxidative stress constitutes a pathological nexus in diverse disease manifestations.[39] Ferroptosis, characterized by the iron-dependent accumulation of LPOs to lethal levels, strongly influences the state of oxidative stress within the cell.[21,23,40] During iron overload or regulatory dysfunction, free iron can catalyse the Fenton

reaction, producing highly reactive hydroxyl radicals (•OH). These radicals react with cellular components, leading to oxidative damage and further increasing the levels of ROS.[41] Iron can also affect mitochondrial function, resulting in instability of the electron transport chain and excessive generation of ROS. As ferroptosis occurs, the loss of the mitochondrial membrane potential and depletion of adenosine triphosphate (ATP) contribute to mitochondrial dysfunction, which may further increase the production of ROS.[42] Additionally, the intracellular components following ferroptosis, such as damage-associated molecular patterns (DAMPs), can trigger inflammatory responses and cause more immune cells to release oxidants, thereby worsening oxidative stress.[43] Furthermore, during ferroptosis, the activity of antioxidant enzymes, such as GPX4, is often suppressed or reduced, leading to redox imbalance and diminished cellular capacity to clear ROS.[44] This augmented ROS production leads to increased oxidative stress, which can deplete cellular antioxidants, particularly GSH, which are essential for protecting cells from oxidative damage.[24,45] As GSH levels decrease, the detoxification of LPOs becomes impaired, increasing the susceptibility of cells to ferroptosis.[46] Furthermore, excessive ROS can lead to peroxidation of polyunsaturated fatty acids (PUFAs) in cell membranes[47] and cause direct damage to proteins and DNA, compounding cellular dysfunction and promoting further inflammation.[48] The resulting cycle of oxidative damage not only facilitates the onset of ferroptosis but also exacerbates tissue injury.

Mechanisms of Ferroptosis in ARDS

In ARDS, ferroptosis is primarily driven by oxidative stress, which is exacerbated by inflammation and the dysregulation of antioxidant defense mechanisms, including GSH depletion and GPX4 inhibition.

Role of Molecular Pathways of Ferroptosis in ARDS

GPX4 Pathway Dysregulation in ARDS

In pulmonary physiology, *GPX4* serves as a critical guardian against oxidative stress and lipid peroxidation in AECs, particularly within the inflammatory-oxidative stress microenvironment characteristic of ARDS. Under normal conditions, *GPX4* helps maintain membrane integrity by preventing excessive lipid peroxidation, which is essential for preserving lung function. However, in ARDS, inflammatory cytokines and oxidative stress both abundant during the disease can downregulate or inhibit *GPX4* expression and activity. This reduction impairs *GPX4*'s ability to counteract lipid peroxidation, leading to the unregulated accumulation of lipid hydroperoxides. As a result, this accumulation triggers ferroptosis in AECs and resident lung cells.[49] Additionally, the inhibition or dysfunction of *GPX4* contributes to the disruption of the alveolar-capillary barrier, exacerbating lung injury, impairing gas exchange, and potentially promoting fibrosis during the later stages of ARDS. Mechanistic studies reveal that pharmacological activation of the Keap1/Nrf2/GPX4 axis restores cellular antioxidant defenses and attenuates ferroptosis in AECs.[50]

System Xc- Dysfunction in ARDS

In ARDS, oxidative stress often impairs the function of system Xc-, leading to a reduction in the intracellular cystine pool and limiting the production of GSH. This redox imbalance reduces *GPX4* activity, accelerating lipid hydroperoxides accumulation and triggering ferroptosis. Inflammatory signals and oxidative stress in ARDS result in the downregulation of system Xc- activity, thereby compromising GSH biosynthesis. This dysfunction further enhances lipid peroxidation and contributes to ferroptosis in lung cells, especially AECs, which are particularly vulnerable to oxidative damage. Additionally, dysfunctional system Xc- exacerbates the imbalance between pro- and anti-oxidant systems, creating a vicious cycle of inflammation, oxidative stress, and cell death. Ma et al collected bronchoalveolar lavage fluid of ARDS patients and found that *SLC7A11* was significantly increased in patients with moderate ARDS compared with patients with mild ARDS. The level of neutrophils in peripheral blood of ARDS patients is positively correlated with the expression level of *SLC7A11*.[51]

Alternative Pathways of Ferroptosis in ARDS

One of the hallmark features of ferroptosis is iron homeostasis disruption. Elevated iron levels in the lungs, either through increased iron uptake or decreased iron sequestration, can promote lipid peroxidation and accelerate ferroptosis. In ARDS, inflammatory cytokines and hypoxia may alter iron metabolism, increasing iron deposition in lung tissues and

driving ferroptosis. While GPX4 and system Xc- constitute principal regulatory nodes in ferroptosis execution, emerging evidence reveals that alternative biochemical pathways contribute to lipid peroxidation when canonical mechanisms become overwhelmed during pathological conditions like ARDS.

Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4) is another key enzyme serving as a critical mediator in lipid peroxidation by catalyzing the esterification of long-chain fatty acids, particularly arachidonic acid, which is a precursor for the production of lipid hydroperoxides.[52] In acute lung injury (ALI), the primary stage of ARDS, dysregulated upregulation of *ACSL4* drives pathological accumulation of lipid peroxides that promotes ferroptosis.[53] Targeting *ACSL4* activity could help mitigate ferroptosis-induced lung damage, knockout of SHP2 can reduce ferroptosis by down-regulating the expression of *ACSL4* in ALI,[54] METTL3 promotes ferroptosis by altering the m6A modification of *ACSL4*.[55]

Beyond its canonical tumor-suppressive functions, p53 emerges as a central regulator of ferroptosis. Loss of SIRT1-mediated acetylation modification of p53 inhibits ferroptosis.[56] In the context of ARDS, p53 can suppress the expression of *SLC7A11*, a subunit of the system Xc- antiporter, thus reducing cystine uptake and GSH synthesis, which promotes ferroptosis.[57]

Heme Oxygenase-1 (HO-1) is an enzyme involved in heme degradation, has been shown to play a dual role in ferroptosis. Under certain conditions, HO-1 activity may alleviate oxidative stress by degrading heme and producing biliverdin, an antioxidant. However, excessive HO-1 activity can lead to iron overload, which accelerates ferroptosis.[58] In ARDS, the balance between protective and pathological effects of HO-1 activity may influence ferroptosis progression. Nrf2 inhibits ferroptosis and protects against ALI via regulating SLC7A11 and HO-1.[59] IL-27 regulates macrophage ferroptosis by inhibiting the Nrf2/HO1 signaling pathway in sepsis-induced ARDS.[60]

Ferroptosis and Oxidative Stress in Early ARDS

Oxidative stress increases the generation of ROS by disrupting normal metabolic processes and cellular structures within AECs.[61] The excessive accumulation of ROS can directly cause cellular damage by harming cell membranes, proteins, and DNA.[62] Additionally, oxidative stress can activate signaling pathways such as the NF-κB and MAPK pathways, leading to the upregulation of enzymes that produce ROS, including NOX and cyclooxygenase-2 (COX-2), thereby promoting the release of inflammatory cytokines and chemokines.[63] Elevated levels of ROS can oxidize ferritin proteins (such as ferritin and iron–sulfur clusters), releasing more free iron, which increases substrates for the Fenton reaction and leads to iron overload, further promoting lipid peroxidation.[64] Moreover, oxidative stress attacks PUFAs on cell membranes, triggering peroxidation reactions that produce LPOs and free radicals; these products can disrupt cell membranes and impair iron metabolism, thus promoting ferroptosis.[65] Oxidative stress also inhibits the intracellular antioxidant system, diminishing the ability of the cell to defend against lipid peroxidation, as evidenced by *GPX4* inactivation and GSH depletion, along with suppressed superoxide dismutase (SOD) and catalase activities.[21,66] Furthermore, oxidative stress interferes with the function of lipid-metabolizing enzymes and alters the composition of lipids in cell membranes, increasing susceptibility to ferroptosis, such as through the upregulation of *ACSL4* expression and activity via the Nrf2-ARE pathway.[67] Similarly, LPOs formed from the oxidation of PUFAs during ferroptosis are a significant source of ROS, directly driving oxidative stress.[68] Iron overload significantly accelerates the Fenton reaction, thereby increasing ROS generation and leading to a rapid increase in the level of intracellular oxidative stress. During ferroptosis, system Xc- consisting of *SLC7A11* and *SLC3A2*, is inhibited, which decreases extracellular cysteine uptake and ultimately causes GSH depletion, exacerbating ROS accumulation and oxidative stress. Additionally, 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which are generated during lipid peroxidation, covalently bind to proteins, DNA, and membrane lipids, which compromises cell membrane integrity, disrupts cellular signaling pathways, and further increases ROS production.[69] This process ultimately creates a vicious cycle of "inflammation–oxidative stress–lipid peroxidation", leading to ARDS (Figure 2).

Ferroptosis and Tissue Repair and Fibrosis in Late ARDS

In the later stages of ARDS, although inflammation gradually subsides, tissue repair and fibrosis become the primary pathological processes.[70] However, ferroptosis persists as a critical pathogenic mechanism during this phase, exerting direct inhibitory effects on tissue repair processes that accelerate pulmonary fibrosis progression.[71] Tissue repair in the later stages of ARDS mainly relies on normal cell regeneration. The ongoing occurrence of ferroptosis further damages

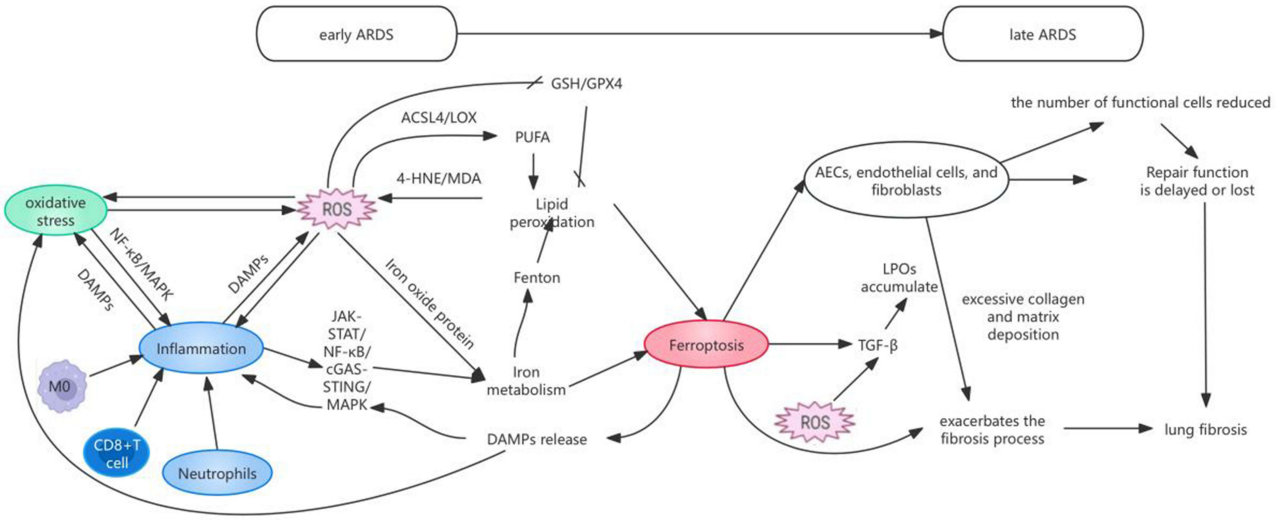

Figure 2 Ferroptosis, inflammation and oxidative stress in AECs. In early ARDS, oxidative stress, driven by reactive oxygen species (ROS), disrupts alveolar epithelial cell (AEC) integrity. Excessive ROS oxidizes polyunsaturated fatty acids (PUFAs), triggering lipid peroxidation (LPO) via ACSL4/LOX pathways, while depleting glutathione (GSH)/GPX4 antioxidant defenses. This results in iron overload, Fenton reaction activation, and ferroptosis, characterized by membrane lipid remodeling (4-HNE/MDA accumulation) and DAMPs release, which amplifies inflammation. In late ARDS, persistent ferroptosis reduces functional cell populations (AECs, endothelial cells, fibroblasts), impairing tissue repair. Ferroptosis sustains oxidative stress through TGF-β/SMAD signaling, promoting collagen deposition and myofibroblast differentiation.

cellular and tissue structures, reducing the number of functional cells available for repair. Key repair cells, such as AECs, endothelial cells, and fibroblasts, lose their function due to ferroptosis, which delays recovery by obstructing the repair process.[72] Moreover, ferroptosis exacerbates the fibrosis process by inducing sustained oxidative stress. Proliferation of lipid peroxidation products (LPOs) and membrane integrity disruption synergistically drive fibroblast-myofibroblast hyperactivation, resulting in aberrant collagen deposition and extracellular matrix remodeling that exacerbates pulmonary fibrosis.[73] Chronic ferroptosis and oxidative stress may ultimately result in lung tissue hardening, contributing to irreversible lung fibrosis, which is one of the leading causes of death in ARDS patients.[74] Furthermore, persistent oxidative stress and ferroptosis create a feedback loop through the accumulation of ROS, further activating the expression of fibrosis-related factors such as transforming growth factor-beta (TGF-β).[75] These factors not only promote fibroblast proliferation and collagen deposition but also inhibit normal cell function, accelerating the progression of fibrosis.[76] Ferroptosis inducer erastin enhances TGF-β1 induced fibroblast-to-myofibroblast differentiation pulmonary fibrosis models in vitro.[77]

Pathological Mechanism of Ferroptosis in AECs

In the lungs, AECs, which include type I and type II cells, are crucial for maintaining the integrity of the alveolar barrier and facilitating gas exchange.[78] Type I epithelial cells form the thin, gas-exchanging surface of the alveoli, whereas type II cells are responsible for surfactant production and alveolar repair.[79] Both types of epithelial cells undergo significant damage during ARDS due to susceptibility to ferroptosis, oxidative stress, inflammation, lung injury repair dysfunction, and alveolar–capillary barrier breakdown.

AECs are Susceptible to Ferroptosis

AECs are particularly susceptible to ferroptosis for several reasons. Firstly, AECs are constantly exposed to elevated levels of oxidative stress due to the continuous influx of oxygen into the lungs.[80] Secondly, these cells contain a substantial amount of PUFAs within their membrane, which renders them more vulnerable to lipid peroxidation.[81] Finally, the epithelial lining fluid contains a high concentration of iron, which can exacerbate oxidative stress and further promote ferroptosis.[82] Together, these factors contribute to the increased susceptibility of AECs to iron-induced cell death, making it a significant pathway in lung injury.

Ferroptosis, Inflammation and Oxidative Stress in AECs

Ferroptosis, inflammation and oxidative stress are closely interconnected processes in AECs. When AECs undergo ferroptosis, cell membranes rupture and mitochondria damage result in DAMPs release, which then activates inflammasomes in nearby immune cells.[83] This inflammasome activation triggers inflammatory cytokines secretion, such as TNF-α, IL-1β, and IL-6. These cytokines promote local inflammation by recruiting neutrophils to the injury site and stimulating the release of additional inflammatory mediators and ROS.[84] Notably, IL-6 not only contributes to inflammation, but also induces lipid peroxidation and disrupts iron homeostasis, leading to an increase in iron accumulation within epithelial cells and further driving ferroptosis.[85] Moreover, these cytokines activate multiple inflammatory signalling pathways, including the JAK-STAT, NF-κB, cGAS-STING, and MAPK pathways, impair the antioxidant defence systems of AECs and lead to the accumulation of ROS and LPOs.[86] Additionally, both cytokines and mechanical stretching activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), an enzyme embedded in the cell membrane, which directly generates ROS and exacerbates oxidative stress.[87,88]

Ferroptosis and Immune Cells in AECs

In ARDS, various immune cells, including neutrophils, macrophages, and lymphocytes, are significantly involved in the inflammatory response, which is crucial for combating pathogens and repairing tissues. However, an excessive or dysregulated immune response can exacerbate lung injury and worsen the severity of ARDS. Ferroptosis not only leads to a reduction in the number and function of immune cells, but also triggers inflammation or specific responses upon recognition by immune cells.[89]

Ferroptosis attracts neutrophils through DAMPs, such as high mobility group box 1 (HMGB1), which recruits and activates neutrophils via the Toll-like receptor 4 (TLR4) signaling pathway.[90] The oxidative products released during ferroptosis (eg, 4-HNE and MDA) can further promote ROS generation or activate NF-κB signaling in neutrophils, leading to their enhanced participation in the inflammatory response.[91] While ferroptosis triggers neutrophil activation, these immune cells reciprocally amplify ferroptotic processes through multifaceted mechanisms. Neutrophils promote ferroptosis by activating the immune response, generating ROS, and secreting proinflammatory factors, such as TNF-α, IL-1β, and chemokines.[92] Research has demonstrated that neutrophil extracellular traps (NETs) increase ROS generation through cell-cell interactions and mediate m6A modification of GPX4, thereby promoting ferroptosis.[93] In ALI, neutrophils regulate hallmark genes related to ferroptosis, including SLC7A11, which is involved in antioxidant stress responses and lipid metabolism.[51] Additionally, neutrophils transfer myeloperoxidase (MPO)-containing granules into target cells, where MPO catalyses the generation of strong oxidants (eg, hypochlorous acid) from hydrogen peroxide (H_2O_2), accelerating lipid peroxidation. MPO also facilitates the release or accumulation of iron, and increased free iron can catalyse ROS production through the Fenton reaction, further promoting ferroptosis.[94]

The sensitivities of inflammatory macrophages and selectively activated macrophages to ferroptosis differ.[95] When cells undergo ferroptosis, DAMPs and other inflammatory mediators can activate macrophage polarization towards a proinflammatory phenotype (M1). Secreted inflammatory mediators further influence the activity of enzymes involved in iron, lipid, and amino acid metabolism.[96] For example, 4-HNE can bind to pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), triggering inflammatory signalling cascades (eg, the NF-κB and MAPK pathways) that lead to macrophage activation.[97,98] Furthermore, iron-requiring cells can produce oxygenated phosphatidylethanolamines, activating TLR2 on macrophages and promoting their clearance.[99] In addition, macrophages recycle stored iron by clearing aged erythrocytes, resulting in the release of free iron and ROS, inducing ferroptosis in macrophages themselves that functionally constrains their immune effector capabilities.[100] M1 macrophages secrete cytokines, such as TNF-α and interferon-gamma (IFN-γ),[101] which transcriptionally upregulate transferrin receptor 1 (TFR1) and ferritin heavy chain (FTH1) expression in neighboring cells. This process increases the cellular uptake and storage of iron and thus promotes ferroptosis.[102,103] Moreover, macrophages can promote tissue repair through the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and TGF-β, in the M2 phenotype, which also induce the expression of antioxidant proteins.[104] This immunoregulatory mechanism maintains systemic iron homeostasis while attenuating oxidative stress, thereby limiting ferroptosis-driven tissue injury and promoting healing. For example, quercetin can enhance M2 macrophage polarization

and the expression of endogenous antioxidants, thereby inhibiting ferroptosis and assisting in tissue repair.[105] Uridine alleviates sepsis-induced ALI by inhibiting macrophage ferroptosis.[106]

Ferroptosis and the involvement of CD4+ and CD8+ T cells in AECs are critical areas of research, especially in ARDS. A bidirectional interaction exists between ferroptosis and T-cell activity. When CD4+ and CD8+ T cells are recruited to AECs, cytokines, such as interleukin-2 (IL-2) and IFN-γ secreted by T helper 1 (Th1) cells of CD4+ T cells, promote ferroptosis by enhancing the inflammatory response, downregulating SLC7A11 and depleting GSH.[107,108] Among the CD4+ subsets, regulatory T cells (Tregs) and T helper 17 (Th17) cells are closely associated with the prognosis of ARDS. Th17 cells promote inflammation, and Tregs play a key role in maintaining immune homeostasis by secreting anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β).[109] Alanyl-glutamine (Ala-Gln) can reduce lipopolysaccharide (LPS)-mediated ALI by increasing the number of Treg cells and decreasing the proportion of Th17 cells.[110] Similarly, losartan treatment inhibited Th17 polarization after LPS-induced ALI.[111] CD8+ T cells not only directly target and kill abnormal or infected cells but also release IFN-γ, which downregulates the expression of the two subunits SLC3A2 and SLC7A11 of system xc-. This reduction impairs the ability of cells to take up cysteine, leading to increased lipid peroxidation and ferroptosis.[112] Due to its ability to inhibit the activity of IFN-γ, proanthocyanidin is considered a potential therapeutic agent for treating ALI induced by ferroptosis.[113] In addition, GPX4 is crucial for maintaining peripheral T-cell homeostasis; the absence of GPX4 in CD8+ and CD4+ T cells leads to rapid accumulation of membrane LPOs and induces ferroptosis.[114] Conversely, CD36-mediated ferroptosis exerts biphasic effects on T-cell immunity: it suppresses CD8+ T cell effector functions while simultaneously disrupting CD4+ T cell homeostasis.[115,116] This regulatory axis becomes pathologically relevant during ferroptosis activation, where danger-associated molecular patterns (DAMPs) from dying cells enhance CD8+ T cell activation through co-stimulatory receptor signaling, creating a feedforward loop with IFN-γ-mediated amplification.[117–119] However, when ferroptosis induces excessive levels of immunosuppressive factors or creates a strong oxidative stress environment, the ROS and 4-HNE produced can directly damage CD8+ T cells, reducing their proliferation and cytotoxic functions.[120] Furthermore, in inflammatory or anti-infective environments, ferroptosis can promote the activity of CD4+ T cells (such as Th1/Th17 cells) by downregulating the xCT-GSH-GPX4 pathway.[121] Conversely, chronic inflammation or immunosuppressive environments may suppress the effector functions of CD4+ T cells through the activation of Treg cells[122] (Figure 3).

Ferroptosis Leads to Impaired Repair Functions in Lung Injury

Type II AECs are responsible for the production of surfactant, a lipoprotein complex that reduces surface tension and prevents alveolar collapse.[123] Ferroptosis in type II cells can impair surfactant production and disrupt normal alveolar fluid clearance, leading to further respiratory compromise.[6,124] In type II AECs, cGAS promotes ferroptosis in lung injury by enhancing NCOA4-mediated ferritin phagocytosis.[125] Additionally, type II cells are involved in the repair of damaged alveolar epithelium, and ferroptosis may hinder this regenerative process, delaying recovery and promoting chronic lung injury.[124] Diminished surfactant production increases the risk of alveolar collapse, which contributes to atelectasis and further impedes gas exchange. This disruption of homeostasis within the alveolar environment not only prolongs the inflammatory state but also promotes the progression of ARDS.[126] In addition to affecting surfactant production and tissue repair, ferroptosis may have broader implications in lung injury. For example, the secretory profile of ferroptotic type II AECs may influence the inflammatory landscape in the lungs, including the recruitment and activation of immune cells.[127] This process could lead to a vicious cycle in which inflammation drives more pronounced ferroptosis, further inhibiting the reparative capacity of type II AECs.

Ferroptosis Leads to Disruption of the Alveolar–Capillary Barrier

Ferroptosis disrupts alveolar-capillary barrier integrity through mechanisms that compromise pulmonary function and gas exchange. This critical barrier, composed of alveolar epithelial cells (AECs) and endothelial cells, prevents vascular leakage while maintaining efficient oxygenation.[128] When AECs undergo ferroptosis, lipid peroxidation occurs, and excessive ROS accumulation can control renin–angiotensin system (RAS) activation of matrix metalloproteinases (MMPs) to degrade the basement membrane, thereby impairing the integrity of the cell membrane.[129] This process results in increased membrane tension in AECs, which activates Piezo1 and transient receptor potential (TRP) channels, thus increasing cation

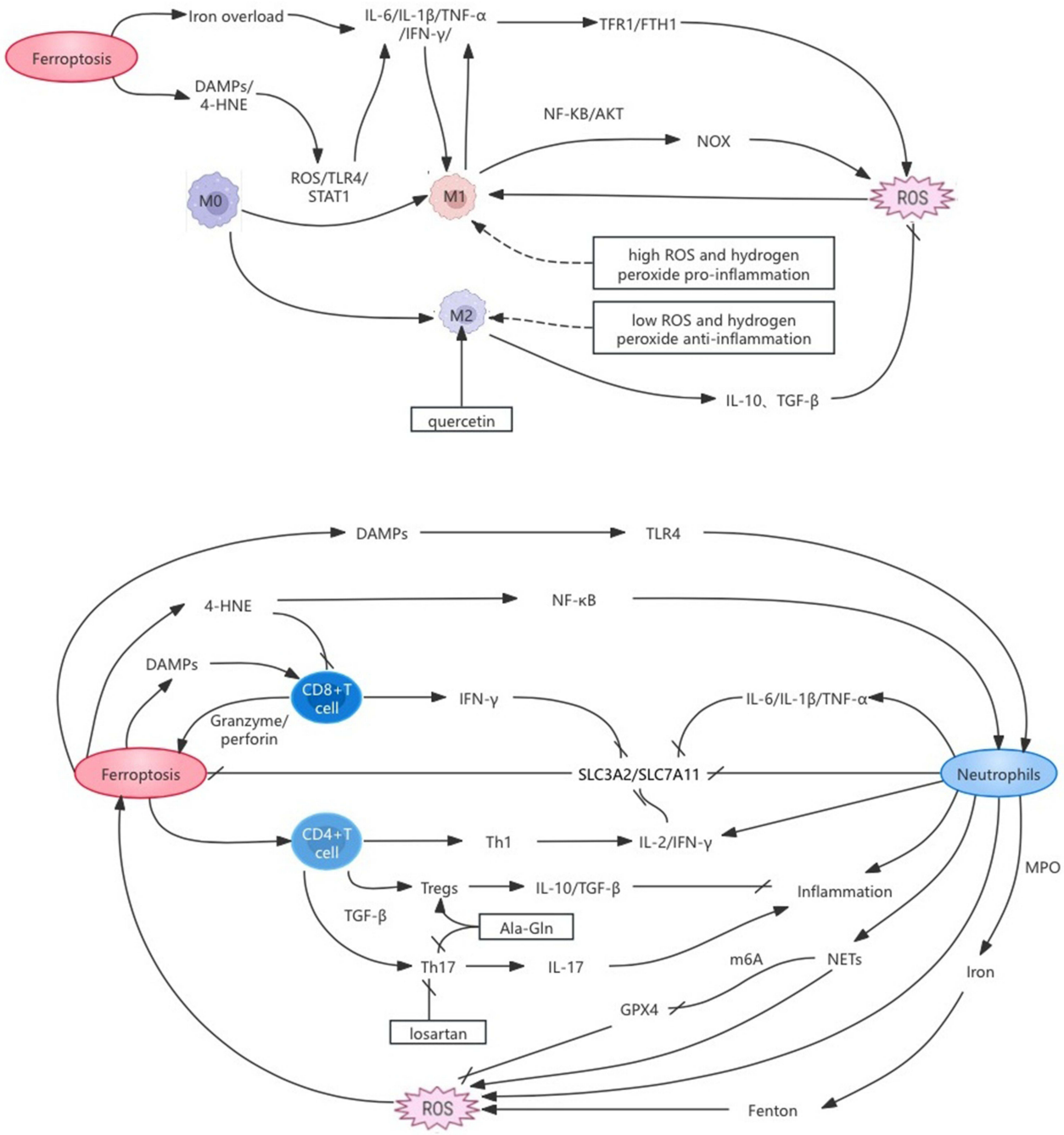

Figure 3 Ferroptosis and immune cells in AECs.

permeability.[130] Concurrently, tight junction protein complexes become dysfunctional, leading to increased paracellular permeability. This barrier breakdown permits protein-rich edema fluid accumulation in alveolar spaces, exacerbating pulmonary edema and hypoxemia. Furthermore, AEC injury can trigger a cascade of inflammatory responses, inviting additional immune cells to the site of injury, which may further perpetuate the cycle of inflammation and oxidative damage. Consequently, the loss of functional AECs due to ferroptosis not only destabilizes the barrier but also hampers the repair processes necessary for recovery from lung injuries, contributing significantly to the progression of ARDS.

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Targeting Ferroptosis as a Treatment Strategy for ARDS

Increasing research has indicated that dysregulated iron metabolism is reported in ARDS patients.[131] Specifically, compared to healthy controls, the levels of total iron and non-heme iron in the plasma and bronchoalveolar lavage fluid of ARDS patients are elevated.[132] It has been found that the levels of iron and iron-related proteins in bronchoalveolar lavage fluid (BALF) are associated with the severity of ARDS.[133] Moreover, iron and iron-related proteins are found to excess in the lower respiratory tract of ARDS patients.[132] Ferroptosis-related genes, such as Cp, Slc7a11 and Slc39a14, have been identified to as key regulators in patients to aggravate ARDS.[51] Lipid hydroperoxides have also been detected in the pulmonary edema fluid of ARDS patients.[134] In experimental models, the use of ferroptosis inhibitor Fer-1 has been shown to alleviate lung injury in ARDS.[135] Furthermore, Panax ginseng activates the Keap1-Nrf2/HO-1 pathway,[136] and adenosine diphosphate (ADP) (by modulating the SOD1/CREB1/HMOX1 pathway),[115] reducing the generation of lipid peroxides, thus mitigating the effects of ferroptosis on LPS-induced ALI in mice. These studies suggest that ferroptosis-targeted therapeutic strategies for ARDS hold promise in reducing lung injury and improving patient prognosis. Because ferroptosis is characterized by iron-dependent oxidative cell death due to lethal lipid peroxidation, interventions aimed at modulating this process may help preserve cellular integrity and reduce inflammation in the lungs. These interventions mainly include the use of antioxidants, alone or in combination with anti-inflammatory drugs.

Antioxidants and Their Role in Preventing Oxidative Damage and Ferroptosis

Pharmacological Antioxidants

One of the primary strategies for targeting ferroptosis involves enhancing antioxidant defences within pulmonary cells, particularly by maintaining or restoring the levels of GSH. Previous study found that total GSH was deficient in the alveolar epithelial lining fluid of patients with ARDS compared to normal subjects.[137] It has been reported that oral and intravenous GSH supplementation could relieve dyspnea in patients with ARDS caused by COVID-19.[138] Studies using animal models have demonstrated that the ROS inhibitors GKT137831 and Apocynin can reduce lung ischaemia/reperfusion injury in mice by blocking Nox4-dependent H2O2 production.[139] Mitochondrial-targeted antioxidants, such as the SOD mimetics MitoQ and MitoTempo,[140] the SOD derivative phospholipated SOD2 (PC-SOD),[141] and recombinant SOD1,[142] have also been shown to significantly improve lung injury in mice. Recent research demonstrates that dipyridamole binds to and activates SOD1 to mitigate ferroptosis and pulmonary damage in ARDS mouse models. Furthermore, the clinical trial further corroborates that dipyridamole adjunctive therapy improves outcomes in ARDS patients.[143] In recent ongoing clinical trials, the role of antioxidants in critical care is being more closely evaluated. For instance, the use of mitochondrial-targeted antioxidants like MitoQ is currently under investigation in ARDS patients, with preliminary findings suggesting improved clinical outcomes through reduction in oxidative stress and enhanced mitochondrial function.[144] Clinical trials are exploring the efficacy of antioxidants like MitoQ in sepsis-induced ARDS, providing key insights into potential therapeutic avenues for modulating ferroptosis and oxidative damage in critically ill patients.[145] Moreover, the organoselenium compound ebselen, which mimics the catalytic mechanism of glutathione peroxidase (GPx), reacts with hydroperoxides, including H2O2, thereby inactivating them and facilitating the regeneration of GSH.[146] By regulating the TLR4/MyD88/NF-κB and Keap1/Nrf2/HO-1 pathway, bakuchiol reduces the levels of MDA and 4-HNE and the expression of proinflammatory cytokines in lung tissue, increases the activities of SOD and GPx, and alleviates LPS-induced ALI.[147] In addition to increasing GSH levels, pharmacological agents that inhibit key enzymes involved in lipid peroxidation can serve as effective treatments. For example, lipoxygenase inhibitors can inhibit the oxidation of polyunsaturated fatty acids, thereby reducing the formation of toxic LPOs and preventing the initiation of ferroptosis.[148] These inhibitors are currently being tested in clinical trials focused on reducing inflammatory responses and cellular damage during the acute phase of ARDS (Figure 4).

Nuclear Factor Erythroid 2-Related Factor 2

In addition to increasing GSH levels, the transcription factor Nrf2 regulates antioxidant gene expression.[149] During oxidative stress, cysteines in Keap1 are oxidized, leading to the release of Nrf2 through the Cullin3/Rbx1 ubiquitination system.[150] Nrf2 can activate the expression of various factors involved in the detoxification of ROS, triggering an antioxidant response, including glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase modifier subunit (GCLM), GPx,

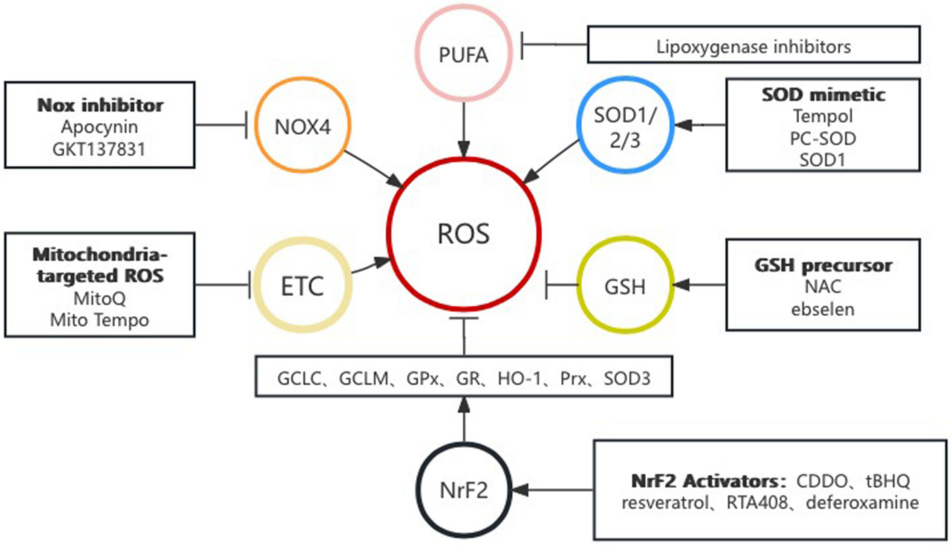

Figure 4 Pharmacological antioxidants.

glutathione reductase (GR), haem oxygenase-1 (HO-1), peroxiredoxins (Prx), and SOD3.[151] Animal models have shown that Nrf2 can bind to antioxidant response elements (AREs) in the promoter regions of target genes, with Nrf2-deficient mice exhibiting exacerbated intestinal ischemia/reperfusion-induced ALI.[152] Additionally, Nrf2 possesses anti-inflammatory functions; it prevents macrophages from activating to the M1 phenotype and promotes alternative activation towards the M2 phenotype.[153] Consequently, studies have shown that pharmacological agents such as tert-butylhydroquinone (tBHQ),[154] bardoxolone (CDDO),[155] and resveratrol[156] can stabilize Nrf2 by altering its binding with Keap1. The Nrf2 activator RTA408 alleviates LPS-induced acute lung injury by inhibiting BACH1-mediated ferroptosis.[157]

Iron Homeostasis

Moreover, manipulating iron homeostasis represents another critical strategy for mitigating ferroptosis. Iron chelators, such as deferoxamine, are molecules that promote tissue regeneration and angiogenesis and possess antioxidant properties;[158] they can be used to reduce excessive intracellular iron levels, thereby decreasing the overall susceptibility of cells to ferroptosis.[159] In recent trials, iron chelation therapy has been shown to reduce iron accumulation in the lungs, with studies investigating the effects of deferoxamine on improving lung function and reducing inflammation in ARDS patients. Deferoxamine reduces iron accumulation, increases dopamine levels, and alters the expression of iron transport proteins, α-synuclein, and oxidative stress markers.[160] By restricting free iron availability, these agents can prevent the catalysis of harmful Fenton reactions that generate ROS, thus protecting AECs from oxidative stress and toxicity.[161] Studies have shown that iron chelators exhibit iron-chelating, antiviral, and immunomodulatory effects both in vitro and in vivo.[162] They can reduce the activity of NF-κB, which inhibits the synthesis of IL-6 and helps alleviate inflammatory responses.[163] By mediating the activation of triggering receptors expressed on myeloid cells-2 (TREM2) through the mTOR signaling pathway, they induce autophagy in microglia following traumatic brain injury, suppressing ferroptosis and reducing brain oedema and neuroinflammation.[164,165] Furthermore, maintaining iron homeostasis helps mitigate cellular ageing and inflammation.[166] Additionally, these agents can inhibit viral replication, decrease iron utilization, increase B-cell activity, and suppress inflammation, which collectively reduces iron accumulation in the lungs and improves lung function.[167]

Intracellular Nutrients Also Support Approaches Targeting Ferroptosis

Various intracellular nutrients, such as Coenzyme Q10 (CoQ10) and vitamins, are closely related to cellular antioxidant systems and participate in the regulation of ferroptosis.[168] CoQ10 increases the phosphorylation of 5′-monophosphate (AMP)-activated protein kinase (AMPK), which can prevent the production of LPOs. Pharmacological CoQ10

supplementation demonstrates potent anti-ferroptotic effects through AMPK-mediated inhibition of lipid peroxidation.[169] Similarly, the CoQ10 analogue idebenone can also block cellular lipid peroxidation by inhibiting excessive autophagy through the ROS-AMPK-mTOR pathway, thereby alleviating ferroptosis.[170] Inhibitors of 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which has a clearance effect on CoQ10, can downregulate GPX4 to induce ferroptosis by inhibiting the mevalonate pathway.[171] In addition, ferroptosis suppressor protein 1 (FSP1), an NAD(P)H-quinone oxidoreductase, inhibits ferroptosis by acting on the CoQ10-NADPH axis and the vitamin K reduction cycle,[172] whereas curcumin induces ferroptosis by inhibiting the FSP1-CoQ10-NADPH pathway.[173]

Among vitamins, vitamin A synergizes with other ferroptosis-inhibitory vitamins (eg, E and K) through redox-modulating mechanisms. Additionally, the metabolites of vitamin A, all-trans-retinal (atRAL) and all-trans-retinoic acid (atRA), directly neutralize lipid-derived free radicals involved in ferroptosis.[174] Similarly, vitamin B6 promotes the expression of antioxidant enzymes by mediating Nrf2 expression, thereby inhibiting LPS-induced ferroptosis.[175] Animal studies have indicated that vitamin C is also an antioxidant with protective effects against ALI in mice.[176] Vitamin D not only alleviates cognitive impairment and mitigates ferroptosis in ageing mice via the Nrf2 signaling pathway,[177] but also reduces inflammation by activating the Klotho/p53 signaling pathway[178] and mediating ACSL4.[179] As a lipid-soluble antioxidant, vitamin E helps stabilize cell membranes, alleviating the impact of lipid peroxidation, and synergizes with GPX4 to protect Treg cells from ferroptosis, thus reducing inflammation.[180] Mucin 1 demonstrates pleiotropic protective effects by simultaneously inhibiting ferroptosis and amplifying vitamin E efficacy through GSK3β/Keap1-Nrf2-GPX4 axis modulation, thereby attenuating sepsis-induced acute lung injury.[181] In addition to its traditional function related to blood coagulation as a cofactor for γ-glutamyl carboxylase, vitamin K possesses strong ferroptosis-inhibitory properties.[182] Vitamin K2 functions by activating GPX4 and suppressing ferroptosis and extracellular matrix degradation.[183,184] FSP1 effectively reduces vitamin K to its hydroquinone form, acting as a potent free radical scavenger and inhibitor of lipid peroxidation, thus protecting cells from harmful lipid peroxidation and ferroptosis.[185]

Additionally, dietary intake of monounsaturated fatty acids (MUFAs) and PUFAs modulates ferroptosis by directly alteration of membrane lipid composition.[186] Moreover, amino acids and glucose intersect with the ferroptosis pathway through nutrient-sensitive kinase mechanistic target of rapamycin complex 1 (mTORC1)[187,188] and AMPK signaling. The inactivation of upstream regulatory factors of mTORC1 and the negative regulator AMPK can promote the expression of SREBP1/SCD1, a key transcriptional regulator of lipogenesis, thereby inhibiting ferroptosis through the production of MUFAs.[189] Synergistic application of these pharmacological antioxidant strategies shows therapeutic potential for redox imbalance management in ARDS (Figure 5).

Summary

In conclusion, ARDS constitutes a life-threatening clinical entity arising from rapid respiratory failure, driven by pathogenic interactions between inflammatory cascades and alveolar-capillary barrier dysfunction. The multifactorial etiology of ARDS, exemplified by pneumonia and sepsis pathogenesis, underscores the imperative for mechanistic elucidation of its pathophysiological underpinnings. Emerging evidence positions ferroptosis—a regulated cell death modality characterized by iron-dependent LPO accumulation—as a central pathological mediator in ARDS. The increased susceptibility of AECs to ferroptosis underscores their potential role in exacerbating lung injury and compromising gas exchange—critical functions necessary for patient survival. Moreover, the inflammatory microenvironment in ARDS further facilitates this unique form of cell death, suggesting that ferroptosis not only contributes to lung damage but may also serve as a therapeutic target.

Importantly, ferroptosis represents a critical intersection between molecular pathology and clinical outcomes in ARDS. The ferroptosis of AECs under oxidative stress transcends mere cellular attrition, functioning as a pathological linchpin that drives disease progression—from acute inflammatory exacerbation to irreversible pulmonary fibrosis. This dual-phase role implies that targeting ferroptosis may not only mitigate epithelial injury in the early stage but also preserve tissue regenerative potential in the late fibrotic phase. These insights underscore the translational significance of ferroptosis, providing a molecular framework for the development of stage-specific diagnostic markers and treatment strategies.

Advancements in understanding the tripartite interplay between ferroptosis, oxidative stress, and inflammation in AECs reveal compelling therapeutic opportunities for targeted modulation of ferroptotic pathways. Strategies aimed at modulating

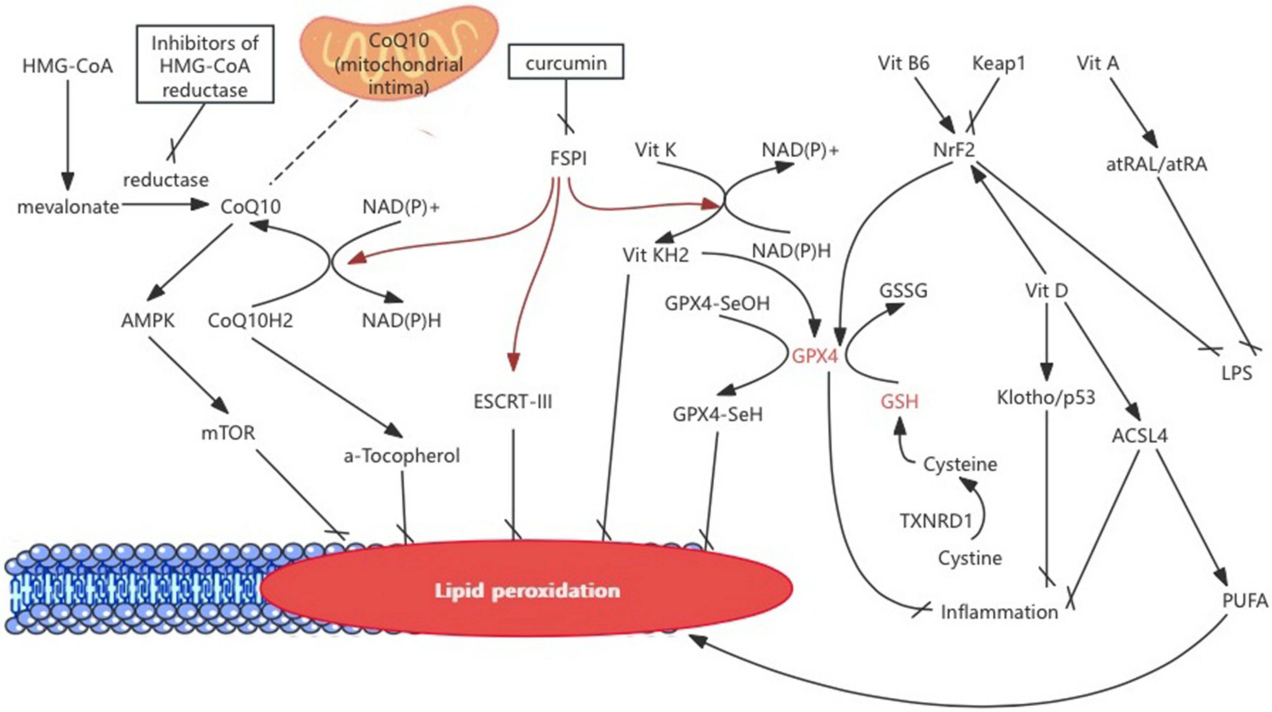

Figure 5 Targeting ferroptosis as a treatment strategy for ARDS.

ferroptosis through antioxidants and nutrient support represent an innovative approach to mitigate oxidative damage and improve lung repair processes. Future research should continue to explore the diverse roles of ferroptosis in ARDS, focusing on clarifying its dual nature as both a facilitator of injury and a potential target for intervention. Translational integration of these mechanistic insights could enhance clinical diagnostics while catalyzing development of phase-specific therapeutics to reduce ARDS-associated morbidity and mortality, ultimately improving patient prognoses.

Abbreviations

ARDS, Acute Respiratory Distress Syndrome; AECs, alveolar epithelial cells; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1β; ROS, reactive oxygen species; LPOs, lipid peroxides; GSH, Glutathione; GPX4, Glutathione peroxidase 4; SLC3A2, solute carrier 3A2; SLC7A11, solute carrier family 7 member 11; Nrf2, nuclear factor E2 related factor 2; ATP, adenosine triphosphate; DAMPs, damage-associated molecular patterns; PUFAs, polyunsaturated fatty acids; NOX, NADPH oxidase; NADPH, nicotinamide adenine dinucleotide phosphate; COX-2, cyclooxygenase-2; SOD, superoxide dismutase; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; HMGB1, high mobility group box 1; TLR4, Toll-like receptor4; NETs, neutrophil extracellular traps; MPO, myeloperoxidase; TLRs, Toll-like receptors; PRRs, pattern recognition receptors; IFN-γ, interferon-gamma; TFR1, transferrin receptor1; FTH1, ferritin heavy chain; IL-10, interleukin-10; TGF-β, transforming growth factor-β; Ala-Gln, Alanyl-glutamine; LPS, Lipopolysaccharide; MMPs, matrix metalloproteinases; TRP, transient receptor potential; RAS, renin-angiotensin system; PC-SOD, phospholipatedSOD2; GPx, glutathione peroxidase; GCLC, glutamate-cysteine ligase catalytic subunit; HO-1, heme oxygenase-1; GR, glutathione reductase; GCLM, glutamate-cysteine ligase modifier subunit; Prx, peroxiredoxins; AREs, antioxidant response elements; tBHQ, tert-butylhydroquinone; CDDO, bardoxolone; TREM2, triggering receptors expressed on myeloid cells-2; CoQ10, CoenzymeQ10; AMPK, AMP-activated protein kinase; AMP, 5′-monophosphate; HMG-CoA, 3-hydroxyl-3-methylglutarylcoenzymeA; FSP1, ferroptosis suppressor protein 1; atRAL, all-trans-retinal; atRA, all-trans-retinoic acid; MUFA, monounsaturated fatty acids; mTORC1, mechanistic target of rapamycin complex 1; FPN, Ferroportin; Fe2+, ferrous iron; Fe3+, ferric iron; LIP, labile iron pool; TCA, mitochondrial tricarboxylic acid cycle; PUFA-PL, phospholipid with polyunsaturated fatty acid; ACSL4, acyl-CoA synthetase long-chain family member

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4; LPCAT3, lysophosphatidylcholine acyltransferase 3; ALOXS, arachidonate lipoxygenase; GLS2, glutaminase 2; ACLY, ATP citrate lyase; IPP, intracisternal A particle-promoted polypeptide; Glu, glutamate; GSSG, L-Glutathione Oxidized; NFE2L2, nuclear factor, erythroid 2-like 2; CARS1, cysteinyl-tRNA synthetase; ARF, cyclin-dependent kinase inhibitor 2A; SCD1, stearoyl CoA desaturase; EGLN1, egl-9 family hypoxia-inducible factor 1; LSH, lymphoid tissue-specific helicase; BCAT2, branched chain amino-acid transaminase.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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