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REVIEW

Unraveling the Molecular Regulation of Ferroptosis in Respiratory Diseases

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Abstract: Ferroptosis, a type of programmed cell death that relies on iron, is distinct in terms of its morphological, biochemical and genetic features. Unlike other forms of cell death, such as autophagy, apoptosis, necrosis, and pyroptosis, ferroptosis is primarily caused by lipid peroxidation. Cells that die due to iron can potentially trigger an immune response which intensifies inflammation and causes severe inflammatory reactions that eventually lead to multiple organ failure. In recent years, ferroptosis has been identified in an increasing number of medical fields, including neurological pathologies, chronic liver diseases and sepsis. Ferroptosis has the potential to cause an inflammatory tempest, with many of the catalysts and pathological indications of respiratory ailments being linked to inflammatory reactions. The growing investigation into ferroptosis in respiratory disorders has also garnered significant interest to better understand the mechanism of ferroptosis in these diseases. In this review, the recent progress in understanding the molecular control of ferroptosis and its mechanism in different respiratory disorders is examined. In addition, this review discusses current challenges and prospects for understanding the link between respiratory diseases and ferroptosis.

Keywords: respiratory system, ferroptosis, iron metabolism, oxidative stress, treatment

Introduction

Cell death, a permanent phenomenon that commonly occurs in healthy tissues, plays a vital role in preserving tissue function and structure.[1] Ferroptosis is one distinct form of programmed cell death that is triggered by the excessive production of reactive oxygen species (ROS) and lipid peroxidation, with both being dependent on iron.[2,3] Coined in 2012, the study of ferroptosis has experienced rapid growth in recent years, and the process is now distinguished from apoptosis, necrosis, autophagy and other typical cell death structures by the reduced sizes of mitochondria, an increased density of bilayer membranes as well as diminished mitochondrial cristae.[4–6] This distinct form of cellular demise, influenced by iron-induced phospholipid peroxidation, is regulated by various cellular metabolic processes which are involved in maintaining redox balance, managing iron levels, regulating mitochondrial function and metabolizing amino acids, lipids and sugars. Additionally, numerous disease-related signaling pathways are also associated with this mode of cell death.[7] Elevated levels of free iron, resulting from disturbances in intracellular iron metabolism, initiate the Fenton reaction which subsequently generates ROS and induces lipid peroxidation. This process then leads to the accumulation of lipid peroxides that depletes glutathione (GSH) and reduces the activity of glutathione peroxidase 4 (GPX4).

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Consequently, lipid peroxides can no longer be metabolized through the GPX4-catalyzed glutathione reductase reaction, resulting in the disruption of cell membrane integrity and subsequent iron toxicity.[8]

Ferroptosis displays distinct characteristics, including the disappearance of mitochondrial cristae, an increase in the density of mitochondrial membranes and unchanged nuclear morphology, with these morphological alterations setting the process apart from other forms of cellular demise. Biochemically, ferroptosis is characterized by a significant release of polyunsaturated fatty acids (PUFAs), inhibition of GPX4 function, reduction of GSH levels and ROS buildup.[3,9] The increase in free iron (Fe^{2+}), which attaches to PUFAs on the cell membrane to stimulate the Fenton reaction and initiate lipid peroxidation by supplying free electrons to produce lipid hydroperoxides (LOOHs), holds the utmost significance in biochemistry. Excessive accumulation of these LOOHs occurs when the antioxidant system is compromised, leading to cytosolic iron toxicity.[10] Usually, a dynamic equilibrium exists between the antioxidant mechanism (comprising the Xc-system, glutathione, GPX4 and various recently identified pathways) and the oxidative mechanism (comprising Fe^{2+}, Fenton reaction and reactive oxygen species).[11] However, infection or inflammation disrupts this equilibrium, causing iron-depleted cells to activate the innate immune system through the release of inflammation-related factors. This activation promotes iron deposition which subsequently triggers an inflammatory reaction that worsens the negative impacts of the disease.[12] Inflammatory responses are associated with common respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), acute lung injury and pulmonary fibrosis.[13]

As the focus on fundamental and applied investigation grows, the significance and mechanism of ferroptosis regulation in respiratory disorders have been progressively unveiled.[14,15] However, further studies are still needed to fully elucidate the role of this type of cell death and to explore whether it can bring breakthroughs in the treatment and diagnosis of respiratory diseases, especially since the role of ferroptosis may vary depending on the etiology of such diseases.[16–18]

This review examines the pathophysiological process of ferroptosis in various respiratory diseases and the current state of research in this field. The aim is to explore its relevance and analyze its impact on such diseases to provide valuable research perspectives for future diagnosis and treatment.

Necessary Conditions for Ferroptosis to Occur

The Presence of Iron Ions is Required for Ferroptosis to Occur

Before the formalization of the term "ferroptosis", scientists had already discovered that the addition of substances that bind to iron or genetic alterations that reduced the number of iron ions significantly suppressed this particular type of cellular demise.[19,20] In 2012, the term "ferroptosis" was officially coined to describe this infrequent type of iron-dependent cellular demise.

The presence of iron ions is crucial for initiating ferroptosis, and various factors can influence its occurrence in cells through the regulation of processes such as the transportation and metabolism of iron ions. One such factor is divalent metal ion transporter protein 1 (DMT1) which can transport divalent metal ions including ferrous iron.[2] DMT1, located in the parietal membrane of small intestinal epithelial cells, maintains body iron homeostasis by translocating iron from food into cells for intestinal iron absorption.[21] It has been suggested that the absence of DMT1 function could be linked to lung injury caused by exposure to metals. In a study that used Belgrade rats to set up an animal model of DMT1 functional deficiency, bronchoalveolar lavage (BAL) after intratracheal injection of lipopolysaccharide (LPS) revealed higher levels of macrophages, lactate dehydrogenase, myeloperoxidase, albumin and hemoglobin in Belgrade rat BAL fluid compared with heterozygous control rats. In addition, following LPS injection, Belgrade rats exhibited a higher ratio of macrophages to overall BAL cell composition, along with elevated levels of albumin and IgM compared with control rats. In contrast, the inflammatory response to LPS was attenuated in Belgrade rats heterozygous for diet-induced iron-deficiency-induced anemia. Altogether, these results suggest that both DMT1 and iron status can alter lung inflammation.[22]

In addition to the absorption of non-heme iron from food, a large percentage of iron absorption in the body comes from heme iron.[23] Heme can be absorbed directly by cells and later broken down by intracellular heme oxidase to release iron. It has been found that in human platelets, heme can release iron ions that mediate lipid peroxidation which, in turn, regulates platelet ferroptosis.[24] Since heme oxygenase (HO-1) is required to catalyze the reaction during heme

degradation to produce free iron, HO-1 is a major source of unstable intracellular iron. In fact, many studies have reported that HO-1 could mediate the occurrence of ferroptosis in cells.[25–27]

Ferroptosis is Dependent on Lipid Peroxidation

Lipid peroxidation of cell membranes is the primary cause of ferroptosis, with genes linked to lipid metabolism, specifically ACSL4 and LPCAT3, playing a significant role in influencing the peroxidation process. These genes encode enzymes that are crucial for esterification and the incorporation of polyunsaturated fatty acids (PUFA) into membrane phospholipids (PL).[28,29] Those phospholipids, into which PUFA are inserted, contain unstable diallyl hydrogen atoms that are particularly susceptible to lipid peroxidation which then triggers cellular ferroptosis.[30] Oxidation of PUFA on membrane phospholipids, especially those containing phosphatidylethanolamine (PE), also generates lipid peroxidation which leads to ferroptosis.[29]

Regulatory Processes in the Development of Ferroptosis

Ferroptosis, as a fatal lipid peroxidation process within cells that relies on iron, results in excess iron, the generation of reactive oxygen species (ROS) and an increase in the amount of polyunsaturated fatty acids found in phospholipids. This cascade then causes deterioration of cell membrane integrity, impairment of regular cell membrane function due to lipid cross-linking as well as oxidative harm to large molecules and cellular structures, with these processes ultimately culminating in cell demise.[5] Two pathways regulate ferroptosis, namely the conventional GPX4-dependent pathway and the GPX4-independent pathway.[31] The former is the systemic GSH-GPX4 pathway which plays a key role in reducing intracellular PLOOH through the absorption of extracellular cystine by cystine-glutamate antitransfer proteins. These proteins facilitate cysteine production by thioredoxin reductase 1, synthesize glutathione and contribute to the GPX4-mediated reduction of intracellular PLOOH, thereby reducing lipid peroxidation.[32] The second pathway is composed of the iron-death suppressor protein 1 (FSP1), ubiquinone, squalene and tetrahydrobiopterin. It primarily functions as an antioxidant and prevents lipid peroxidation by engaging in reduction reactions and capturing endogenous free radicals.[33]

Mechanisms of Ferroptosis

Abnormalities in Iron Ion Metabolism

The iron ion, a crucial trace element within the human body, exists primarily as Fe^{2+} or Fe^{3+} during cellular activities. It not only serves as a vital cofactor for multiple enzymes that contain iron but it also plays significant roles in biochemical and physiological processes, including the movement and retention of oxygen as well as the proper functioning of the nervous system.[34,35] However, an excess of iron ions in the body can lead to a range of diseases and injuries. Therefore, the body requires a system that controls and regulates iron levels to maintain an appropriate physiological state. When the amount of iron ions in a cell exceeds its capacity, ferroptosis takes place as a type of cellular demise. This type of cellular demise distinguishes itself from other forms by being primarily caused by an abundance of iron ions within the cellular structure. This is in contrast to other types of demise which are predominantly triggered by a cell's exposure to external elements.[6]

Iron relies on the assistance of transferrin (TF) and transferrin receptor (TF receptor, TFR) 1 for its proper functioning.[36] TF has a high affinity for ferric iron, binding it tightly but reversibly. The protein can adjust its iron ion load based on the body's iron availability, appearing in diferric form when iron ions are abundant and monoferric form when iron ions are scarce.[37] The flexibility of transferrin allows it to regulate its iron-binding capacity accordingly.[38] Although iron concentration is a key factor in ferroptosis, the exact iron concentration required to induce ferroptosis remains unclear.[39] Previous studies have shown that the mechanism of iron metabolism-regulating ferroptosis involves the formation of the TfR1/Tf-$(Fe^{3+})2$ complex, highlighting the intricate interplay between iron and cell death processes.[40]

Since food-derived iron is mainly Fe^{3+}, it is not absorbed directly but is instead assisted by the iron transporter TF. In this case, the extracellular iron (Fe^{3+}) attaches to TFR1 through endocytosis to create endosomes which serve as the primary supplier of intracellular iron by being conveyed into the cell by TFs. After entering the cell, the Fe^{3+} in endocytosed vesicles undergoes reduction to Fe^{2+} by Six-transmembrane epithelial antigen of the prostate 3 (STEAP3). The reduced Fe^{2+} is then stored in different iron pools through divalent metal transporter 1 (DMT1), while the remaining ions are oxidized and recycled outside the cell to maintain iron balance in the body. Hence, throughout these processes, iron circulates in the form of Fe^{2+} and

Fe^{3+}. Iron overload occurs in diseased tissue states when an excessive amount of iron in the body causes an accumulation of reactive iron (Fe^{2+}) in vital organs and tissue cells. This overload can then trigger the production of ROS. Indeed, excess Fe^{2+} can react with hydrogen peroxide to form Fe^{3+} which subsequently generates hydroxyl radicals due to its strong oxidizing capabilities. Through the Fenton reaction, these hydroxyl radicals eventually enhance the production of ROS that are harmful to cells. Additionally, excess Fe^{2+} actively contributes to the progression of ferroptosis.[41]

However, Fpn is the sole protein responsible for iron transportation that can mitigate ferroptosis by decreasing iron levels within cells. Studies have confirmed that overexpression of TFR1 or the knockdown of Fpn leads to intracellular ferroptosis. Conversely, the up-regulation of Fpn through ferroportin-1 (Fer-1) decreases intracellular iron levels, improves lipid peroxidation and reduces the incidence of ferroptosis.[42] Under normal body conditions, surplus Fe^{2+} within cells undergoes oxidation to Fe^{3+} and is then accumulated in ferritin. Therefore, the interplay between proteins like TFR1, Fpn, and Fer-1 is crucial in regulating iron levels within cells and influencing the occurrence of ferroptosis.

Disorders of Lipid Metabolism

Accumulation of lipid peroxides due to disorders of lipid metabolism mediates plasma membrane damage, with this process being a central aspect of ferroptosis occurrence.[43] Essentially, it is a process, primarily facilitated by lipoxygenase, in which biological membranes are oxidized by ROS, leading to alterations in cellular structure, and functions. Due to their reactive nature, PUFA on cellular membranes, especially arachidonic acid (AA) or adrenergic acid (AdA), are highly vulnerable to oxidative reactions during ferroptosis.[44,45] As previously stated, ACSL4 and LPCAT3 have important functions in the regulation of lipid peroxidation.[46] Specifically, the former can bind PUFAs such as AA or AdA to catalyze the formation of arachidonoyl-coenzyme A and adenosyl-coenzyme A. These compounds are then esterified to PE by LPCAT3 to generate AA-PE and AdA-PE which are eventually oxidized to lipid peroxides (LPOs) by lipoxygenase. Studies have therefore shown that knockdown or inhibition of ACSL4 inhibits the development of ferroptosis.[47] The breakdown and metabolism of LPO further produce harmful aldehydes, such as 4-hydroxy-2-nonenal or malondialdehyde (MDA), which react with ongoing oxidation processes on the cell and plasma membranes. This reaction ultimately causes irreversible damage to the membranes' structure and functions, thereby resulting in cell death. Hence, high levels of ACSL4 and LPCAT3 are also considered to be a significant indication of ferroptosis.[48]

Imbalance in the Glutamate-Cystine Antioxidant System

Ferroptosis is significantly influenced by amino acids, with cystine/glutamate reverse transporter protein (system Xc-) being an important amino acid transporter in the process.[49] The protein, which is composed of a non-sugar light chain subunit as well as a sugar-containing heavy chain subunit at the beginning, facilitates the transport of cystine and the exchange of glutamate within cells. Cysteine, a precursor for the synthesis of glutathione (GSH), is produced through intracellular cystine degradation. As such, an adequate supply of cysteine is the rate-limiting step for GSH production. Under normal body conditions, the Xc- system, which includes the solute transporter family 7A11 (SLC7A11) and SLC3A2, moves cystine into the cell and converts it to cysteine for GSH production. As the primary antioxidant inside cells, GSH is exclusively used by glutathione peroxidase (GPX4) to convert reduced GSH to oxidized GSH. GPX4 also functions as an internal antioxidant in vivo by decreasing LPO and eliminating lipid peroxides and ROS from cells, thereby reducing damage caused by oxidative stress. By using this carrier, extracellular cystine can be transferred into the intracellular compartment of healthy organisms to facilitate the production of GSH. GSH functions as an antioxidant and detoxifier, transforming harmful substances within the body into harmless compounds that are eventually eliminated. GSH also helps to eliminate the substantial quantity of ROS that builds up in the body, thereby aiding GPX4 in carrying out its antioxidative function. Blocking the Xc- system has been shown to restrict the influx of cysteine, leading to a decrease in GSH production as well as a weakening of GPX4's reactivity. As a result, ROS accumulation occurred, increasing the likelihood of ferroptosis.[50]

GPX4-Dependent Regulatory Pathways

Cells depend on lipids to regulate cell membrane structure, morphology, metabolism and other functions. The presence and positioning of PUFA-PL largely influence cell membrane fluidity, and this represents a significant factor among the numerous

lipids constituting cell membranes.[51] Indeed, the cis conformation in double-bonded PUFA prevents stacking of the unsaturated fatty acid tails, thereby contributing to increased membrane fluidity, especially at high PUFA-PL levels. However, the presence of PUFA also makes membrane susceptible to oxidation since the hydrogen atom located at the bis-allyl position can be readily absorbed by reactive oxygen fragments. This process generates lipid radicals that can be further oxidized, resulting in the formation of lipid peroxides (PL-OOH). In this context, cells rely on a specific protein network that includes GPX4 as a key protein to repair PUFA-PL peroxidation. GPX4, a selenoprotein, acts as an antioxidant by identifying and transforming harmful lipid peroxides into safe lipid alcohol compounds in biological membranes with the help of GSH. Hence, when GPX4 activity is compromised, iron-dependent cellular ferroptosis can occur due to the accumulation of lipid peroxidation. Since GPX4 decreases lipid oxidation, this antioxidant mechanism can counter the transfer of cysteine to glutathione through the Xc- system. Moreover, GPX4 includes selenocysteine which bears similarity to cysteine in terms of structure, except for the fact that it incorporates selenium instead of sulfur. By employing selenocysteine which acts as a catalytic component to ensure rapid reduction of GPX4, the latter offers exceptional protection against irreversible peroxidation by removing lipid ROS and peroxides through scavenging. Nrf2 (nuclear factor E2-related factor 2) plays a crucial role in the antioxidant mechanism of GSH and is vital for preventing ferroptosis. By inducing the expression of the Xc- system and GPX4, Nrf2 decreases lipid peroxidation and maintains GSH levels, thereby directly inhibiting ferroptosis.[52]

GPX4 Non-Dependent Regulatory Pathway

Recent studies regarding ferroptosis have primarily concentrated on cancer research, and the response of tumor cells to GPX4 inhibitors differed significantly, indicating the potential influence of additional factors on an organism's vulnerability to ferroptosis. AIMF2, a mitochondrial factor associated with apoptosis induction, is a gene targeted by P53 to enhance P53-mediated cell death. Bersuke et al later discovered that AIMF2 could inhibit the occurrence of ferroptosis and referred to it as FSP1. FSP1, a powerful factor in resisting ferroptosis, decreases this type of cell death when overexpressed.[53] However, when treated with apoptosis inducers, FSP1 could not prevent ferroptosis.

FSP1 can function as an oxidoreductase in the cytoplasm, leading to a reduction in ubiquinone. Due to the decrease, there is production of ubiquinol which acts as an antioxidant by eliminating lipophilic free radicals and preventing the buildup of lipid peroxidation. Research has also indicated that FSP1 can offer protection against ferroptosis resulting from GPX4 insufficiency by capturing unbound radicals produced during lipid peroxidation. At the same time, FSP1 facilitates the restoration of ubiquinone using NAD(P)H, while, in combination with GSH-GPX4, it also hinders the oxidation of phospholipid lipids to prevent ferroptosis. Therefore, FSP1 operates independently from GPX4 without impacting other iron-binding mechanisms.[53,54]

The Function of P53 in the Control of Ferroptosis

Despite being widely recognized as a tumor suppressor gene, the P53 gene also has a crucial role in regulating cellular stress and DNA damage. The buildup of excessive cellular iron is linked to ferroptosis, and evidence suggests that P53 could regulate the process. Multiple studies have demonstrated that P53 can control the expression of genes associated with iron metabolism, including iron transporter proteins that regulate iron uptake and release.[55] In addition, P53 can also regulate some signaling pathways related to iron metabolism. For instance, by controlling the levels of ferritin and ferroportin as well as suppressing the expression of associated genes, P53 can influence the intracellular balance of iron and consequently impact cellular iron metabolism.[56] P53 has further been shown to regulate both GPX4-dependent and GPX4-independent ferroptosis pathways. Through the former pathway, P53 can increase GPX4 expression, thereby reducing lipid peroxidation and preventing ferroptosis.[57] On the other hand, through the GPX4-independent pathway, P53 can increase ROS levels and lead to lipid peroxidation.[58] Furthermore, P53 can suppress elements of the Xc- system that makes cells more susceptible to ferroptosis by blocking the absorption of cysteine and triggering cellular ferroptosis when confronted with stress caused by ROS.[59]

It should be noted that these investigations on the functions of P53 in ferroptosis are still preliminary, and hence, additional research is required to further confirm and enhance current understanding. Nevertheless, these discoveries offer an insight into the function of P53 in cellular iron metabolism and lay the groundwork for advancements in therapeutic approaches.

Respiratory System Profile

The respiratory system consists of the airways and the lungs, and since the respiratory tract is connected to the outside world, harmful gases, dust particles and pathogenic microorganisms in the air can enter the lungs. As a result, the lungs are susceptible to tracheal, bronchial and lung diseases such as chronic obstructive pulmonary disease, lung infections, asthma, pulmonary fibrosis, pulmonary ischemia-reperfusion injury, acute lung injury/acute respiratory distress syndrome, obstructive sleep apnea syndrome and lung carcinoma, amongst others.

Over the past few years, research has identified a strong correlation between ferroptosis and the emergence and progression of respiratory disorders. Therefore, understanding the specific pathogenesis and molecular features of these diseases as well as their relationship with ferroptosis can guide effective treatment strategies.[60,61]

Ferroptosis in Respiratory Diseases

Chronic Obstructive Pulmonary Disease and Ferroptosis

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory illness marked by persistent blockage of airflow and recurrent respiratory infections. This condition, ranked as the fourth major cause of morbidity and mortality worldwide and for which prevalence is on the rise, significantly impacts patients' quality of life and safety.[62] Recent research indicates that patients with COPD experience a disruption in their iron metabolism, which is partially associated with the onset of ferroptosis.[17] In this case, disturbances in iron metabolism are mainly characterized by alternation between a state of iron deficiency and a state of excessive iron accumulation in the body. Studies have shown that COPD patients have excessive iron levels in both lung tissues and peripheral blood, possibly due to common inflammatory responses, oxidative stress and genetic factors.[61,63]

Common causes of COPD include smoking, air pollution (eg, PM 2.5), genetic factors and occupational exposures.[64] Of these, active or passive smoking may lead to an excessive intake or improper utilization of iron as cigarette smoke (CS) contains high levels of ROS.[65] The ensuing cellular oxidative stress then triggers inflammation, cellular senescence and death. Initial research has indicated that exposure to CS induces the buildup of iron and ferritin in cells that line the lungs and in immune cells within the air sacs, while increasing levels of ferritin and non-heme iron in the bloodstream.[63] In this case, subsequent mitochondrial malfunction and endoplasmic reticulum strain typically occur within the cytoplasm, while ferroptosis takes place in the bronchial epithelial cells.[66] Research has further demonstrated that long-term smoking causes lung epithelial cells to initiate nuclear receptor coactivator 4 (NCOA4) iron autophagy, resulting in the excessive buildup of iron. This accumulation subsequently triggers phospholipid peroxidation and ferroptosis in the lung epithelial cells, thereby increasing the levels of free iron.[67] GPX4 has been identified as a therapeutic target in a mouse model of COPD-related ferroptosis. Indeed, knockdown of GPX4 directly exacerbated long-term smoking-induced COPD, while a reduction of iron intake or the use of iron chelators significantly attenuated long-term smoking-induced COPD.[63] PM2.5 represents another significant risk factor for COPD.[68] Indeed, at high concentrations, PM2.5 particulate matter, which can potentially include detrimental compounds, such as toxic metals and polycyclic aromatic hydrocarbons (PAHs), can be inhaled into the respiratory tract and directly into lung tissue. In turn, these particles can disrupt internal iron metabolism, resulting in a buildup of excessive iron ions and subsequent oxidative stress to initiate ferroptosis.[69] In addition, PM2.5 may also indirectly affect the balance of iron metabolism by activating inflammatory pathways and oxidative stress. It was found that the relationship between PM2.5 and ferroptosis could be closely related to factors such as antioxidant capacity, inflammatory response and iron regulatory pathways in the body.[70]

The latest study reported that N6-methyladenosine-modified circSAV1 promotes ferroptosis in COPD by recruiting YTHDF1 to facilitate the translation of IREB2, and elevated levels of N6-methyladenosine-modified circSAV1 were associated with COPD progression and ferroptosis.[71] Besides, Sauler et al indicated that the diminished expression of NUPR1 in alveolar epithelial type II of COPD heightens their susceptibility to cell death, potentially by enhancing ferroptosis.[72] Based on available research, ferroptosis proves to be a critical factor in COPD, ferroptosis occurring in airway epithelial cells leads to airway remodeling, while in alveolar epithelial cells, it triggers emphysema. These conditions collectively contribute to the development of COPD, and it emphasizes the need for precise ferroptosis inhibitors that can delay disease progression or even its occurrence.[61]

Lung Infections and Ferroptosis

Inflammation of the lungs, known as lung infections, can be caused by different types of microorganisms including bacteria, viruses, mycoplasma and chlamydia. This condition represents a growing threat to public health, with pneumonia-related deaths now frequently observed on a global scale. In this case, the lung parenchyma becomes vulnerable to harmful organisms due to regular contact of the lung's epithelial surfaces with air that contains microbial contaminants. At the same time, other respiratory illnesses and unhealthy habits, such as smoking and alcohol consumption, further exacerbate the disease. Activation of ferroptosis is associated with host tissue damage caused by bacterial infection. In particular, it involves the targeted oxidation of arachidonic acid-phosphatidylethanolamine (AA-PE) by 15-lipoxygenase, resulting in programmed cell death. In one study, Pseudomonas aeruginosa secreted lipoxygenase (proxy) that oxidized the host's arachidonic acid-phosphatidylethanolamine (ETE-PE) to the pro-ferritin 15-hydroxy peroxy phosphatidylethanolamine (15-HpETE-PE), thereby inducing lipid peroxidation and ferroptosis in the host's bronchial epithelial cells.[73] Furthermore, Pseudomonas aeruginosa could also diminish the host's GPX4 defenses through the activation of lysosomal chaperone-mediated autophagy (CMA).[74] Additional research further demonstrated that macrophages infected with Mycobacterium tuberculosis (Mtb) could exhibit various characteristics of ferroptosis, such as heightened levels of unbound iron, reduced GSH and GPX4, the buildup of mitochondrial superoxide as well as lipid peroxidation.[60] Th1 cells are the main drivers of immunity against Mtb infection as they initiate the sterilization of macrophages. However, re-exposure to Mtb or reactivation of the infection triggers a quick immune response that may lead to greater tissue necrosis and destruction. Furthermore, Mycobacterium tuberculosis enhances the expression of HO-1, potentially facilitating the survival and proliferation of the bacterium due to the higher availability of iron. Furthermore, Ferrostatin-1 significantly attenuated Mtb-induced necrosis in macrophages and mouse lungs in addition to its role as an antioxidant inhibitor. Finally, Fer-1 effectively relieved the symptoms of infected animals, opening up novel therapeutic possibilities for tuberculosis.[75]

Bronchial Asthma and Ferroptosis

Bronchial asthma, a long-lasting inflammatory condition affecting the bronchial tubes, is marked by reversible spasms caused by different internal and external factors that trigger an allergic response in the respiratory system. This results in periodic wheezing, difficulty in breathing, tightness in the chest and coughing. The etiology of bronchial asthma is mostly thought to be related to polygenic inheritance, but may also occur through interactions with environmental factors. Although the pathogenesis of bronchial asthma is currently unknown, the disease is characterized by intermittent and reversible blockage of the airways, persistent bronchitis, enlargement and hyperactivity of bronchial smooth muscle cells as well as heightened production of mucus.[76]

The involvement of phosphatidylethanolamine-binding protein 1 (PEBP1) in the regulatory pathway of ferroptosis in asthmatic airway epithelial cells has been extensively described in 2017 by Wenzel et al who elucidated the precise mechanisms. Ferroptosis has the potential to induce numerous acute and chronic ailments, and this process occurs when polyunsaturated phosphatidylethanolamine (PE) undergoes oxidation by 15-lipoxygenase (15-LO), an enzyme that typically utilizes unbound polyunsaturated fatty acids as its substrates. In this case, PEBP1 functions as a scaffold protein inhibitor of a protein kinase cascade, interacting with both 15-LO isoforms (15-LO1 and 15-LO2) to modify their competition for substrates and influence the generation of peroxidized pro-ethylene. Insufficient reduction of hydroperoxy PE due to insufficient or deficient GPX4 triggers ferroptosis, hence highlighting its crucial role in causing pulmonary edema death in airway epithelial cells of individuals with bronchial asthma, in renal epithelial cells of individuals with renal failure as well as in cortical and hippocampal neurons following traumatic brain injury.[77]

In an inflamed environment, numerous cells from both the innate and adaptive immune systems engage with airway epithelial cells, leading to various structural alterations in the airways, including mucous metaplasia, airway hyperresponsiveness, airway remodeling, and inflammation, among others.[78] Asthma predominantly manifests as type 1 (T1) and type 2 (T2) inflammation. T1 inflammation is primarily linked to neutrophilic activity, while T2 inflammation is predominantly associated with eosinophils.[79] Most asthma patients exhibit T2 inflammation, typically characterized by eosinophilic inflammation and elevated levels of interleukins (IL)-4, IL-5, and IL-13.[80] IL-4 then stimulates B cells to

produce IgE, while IL-5 activates eosinophils. Additionally, IL-13 stimulates the production of mucus and IgE. At the same time, mast cells, macrophages, neutrophils and T cells become active and gather in the air passages to release inflammatory substances, resulting in persistent inflammation of the respiratory system. Recent studies have confirmed that IL-4/IL-13 induces 15-LO1 expression, with the respiratory epithelial cells in asthmatics also actively producing 15-LO1. This process promotes the binding of 15-LO1 and PEBP1, and the subsequent activation of the 15-LO1-PEBP1 complex further stimulates IL-13/IL-4-mediated Th2 inflammation which exacerbates the deterioration of bronchial asthma. Additional research has also indicated that the 15-LO1-PEBP1 complex could trigger autophagy and ferroptosis. In HAEC from stable, non-worsening patients, higher 15-LO1 levels have been closely associated with PEBP1, while GPX4 was found to degrade oxygenated PEs. In human respiratory epithelial cells, the small molecule 3 (RSL3), which induces ferroptosis selectively in RAS, greatly enhanced lipid peroxidation and ferroptosis induced by IL-13. Moreover, in IL-13-cultured hemocytes, RSL3-induced inactivation of GPX4 resulted in the accumulation of large amounts of oxygenated PES. In addition, the blockade of PEBP1 reduced ferroptosis sensitivity. Hence, boosting GPX4 function amidst asthma exacerbation could potentially avert ferroptosis and alleviate the symptoms of asthma. However, its clinical potential requires further investigation.[60,81]

Pulmonary Fibrosis and Ferroptosis

The development of numerous respiratory diseases has been attributed to an imbalance in redox reactions. Currently, the etiology of pulmonary fibrosis (PF) is not fully understood. PF typically arises from chronic exposure to causative factors, such as CS and dust (such as asbestos, silica, and coal), medications (like bleomycin and amiodarone), accidental exposure to paraquat or radiation therapy, all of which lead to lung injury and interstitial lung disease.[82] PF has been strongly associated with the development of ferroptosis as disease development involves the buildup of iron ions, reactive oxygen species (ROS), lipid peroxidation and the suppression of GPX4 activity.[83] Therefore, PF is frequently accompanied by irregular iron metabolism and lipid peroxidation.[84] Earlier research has indicated that elastin facilitates the transformation of fibroblasts into myofibroblasts in response to transforming growth factor β1 (TGF-β1) by enhancing the production of reactive oxygen species (ROS) and lipid peroxidation. Additionally, it hinders the expression of GPX4, resulting in the accumulation of collagen and the disruption of alveolar structure. However, these processes could also potentially be hindered by ferritin-1. Thus, preventing intracellular lipid peroxidation and iron buildup could represent a successful strategy in averting the iron-induced demise of alveolar cells as well as progression of PF.[85]

Radiation-induced pulmonary fibrosis (RIPF), a frequently fatal outcome of radiation treatment for lung carcinoma, is commonly manifested within the first few months after treatment and it persists for a maximum of two years, with no known successful remedy.[61] In this case, ionizing radiation (IR) used in radiation therapy causes an excessive buildup of ROS and the generation of numerous inflammatory substances. The build-up ROS and the presence of TGF-β1 are crucial for the onset and progression of RILF, and, in fact, suppressing TGF-β1 expression has been regarded as a successful therapy for RILF. New research has now indicated that ferroptosis is an innovative cancer cell death process caused by radiation. Inducers of ferroptosis cause biomolecular oxidation (eg, lipid oxidation) by enhancing radiation-generated ROS and driving ferroptosis through phospholipid peroxidation.[86] Studies have also demonstrated that Lip-1, a ferroptosis inhibitor, could effectively decrease the concentrations of pro-inflammatory cytokines IL-6, TNF-α, IL-10 and TGF-β1. Additionally, it could reduce ROS buildup, inhibit collagen deposition and reduce hydroxyproline (HYP), thereby mitigating RILF. Nrf2, an antioxidant compound, protects cells against oxidative harm caused by radiation. Specifically, its activation reduces the expression of TGF-β1 and mitigates fibrotic tissue disorders. Furthermore, Nrf2 signaling also protects against ferroptosis in numerous ailments. Thus the Nrf2 pathway may be involved in the process of RILF ferroptosis inhibition. Activation of the Nrf2 pathway was observed when ferroptosis inhibitors were used, and this led to decreased production of ROS, decreased expression of TGF-β1 as well as RILF inhibition.[87] Furthermore, erastin was found to worsen RILF by promoting the differentiation of fibroblasts into myofibroblasts through the suppression of GPX4 expression and accelerated lipid peroxidation.[88]

The cause of idiopathic pulmonary fibrosis (IPF), a disease characterized by refractory and irreversible progressive lung fibrosis, is not fully understood.[89] This condition, for which repeated epithelial activation and injury are the main causes of progression, is marked by sporadic but gradual bilateral interstitial fibrosis, resulting in profound hypoxemia

and bluish discoloration in advanced instances. Indeed, the presence of impaired epithelial repair and inflammation at the site of injury causes excessive growth of fibroblasts and myofibroblasts that ultimately lead to the formation of characteristic fibroblastic foci. Elevated levels of genes associated with ferroptosis, such as neuroblastoma RAS virus (v-ras) oncogene homolog (NRAS) and MUC1, have been observed in bronchoalveolar lavage fluid and cells of patients with IPF. It is suggested that the involvement of ferroptosis in the development of IPF and its potential as a prognostic marker of the disease.[90] Of note, although certain studies have implied the important role of ferroptosis in PF, the evidence remains limited as the regulatory network of ferroptosis is complicated.

Additional research has indicated a correlation between ferroptosis and lung injury caused by paraquat (PQ), suggesting that employing iron porphyrin inhibitors could potentially serve as a viable remedy for alleviating PQ toxicity.[91] Studies of fibrosis of various organs, such as the liver and heart, have also revealed the involvement of ferroptosis. Therefore, strategies to regulate iron metabolism and control ferroptosis could be developed to slow the progression of fibrotic diseases in future experiments and clinical practice.[92]

Lung Ischemia-Reperfusion Injury and Ferroptosis

Lung ischemia-reperfusion injury (LIRI), a severe medical condition linked to lung ischemia-reperfusion, can occur due to lung thromboembolism, thrombolysis, lung resection, trauma, lung transplantation and various surgical procedures. Ischemia-reperfusion damage takes place during the early phases of vascular injury, where respiratory epithelial cells exhibit a certain degree of resilience towards temporary oxygen deprivation. The injury is then associated with the restoration of blood flow that leads to reperfusion injury. During LIRI, cellular hypoxia and metabolic disturbances activate multiple signaling pathways, such as oxidative stress, inflammatory response and apoptosis, leading to the buildup of iron ions and ferroptosis. In this context, studies have demonstrated that LIRI could be induced using a mouse lung portal clamp model as well as a cellular hypoxia-reoxygenation model, with these experiments establishing the significant role of ferroptosis in the process of lung injury. Moreover, inhibiting ACSL4 has been found to reduce the severity of the injury. Overall, ischemia-reperfusion lungs are characterized by increased iron levels, accumulation of lipid peroxidation, reduced GPX4 and increased expression of ACSL4.[93,94]

Unlike other modes of organ transplantation, donor lungs are usually preserved by inflation with 50% oxygen prior to transplantation. It has been reported that, in the 20th century, a hyperoxic environment could exacerbate hypothermia-induced hepatocyte injury, with hypoxia triggering the opposite effects.[95] Prolonged exposure to hyperoxia can therefore generate ROS, thereby contributing to ferroptosis.[96] Hyperoxic mechanical ventilation can cause significant lung injury and decrease amounts of lung surface-active proteins. It has also been found that injection of DFO during hyperoxic ventilation in rats increased the levels of these proteins and reduced lung injury, with the underlying mechanism being related to enhanced activity of lung tissue glutathione reductase and reduced activity of xanthine oxidase. It can therefore be inferred that, in ischemia-reperfusion injury, ferroptosis in lung transplantation may occur mainly during cold ischemia. Moreover, increased iron levels occur in both the alveolar fluid and tissues during human lung transplantation, and as a result, the likelihood of allogeneic lung transplantation being exposed to iron radicals, ROS, fibrosis and chronic rejection is heightened.[97] For instance, in a preliminary investigation, increased levels of HO-1 were noted in lung transplants of humans that experienced acute cellular rejection and occlusive capillary bronchiolitis.[98] Poor prognosis after lung transplantation has also been linked to iron overload and hyperferritinemia in recipients.[99] LIRI is closely linked to ferroptosis, and as such, it could potentially damage or impair lung tissues. Consequently, selectively inhibiting ferroptosis could represent a potential strategy to protect against ischemia-reperfusion injury and minimize complications caused by ferroptosis-induced cellular damage.[60]

Acute Lung Injury/Acute Respiratory Distress Syndrome and Ferroptosis

Acute lung injury (ALI) is a severe respiratory condition and a prevalent clinical syndrome caused by factors affecting the lungs and other parts of the body. It typically involves damage to the cells lining the blood vessels and air sacs in the lungs as a result of an inflammatory reaction as well as the accumulation of fluid in the lungs. The most severe outcome of ALI is acute respiratory distress syndrome (ARDS), characterized by life-threatening breathing problems, bluish discoloration of the skin and low oxygen levels that do not improve with oxygen therapy. In addition, ARDS can rapidly

lead to multiple organ failure and hence, it is of significant interest in the field of critical care medicine,[100] especially since in the absence of effective targeted interventions, it can lead to high morbidity and mortality. Research has confirmed that inflammation, coagulation and oxidative stress are significant factors in the development of ALI. These processes result in the infiltration of inflammatory cells, pulmonary edema, arterial hypoxemia and ultimately dysfunction of lung tissues.[101] Ferroptosis can be triggered by physiological factors, such as elevated glutamate levels outside cells, lack of cystine, insufficient levels of amino acids and inhibition of the Xc- system or GPX4. The transport of extracellular cysteine for iron overload is regulated by SLC7A11 which, in addition to being a crucial component of the Xc- System, also significantly impacts ferroptosis regulation. Inhibition of SLC7A11 reduces glycine uptake and enhances intracellular lipid peroxidation and ferroptosis.[102] This is achieved through acetylated P53 which inhibits SLC7A11, and in turn, inhibits cysteine uptake and promotes ferroptosis.[103] A different pathway involves modulating STAT6 that can hinder the inflammatory response by facilitating M2 macrophage polarization, as STAT6 serves as a crucial controller of the innate immune response.[104] Studies have demonstrated that in ALI, the upregulation of STAT6 expression and its activation coincided with the initiation of ferroptosis. In contrast, suppressing STAT6 in lung epithelial cells exacerbated ferroptosis and led to a deterioration of lung injury. Reducing P53 acetylation decreases its inhibitory effects on SLC7A11 and ultimately inhibits ferroptosis.[105] For example, in a mouse model of ALI caused by intestinal ischemia-reperfusion and oleic acid, alveolar type II epithelial cells (AEC2) exhibited mitochondrial constriction alongside a disrupted mitochondrial membrane. The occurrence of ferroptosis can be identified by certain indicators, including iron overload, a reduction in GSH levels, accumulation of MDA and the down-regulation of GPX4 and ferritin in lung tissues.[106] In addition, ferroptosis seems to play a role in LPS-induced ALI, as reflected in the increased levels of MDA, 4-HNE and total iron as well as the decreased expression of SLC7A11 and GPX4 in both an animal model of ALI and in a bronchial epithelial cell line stimulated with lipopolysaccharide (LPS).[107]

As ALI progresses to ARDS, neutrophils and their substances, including oxidants, proteolytic hydrolases, platelet-activating factors and leukotrienes, become increasingly important in the pathological development of ARDS by negatively impacting the alveolar-capillary membranes. In turn, the disruption and balance of endogenous antiproteases, antioxidants and anti-inflammatory cytokines determine the extent of tissue damage and the severity of clinical symptoms. ARDS is typically identified by the appearance of hyaline membranes, which are made up of edema fluid rich in fibrin and remnants of necrotic epithelial cells. These membranes are particularly found in enlarged endovascular alveolar ducts. Interestingly, the use of ferroptosis inhibitors, such as Ferrostatin-1 and Liproxstatin-1, exhibited protective effects in both ALI/ARDS models.[108] Furthermore, ginseng diol (Px), derived from the root of ginseng, was used to induce ALI/ARDS by LPS. These findings indicated that Px mitigated the pathological harm to the lung tissues of mice and suppressed ferroptosis by enhancing the Kelch-like ECH-related protein 1 (Keap1)/Nrf2/HO-1 pathway.[109] The above studies, albeit preliminarily, confirmed that ferroptosis has a close and complex correlation with ALI/ARDS, thus establishing it as a potentially new therapeutic target.

Obstructive Sleep Hyponea and Apnea Syndrome and Ferroptosis

Obstructive sleep hypopnea and apnea syndrome (OSHAS) is a prevalent respiratory disorder characterized by repeated episodes of apnea and hypoventilation during sleep. These events occur due to the complete or partial blockage of the upper airway, resulting in intermittent reductions in oxygenated hemoglobin and disturbances in sleep patterns. From a pathophysiological perspective, chronic intermittent hypoxia (CIH) is considered to be the primary characteristic of OSHAS,[110] with the primary health hazards for individuals with obstructive sleep apnea syndrome being diseases related to the cardiovascular system, liver and metabolism. While respiratory diseases have not been associated with ferroptosis caused by hypoxia-reperfusion, it has nevertheless been documented that oxidative stress and lipid peroxidation could lead to potential liver injury in OSHAS. Furthermore, it has been shown that ferroptosis could mediate CIH-induced liver injury in rats, as evidenced by increased lipid peroxidation, decreased GPX4 expression and increased ACSL4 expression.[111] Hence, conducting further research on the intricate relationship between OSHAS and ferroptosis is essential to gain novel insights into potential treatments for OSHAS.

Lung Cancer and Ferroptosis

Lung cancer is a highly dangerous form of cancer that presents a significant risk to human well-being and survival. Numerous studies have indicated a strong correlation between the onset and metastasis of lung cancer as well as the inhibition of ferroptosis. The occurrence of this disease is closely associated with the mutation of the P53 oncogene which, under normal conditions, would induce cancer cells to produce ferroptosis, ie, mutated P53 can inhibit ferroptosis in lung carcinogenesis so that cancer cells avoid cell death.[112] In the process of lung cancer development, it has been found that lung cancer tissues highly express ferritin, but it remains to be established whether this represents the underlying mechanism through which lung cancer cells avoid ferroptosis. In terms of classification, lung cancer is typically divided into two types, namely small cell lung cancer and non-small cell lung cancer, with both representing 15% and 85% of total cases, respectively. Due to the increasing use of chemotherapeutic agents in the clinical treatment of patients with non-small cell lung cancer, the emergence of drug resistance in this type of cancer has been inevitable. Recent research has shown that a combination of erastin (a substance that induces ferroptosis) and cisplatin (a chemotherapy medication) was more efficient in treating non-small cell lung cancer compared to using cisplatin alone.[113] However, the mechanism of action of erastin remains unknown. Another study unveiled that Timosaponin AIII, a steroid saponin, induces lipid peroxidation and ferroptosis in NSCLC cells by targeting and facilitating heat shock protein 90 mediated-GPX4 ubiquitination and degradation, thus serving as a potential candidate for NSCLC treatment.[114] Therefore, we hypothesize future research could assess whether other chemotherapeutic agents can induce ferroptosis in cancer cells through the same mechanism.

The prevalence of lung adenocarcinoma (LUAD) has increased compared to other lung cancer subtypes. An increasing number of nonsmokers are now developing LUAD for which cell survival relies on the presence of excessive oxygen in lung tissue as well as elevated levels of the iron-sulfur cluster biosynthetic enzyme NFS-1. Inhibition of the NFS-1-induced iron starvation response, synergized with inhibition of GPX4 during in vitro experiments, triggered ferroptosis, thereby slowing the growth of lung cancer tissues.[115] Based on the above, future clinical drugs could focus on blocking NFS-1 in vivo to exert therapeutic effects. In addition to chemotherapeutic agents, ferroptosis can also strengthen the therapeutic effects of radiotherapy for lung cancer, with one example being sorafenib, a specific medication that is able to trigger ferroptosis in lung tumor cells by blocking the Xc- System. However, there is insufficient evidence to determine whether immunotherapy for lung cancer could also be linked to ferroptosis.[113,116] Despite extensive research in recent years, the relationship between tumor immunity and ferroptosis, including its effects on tumor susceptibility, is not well understood.

A comprehensive examination of the molecular mechanisms involved in the suppression of lung cancer cell growth through the ferroptosis pathway may offer novel opportunities for lung cancer treatment and the discovery of innovative medications.

Summary and Prospects for Future Research

Despite increasing research indicating the intricate involvement of ferroptosis in human well-being, exploring its impact on lung-related illnesses is still at an early stage. Recent studies have shown that ferroptosis plays a crucial role in the development and progression of various lung diseases, including acute lung injury, pulmonary ischemia-reperfusion injury, lung cancer, chronic obstructive pulmonary disease, and pulmonary fibrosis. The molecular mechanisms underlying ferroptosis in respiratory diseases involve intricate regulatory pathways related to iron metabolism, lipid metabolism, amino acid metabolism, and various signaling pathways. Specifically, the cystine/glutamate reverse transport system and the glutathione peroxidase 4 pathway are key regulators of ferroptosis in lung diseases. In this review, we summarized the latest studies about the molecular mechanisms of ferroptosis involved in common lung diseases (Figure 1). And respiratory diseases may be caused by substances that induce ferroptosis (erastin, RSL3) or substances that inhibit it (Fer-1, DFO, and Lip-1). In addition, the PEBP/15-LO complex, a major regulator of ferroptosis, has significant effects on human diseases and represents a novel target for drug development.[77] Furthermore, certain treatment combinations that focus on the possible connections between ferroptosis and alternative forms of cellular demise have provided valuable resources in fundamental studies about the management of pulmonary disorders. Nevertheless, additional investigation is still needed not only to further explore the effects of ferroptosis therapy on patients with respiratory diseases but also to establish animal models that provide deeper insights into the relationship

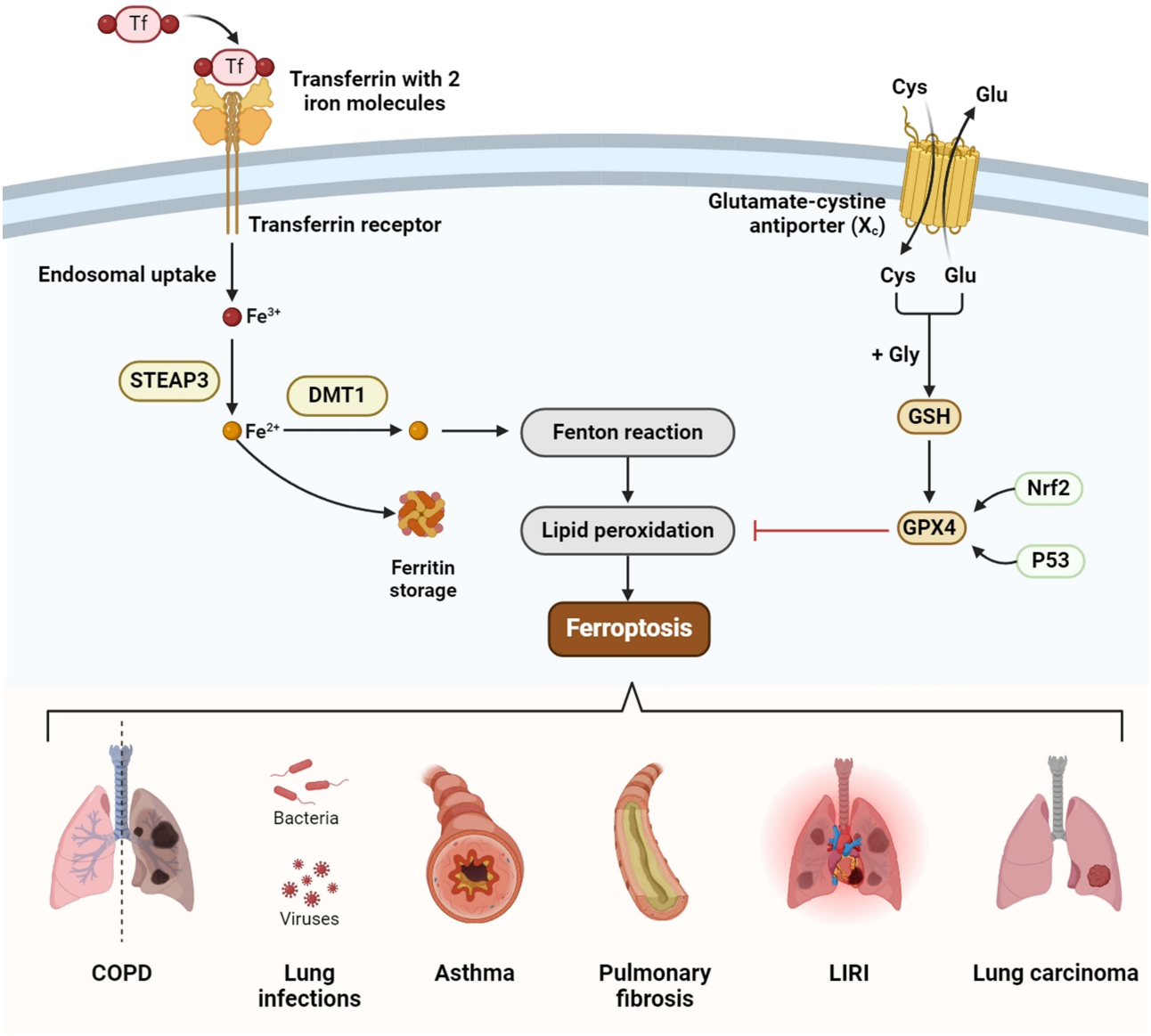

Figure 1 Schematic diagram of the main molecular regulation of ferroptosis involved in common lung diseases.
Note: This figure is originally drawn by Figdraw platform (www.figdraw.com).

between respiratory diseases and ferroptosis. Despite rapid progress in the study of ferroptosis in animal models of respiratory diseases, challenges still exist in its clinical applications. Overall, the onset and development of ferroptosis has important theoretical and practical implications for the management and treatment of human diseases and therefore, further exploration will undoubtedly provide new knowledge for the design of ferroptosis-based clinical interventions.

Data Sharing Statement

There are no data and no material associated with this manuscript.

Ethics Approval and Consent to Participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution 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.

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