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Review Article

Ferroptosis Is a Potential Therapeutic Target for Pulmonary Infectious Diseases

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Ferroptosis is a new type of iron-dependent cell death caused by lipid peroxide (LPO) accumulation and involved in disease of pulmonary infection. The dysregulation of iron metabolism, the accumulation of LPO, and the inactivation and consumption of glutathione peroxidase 4 (GPX4) are the crucial cause of ferroptosis. Pulmonary infectious diseases caused by Pseudomonas aeruginosa (PA), Mycobacterium tuberculosis (MTB), and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) are associated with ferroptosis. Ferroptosis may be a potential therapeutic target for pulmonary infectious diseases. However, the mechanisms by which these infections are involved in ferroptosis and whether pulmonary infectious diseases caused by Staphylococcus aureus, Klebsiella pneumoniae, and Leishmania spp are related to ferroptosis are unclear. Accordingly, more researches are needed.

1. Introduction

Cell death is an essential process for maintaining tissue morphology and function and includes accidental cell death (ACD) and regulatory cell death (RCD). RCD under physiological conditions is also known as programmed cell death (PCD) [1]. Currently, known PCD includes apoptosis [2], ferroptosis [3], necroptosis [4], pyroptosis [4, 5], autophagy-dependent cell death [6], invasive cell death [7], lysosomal dependent death [8], NETosis [9], parthanatos [10], oxeiptosis [11], alkali death [12], etc. [13]. Ferroptosis is a way in which excessive accumulation of lipid oxides in cells destroys normal metabolic reactions of cells and eventually leads to cell death [3, 14]. The main causes of ferroptosis are abnormal iron metabolism, reactive oxygen species (ROS) metabolism, etc.

Pulmonary infection is a disease caused by pathogenic microorganisms [15]. A variety of microorganisms cause abnormalities in iron metabolism which is an important cause of ferroptosis [16, 17]. Recently, accumulating studies confirm that ferroptosis plays an increasingly important role in pulmonary infection [18]. This article summarized the relationship between ferroptosis and pulmonary infection disease.

2. Overview of Ferroptosis

It was reported that xCT, also commonly known as solute carrier family 7 member 11 (SLC7A11), a key membrane protein associated with ferroptosis, was identified as early as the 1980s [19], but not until 2012, ferroptosis was formally named as an iron-dependent and nonapoptotic mode of cell death [3]. In 2017, Stockwell et al. defined ferroptosis as an iron-dependent way of RCD through the accumulation of intracellular lipid peroxidation to a lethal level [20].

Ferroptosis is mainly characterized as the aggregation of iron ions (Fe^{2+}) and ROS, activation of mitogen-activated protein kinase system (MAPK), reduction of cystine intake, depletion of glutathione, and inhibition of cystine/glutamate antiporter (System Xc-) [21], which leads to the release of damage-associated molecular patterns (DAMPs) that promote inflammatory responses and thereby results in cell

death [22]. There are multiple genes involved in ferroptosis, such as ribosomal protein L8 (RPL8), iron response element binding protein 2 (IREB2), tetratricopeptide repeat domain 35 (TTC35), citrate synthetase (CS), acyl-CoA synthase family member 2 (ACSF2), ATP synthase F0 complex subunitC3 (ATP5G3), and various storage and metabolic genes [23].

Different types of RCD cause cell death in different ways, resulting in different morphological changes and immune consequences. In addition, the evolutionary relationship between the different RCD pathways remains unknown. However, there are some relations among these kinds of RCD. It is suggested that knockout or knockdown of autophagy-related 5 (ATG5) and autophagy-related 7 (ATG7) limits erastin-induced ferroptosis, thereby reducing intracellular ferrous levels and lipid peroxidation [24]. Additionally, many ferroptosis inducers cause overactivation of autophagy [25]. Moreover, ROS-mediated autophagy increases ferroptosis by ferritin and transferrin receptor regulation and glutathione peroxidase 4 (GPX4), a key regulator of ferroptosis, inhibits apoptosis [26], necrosis [27], and pyroptosis [28]. Accordingly, ferroptosis is related to other types of RCD.

3. The Control Mechanism of Ferroptosis

3.1. Iron Metabolism. Under normal circumstances, Fe^{2+} absorbed by the human body is oxidized to Fe^{3+} by ceruloplasmin in the epithelial cells of the small intestine; then, Fe^{3+} is combined with transferrin in the plasma before being transported into the cell. Under the action of ferrireductase prostate six-transmembrane protein 3, Fe^{3+} is reduced to Fe^{2+}, and then, Fe^{2+} is stored in the cytoplasmic ferritin or pumped out with the aid of the iron transporter on the membrane, participating in the iron recycling and maintaining iron homeostasis of the body [29]. When the iron homeostasis in the organism is broken, a large amount of free Fe^{2+} will appear and the free Fe^{2+} easily undergoes a Fenton reaction with H_2O_2 to generate many hydroxyl radicals, thereby causing oxidative damage to DNA, proteins, and membrane lipids [30]; then, the ferroptosis occurs [31]. Iron-containing proteins include three main groups: iron-containing sulfur clusters, heme-containing proteins, and iron-containing enzymes [32]. The activity of iron-containing proteins depends on the binding to iron cofactors to influence the balance of iron metabolism as a buffer system for regulation of iron in the cells, subsequently causing ferroptosis [33]. Accordingly, iron metabolism is closely related to ferroptosis.

3.2. Lipid Peroxidation. Lipid peroxidation is a process in which oxygen free radicals or lipid peroxidase reacts with the side chains of polyunsaturated fatty acids associated with phospholipids, enzymes, and membrane receptors to form a lipid peroxide (LPO) which changes the fluidity and permeability of cell membrane and ultimately leads to lipid oxidation degradation reactions, leading to the change of cell structure and function [34]. Compared with other fatty acids, polyunsaturated fatty acids (PUFA) are more prone to lipid peroxidation, resulting in ferroptosis [35]. In addition, ROS plays an important role in ferroptosis, which reacts with lipids to produce LPO through lipid peroxidation; thereby, the damage of cells occurs [34]. Meanwhile, the Fenton reaction generates many hydroxyl radicals to damage cells [30]. Cellular antioxidant systems mainly consist of glutathione, selenium, and CoQ systems. Inactivation of these antioxidant systems will lead to the accumulation of lipid hydroperoxides, resulting in ferroptosis [36]. In addition to ROS, reactive nitrogen species (RNS) also contributes to the occurrence of ferroptosis [37]. Nitric oxide (NO) and peroxynitrite (ONOO−) can interact with unsaturated fatty acids to form nitration oxidation products [38–40]. Also, the RNS attacks PUFA in the plasma membrane and intracellular organelles to produce LPO [41]. It is suggested that mouse double minute 2 (MDM2) and mouse double minute 4 (MDM4) and the negative regulators of tumor suppressor P53 mediate lipid metabolism through one or more main regulators and thus cause ferroptosis [42]. Moreover, studies suggested that cytochrome P450 oxidoreductase (POR) mediates ferroptosis through upregulating peroxidation of membrane polyunsaturated phospholipids [43]. In addition, the oxidoreductases, POR, and NADH-cytochrome b5 reductase (CYB5R1) induce the membrane damage caused by phospholipid oxidation during ferroptosis [44]. Zhang et al. proposed that protein kinase C βII (PKCβII) phosphorylation of acyl-CoA synthetase long-chain family member 4 (ACSL4) amplified ferroptosis induced by lipid peroxidation [45]. Accordingly, lipid peroxidation, ROS, and RNS metabolism may play an important role in ferroptosis.

3.3. System Xc-. System Xc- is formed by SLC7A11 and solute carrier family 3 member 2 (SLC3A2) and located on the phospholipid bilayer of cell membrane where glutamate and extracellular cysteine are exchanged by System Xc- in a 1 : 1 ratio [19, 46]. Studies confirm that glutamate-induced neurotoxin is an iron-dependent oxidation process, which indicates that glutamate is related to ferroptosis [35]. Cystine exchanged into the cell is converted into cysteine which provides the synthesis raw material for glutathione (GSH) [46]. GSH presents the antioxidant effect and the integrated detoxification effect, reduces the toxic lipid peroxide to nontoxic alcohols, and subsequently plays a key role in protecting cells from peroxide damage [47]. The abnormalities of exchange between cystine and glutamate with the System Xc- blocked lead to a large amount of glutamic acid accumulating and failure of the extracellular cysteine being transferred into the cell, which results in insufficient synthesis of GSH and in turn induces the occurrence of ferroptosis [48]. In addition, it is suggested that activating transcription factor 3 (ATF3) induces ferroptosis by inhibiting System Xc- [49].

3.4. Glutathione Peroxidase 4. Glutathione in humans includes GSH and oxidized glutathione (GSSG) [50]. GSH is an important antioxidant, and GPX4 is a peroxidase decomposition enzyme widely existing in the body which is a key regulator of ferroptosis [51]. GPX4 decomposes LPO into corresponding lipid alcohols and protects cells from oxidative damage [52]. With the participation of

GPX4, GSH maintains dynamic balance with GSSG [47]. Accordingly, inhibition of GPX4 leads to the accumulation of LPO, which induces ferroptosis [53]. Additionally, $FINO_2$, a 1, 2-dioxane-containing endoperoxide, induces ferroptosis through a combination of direct iron oxide death-related substrates and indirect GPX4 inactivation though the mechanism of GPX4 inactivation by $FINO_2$ is not clear [54]. Meanwhile, ferroptosis inducers RAS-selective lethal 3 (RSL3) and erastin both directly and indirectly inhibit GPX4 to cause ferroptosis in cells [53]. Accordingly, GPX4 is closely associated with the occurrence of ferroptosis.

The regulatory mechanism of ferroptosis is shown in Figure 1.

4. Ferroptosis and Pulmonary Infectious Diseases

Increased studies focus on ferroptosis in several diseases [55]. It is reported that ferroptosis is related with traumatic brain injury [56], stroke [57], heart injury [58], and Parkinson's disease [59] and is considered a therapeutic target for a variety of diseases [60, 61]. Importantly, there are increasing studies on the relationship between ferroptosis and pulmonary infectious diseases [62–64]. With the condition of different pulmonary infections, several factors are changed, such as ROS, GPX4, Fe^{2+}, and LPO, and these changes trigger the occurrence of ferroptosis (Table 1).

4.1. Bacterial Infection

4.1.1. Pseudomonas aeruginosa Infection. Pseudomonas aeruginosa (PA) is a gram-negative bacterium that exists widely in nature [65, 66]. PA is the most common opportunistic pathogen causing nosocomial infection and is prone to causing respiratory tract diseases such as cystic fibrosis (CF) and persistent lower respiratory tract infection [67–69] and often causes acquired pneumonia in the intensive care unit (ICU) [70]. It is reported that PA without arachidonic acid-phosphatidyl ethanolamine (AA-PE) produces lipoxygenase (pLoxA) to transform the AA-PE contained in human bronchial epithelial cells into 15-hydroperoxy-AA-PE (15-HOO-AA-PE), which produces ROS, thereby resulting in ferroptosis of host bronchial epithelial cells [71]. NO• is a reactive molecule produced by the nitric oxide synthase (NOS). NO• directly binds and inactivates iron-containing enzymes or reacts with the superoxide anion radical O2•- to form highly active pernitrite (OONO-), thus attacking pathogens [72–75]. It is shown that NO• produced by macrophages inhibits PA-induced ferroptosis by inhibiting phospholipid peroxidation, especially the production of 15-HOO-AA-PE [76]. Meanwhile, PA generates proferroptotic signal 15-HOO-AA-PE through 15-pLoxA, which suggested that pLoxA inhibitors might be a promising treatment for PA infection [77]. Ferroptosis is a kind of cell death induced by iron-dependent oxidative stress [78]. It is shown that oxidative stress impacts on the antibiotic sensitivity of PA. Under the conditions of oxidative stress, the minimum inhibitory concentration (MIC) of antibiotics tends to increase or decrease and oxidative stress significantly reduced the pathogenesis of PA in the host [79]. Removal of OsaR (PA0056), a regulator of oxidative stress and antibiotic tolerance produced by PA, increases PA tolerance to aminoglycosides and beta-lactam antibiotics as well as hydrogen peroxide [80]. Accordingly, ferroptosis may be related with respiratory tract infection caused by PA infection (Figures 2 and 3).

4.1.2. Mycobacterium tuberculosis Infection. Mycobacterium tuberculosis (MTB) is a pathogen causing tuberculosis and invades many organs. MTB infection in the lungs is the most common [81]. Pulmonary MTB is considered a global public health problem [82, 83] because pulmonary MTB is not completely under control due to the lack of adult MTB vaccine and the long-term use of antibiotics to treat MTB [84]. When MTB infects the host, macrophages respond quickly to the MTB infection and induce anti-MTB immunity in the host, such as phagocytosis and apoptosis [85]. It has been reported [53, 62] that the death of host macrophages induced by acute lung necrosis induced by MTB may be related to the decrease of GPX4 level and the increase of LPO, mitochondrial peroxide, and free iron. And MTB-infected macrophages also produce ROS. The decrease of GPX4 level and the increase of LPO, mitochondrial peroxide, free iron, and ROS are the important characteristics of ferroptosis (Table 2). In addition, the process of the acute lung necrosis inducing the death of host macrophages is promoted by iron supplementation and inhibited by the iron-chelating agent pyridoxal isonicotinoyl hydrazone (PIH) which is a compound that prevents Fenton reaction from producing hydroxyl radicals [86, 87]. Moreover, the process is inhibited by ferrostatin-1 (Fer-1), a ferroptosis inhibitor [62]. RNS and ROS induce ferroptosis in macrophages and kill intracellular MTB during MTB infection [88, 89]. Studies showed that there are many MTB-secreted proteins which are the necrosis inducers of macrophages and the important virulence factors of MTB [90]. However, MTB evolves several proteins and enzymes to detoxify ROS and RNS [91–94]. It is reported that the MTB-secreted protein Rv1324 may present oxidoreductase activities against ROS and RNS in the process of MTB infection and is a potential virulence factor of MTB, which promotes host cell ferroptosis, inflammatory response, and the survival and spread of MTB during infection [95]. Meanwhile, ferroptosis-related gene suppressor of cytokine signaling 1 (SOCS1) is a biomarker for the diagnosis and treatment of MTB [96] (Table 2). A recent study found that heme oxygenase-1 (HMOX1) is an important regulator of MTB-induced ferroptosis, regulating ROS production and iron accretion, thus changing the outcome of macrophage death after MTB infection [97]. It is suggested that excess iron significantly reduces resistance to mycobacterial infection now that macrophages lose their ability to kill intracellular pathogens in a NO-mediated mechanism during iron overload [98–100]. In addition, NOS inhibitors lead to latent MTB infection reactivation [101], which suggested that the use of iron chelation therapy may prevent latent MTB infection to be activated. Moreover, the standard antibiotic combination with chelation can promote extraction of host iron and reduce availability of iron for MTB to promote MTB infection

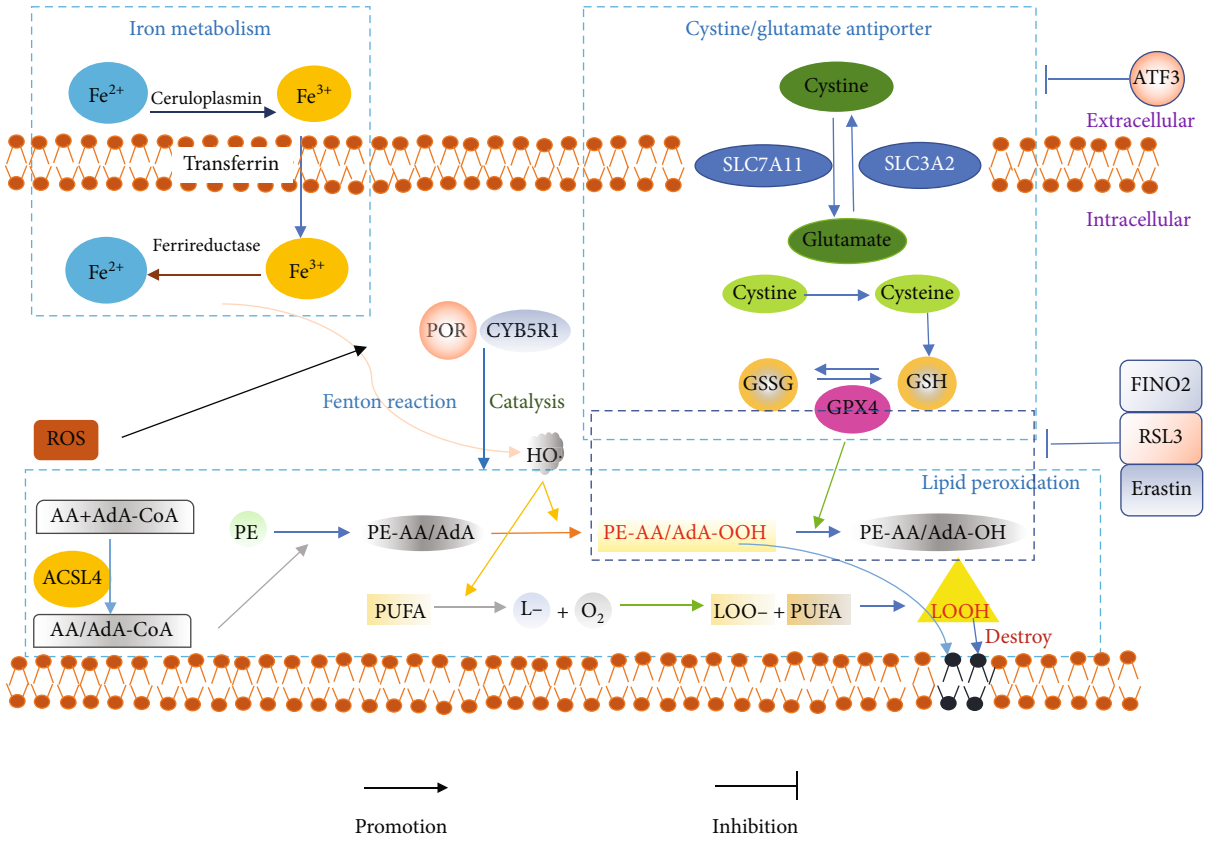

Figure 1: The regulatory mechanism of ferroptosis. The regulatory mechanisms of ferroptosis include iron metabolism, lipid peroxidation and ROS metabolism, cystine/glutamate antiporter, and glutathione peroxidase 4. The different mechanisms interact with each other. ROS: reactive oxygen species; POR: cytochrome P450 oxidoreductase; CYB5R1: NADH-cytochrome b5 reductase; PUFA: polyunsaturated fatty acids; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; ATF3: activating transcription factor 3; GSH: glutathione; GSSG: oxidized glutathione; GPX4: glutathione peroxidase 4.

Table 1: Changes in lipid peroxidation and ferroptosis-related features in the case of different factors associated with pulmonary infection.

Infectious factor	ROS	GPX4	Fe^{2+}	LPO
PA	Increase	/	/	/
MTB	Increase	Decrease	Increase	Increase
SARS-CoV-2	Increase	Decrease	/	/
Staphylococcus aureus	Increase	/	/	Increase
Klebsiella pneumoniae	Increase	/	/	/
Leishmania spp	/	Deficiency	/	Increase

PA: Pseudomonas aeruginosa; MTB: Mycobacterium tuberculosis; SARS-CoV-2: severe acute respiratory syndrome coronavirus Type 2; LPO: lipid peroxides; GPX4: glutathione peroxidase 4; ROS: reactive oxygen species.

recovery [102]. Accordingly, ferroptosis may be associated with pulmonary MTB (Figures 4 and 3).

4.1.3. Staphylococcus aureus Infection. Staphylococcus aureus is an important pathogenic bacterium of human beings [103]. It is the most important pathogen causing bacteremia, infective endocarditis, pneumonia, and other diseases [104]. It is shown that Staphylococcus aureus gradually becomes the main pathogen that causes bacterial pneumonia [105]. At present, no evidence shows the exact relationship between pulmonary infectious diseases caused by Staphylococcus aureus and ferroptosis. However, Staphylococcus aureus is sensitive to arachidonic acid and lipid peroxidation of the host, which provides conditions for the possible involvement of ferroptosis in Staphylococcus aureus infection [106, 107]. A recent study found that $FeSO_4$ promotes ferroptosis-like cell death in Staphylococcus aureus in mouse keratitis models, and its key features are ROS production and lipid peroxidation [108]. Accordingly, whether ferroptosis is involved in Staphylococcus aureus infection may become a new research direction in the future [109] (Figure 3).

4.1.4. Klebsiella pneumoniae Infection. Klebsiella pneumoniae, as a gram-negative bacterium, is the most important class of Klebsiella in Enterobacteriaceae Klebsiella genus [110]. Klebsiella pneumoniae is ubiquitous in nature, including plants, animals, and humans [111]. It is the pathogen of a variety of human infections, including respiratory tract infections, urinary tract infections (UTIs), and bloodstream infections. Pulmonary infection is the most common clinically [112, 113]. It is suggested that liproxstatin-1 can synergize with rifampicin to enhance its antibacterial effect against Klebsiella pneumoniae [114], while liproxstatin-1 (Lip-1) is a derivative of spiroquinoxaline which inhibits

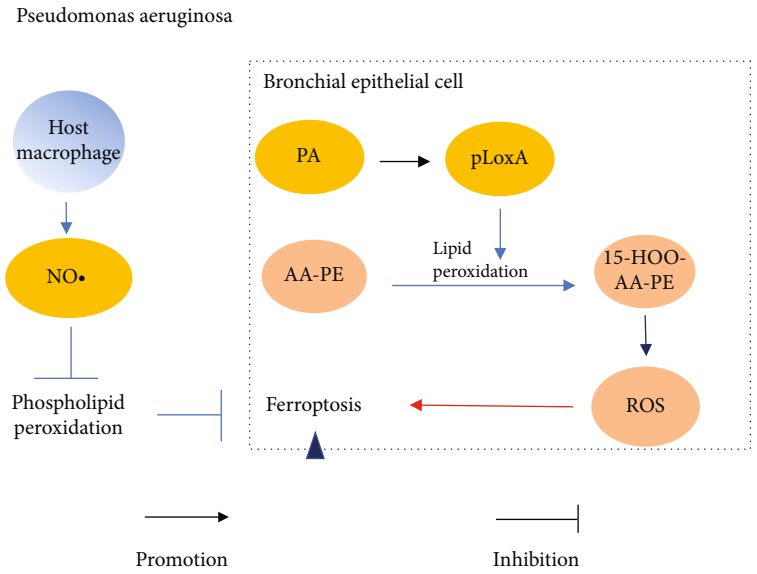

Figure 2: Ferroptosis and pulmonary infection caused by Pseudomonas aeruginosa. The PA without AA-PE produces pLoxA to transform the AA-PE contained in human bronchial epithelial cells into 15-hydrogenation oxygen-AA-PE, which produces ROS, thereby resulting in ferroptosis of host bronchial epithelial cells. NO• produced by macrophages inhibits PA to induce ferroptosis by inhibiting phospholipid peroxidation, especially by producing 15-hydrooxidation-AA-PE signal. PA generates proferroptotic signal 15-HPET-PE through 15-lipoxygenase. PA: Pseudomonas aeruginosa; AA-PE: arachidonic acid-phosphatidyl ethanolamine; pLoxA: lipoxygenase; 15-HOO-AA-PE: 15-hydrogenation oxygen-AA-PE; ROS: reactive oxygen species.

ferroptosis [115, 116]. Klebsiella pneumoniae induces metabolic stress in the host and promotes tolerance to pulmonary infections, and this tolerance may be related to ROS [117, 118]. However, it is unclear that the ROS changes in this tolerance lead to ferroptosis. Accordingly, more researches are needed to confirm the relationship between ferroptosis and Klebsiella pneumoniae infection in the lung (Figure 3).

4.2. Virus Infection

4.2.1. Severe Acute Respiratory Syndrome Coronavirus Type 2 Infection. In 2019, the world suffered a pandemic of Coronavirus Disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection [119, 120]. It is shown that patients with SARS-CoV-2 infection have altered tryptophan metabolism; dysregulated nitrogen metabolism; altered levels of most amino acids; increased markers of oxidative stress (such as methionine sulfoxide and cystine), proteolysis, and renal dysfunction (such as creatine, creatinine, and polyamine); and increased levels of circulating glucose and free fatty acids. Levels of metabolites in these biological processes correlate with clinical laboratory markers of inflammation (i.e., interleukin-6 (IL-6) and C-reactive protein) and renal function (i.e., blood urea nitrogen) [121]. Patients with SARS-CoV-2 infection present malfunctioning iron metabolism, which leads to iron accumulation and overload [122, 123]. It has been shown that SARS-CoV-2 increases mitochondrial ROS production, thereby accelerating SARS-CoV-2 replication [124]. Studies showed that [63] SARS-CoV-2 inhibits the expression of GPX4 and then promotes ferroptosis. It is reported that GPX4 reduces LPO in biofilms, so upregulation of GPX4 activity reduces inflammatory factors and promotes inflammation regression [125] (Table 2). Selenium is an important component of selenocysteine proteins (including GPX4) [36]. As a member of the cellular antioxidant system, selenium also increases the number of T cells, enhances the response of mitotic lymphocytes, increases the secretion of interleukin-2 (IL-2) cytokines, enhances the activity of NK cells, and reduces the risk of SARS-CoV-2 infection through the antioxidant systems [126]. Accordingly, selenium supplementation may increase resistance to respiratory infections [127]. It was reported that a ferroptosis inducer, acyl-CoA synthetase long-chain family member 1 (ACSL1), inhibits syncytial formation induced by hepatitis virus A59 strain (MHV-A59) infection and viral transmission in primary macrophages, while reducing lung inflammation and injury in the mouse model of coronavirus infection [64, 128] (Table 2). Syncytium is the product of cell-to-cell fusion after coronavirus infection and is considered a marker of infection with COVID-19 [129, 130]. It is reported that alveolar epithelial cells are sensitive to SARS-CoV-2 and alveolar macrophages also suffer from the infection of SARS-CoV-2 [131, 132]. In addition, MHV-A59 infects mouse bone marrow-derived macrophages (BMDMs) and peritoneal macrophages (PMs) [133], while neuropilin-1 (NRP1) mediates SARS-CoV-2 to infect mouse BMDMs [134]. Accordingly, the infection of coronavirus is closely related with ferroptosis, which may provide a new therapeutic target for the treatment of COVID-19. In recent years, ferroptosis is found in hamster lung infected with SARS-CoV-2 [135, 136]. It is confirmed that iron chelation is beneficial to various viral infections, such as HIV-1 [137], hepatitis B virus [138], and enterovirus 71 [139]. In addition,

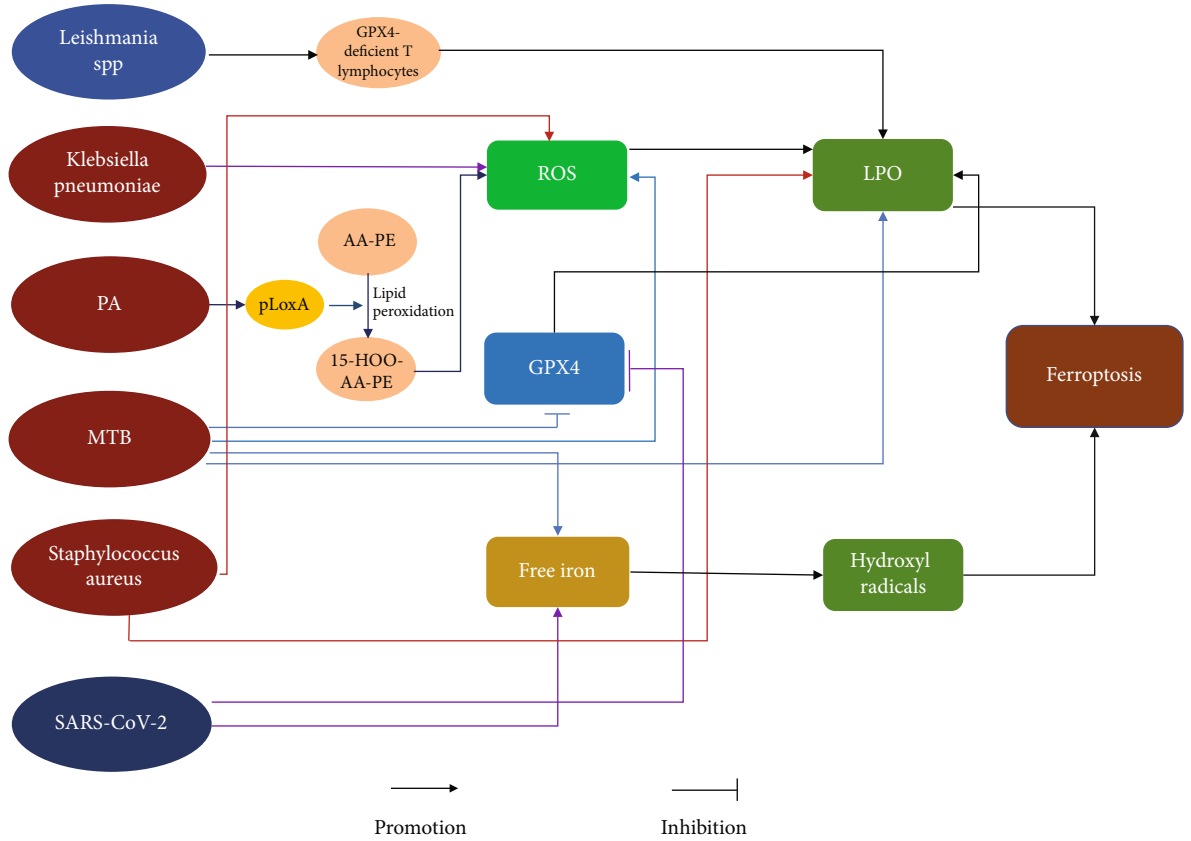

Figure 3: The cascade of these substances during infection. The PA without AA-PE produces pLoxA, which converts AA-PE contained in human bronchial epithelial cells into 15-HOO-AA-PE and produces ROS. MTB infection induces a decrease in GPX4 levels and an increase in LPO, free iron, and ROS. SARS-CoV-2 inhibits GPX4 expression. In addition, ROS can be produced and lipid peroxidation can be promoted to generate LPO during Staphylococcus aureus infection. Also, ROS are also produced during Klebsiella pneumoniae infection. Meanwhile, Leishmania spp infection of GPX4-deficient T lymphocytes causes LPO accumulation. A decrease in GPX4 levels weakens its ability to break down LPO, leading to the accumulation of LPO. Additionally, ROS can also produce LPO through lipid peroxidation. Meanwhile, the increase of free iron leads to the increase of oxygen free radical produced by Fenton reaction. Both LPO and hydroxyl radicals can damage cells and eventually lead to ferroptosis. PA: Pseudomonas aeruginosa; AA-PE: arachidonic acid-phosphatidyl ethanolamine; pLoxA: lipoxygenase; 15-HOO-AA-PE: 15-hydrogenation oxygen-AAPE; ROS: reactive oxygen species; MTB: Mycobacterium tuberculosis; LPO: lipid peroxides; SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; GPX4: glutathione peroxidase 4.

Table 2: Ferroptosis-associated genes associated with pulmonary infection.

Gene	Infectious factor	Function
GPX4	MTB	Decreased GPX4 levels lead to acute lung necrosis induced by MTB and thus host macrophage death
	SARS-CoV-2	Reduces LPO in biofilms
	Leishmania spp	GPX4-deficient T lymphocytes have difficulty resisting pulmonary infections caused by leishmaniasis
SOCS1	MTB	As a biomarker for the diagnosis and treatment of MTB
ACSL1	SARS-CoV-2	Inhibits syncytial formation and viral transmission in primary macrophages; reduces lung inflammation and injury

GPX4: glutathione peroxidase 4; SOCS1: suppressor of cytokine signaling1; ACSL1: acyl-CoA synthetase long-chain family member 1; MTB: Mycobacterium tuberculosis; SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; LPO: lipid peroxides.

SARS-CoV-2 infection presents high IL-6 ferritin levels [140], while the iron-chelating agent deferoxamine (DFO) completely blocks production of IL-6, delaying severe systemic inflammatory response syndrome (SIRS) and circulatory collapse in animal models [141–143]. Moreover, iron chelation prevents excessive inflammatory reactions and tissue damage by blocking free iron and preventing oxygen free radical formation and lipid peroxidation [144]. Accordingly, iron chelation therapy improves SARS-CoV-2 infection. Depletion of intracellular iron or the development of new

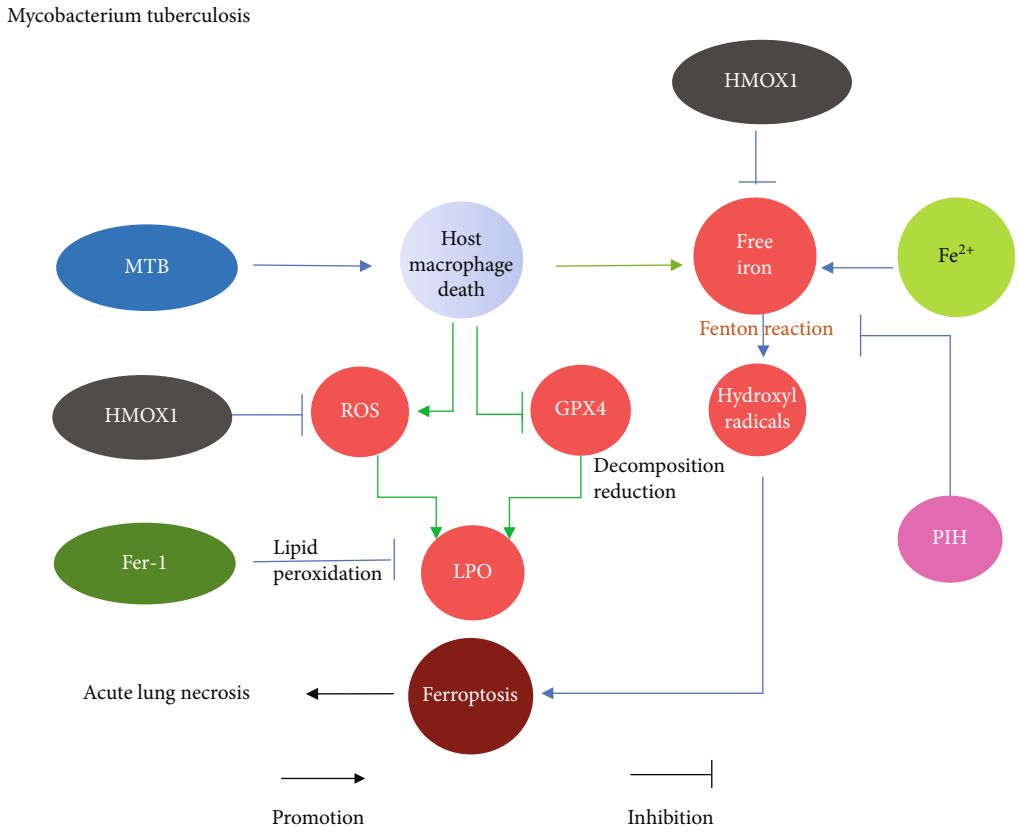

Figure 4: Ferroptosis and pulmonary infection caused by Mycobacterium tuberculosis. In the process of ferroptosis in host macrophages induced by acute lung necrosis induced by MTB, GPX4 levels are decreased and LPO, mitochondrial peroxide, free iron, and ROS are increased. The decreased level of GPX4 reduces its ability to decompose LPO, leading to the accumulation of LPO. ROS can also produce LPO through lipid peroxidation. At the same time, the increase of free iron leads to the increase of oxygen radicals produced by Fenton reaction. Both LPO and oxygen free radicals can damage cells. Iron supplementation promotes the Fenton reaction to produce oxygen free radicals and promotes the process of acute lung necrosis inducing host macrophage death, while the iron-chelating agent PIH inhibits this process by preventing Fenton reaction. Similarly, the ferroptosis inhibitor ferrostatin-1 inhibits this process by inhibiting lipid peroxidation. And HMOX1 can regulate the production of ROS and the increase of iron, thus changing the outcome of macrophage death after MTB infection. MTB: Mycobacterium tuberculosis; LPO: lipid peroxides; PIH: pyridoxal isonicotinoyl hydrazone; ROS: reactive oxygen species; GPX4: glutathione peroxidase 4; HMOX1: heme oxygenase-1.

ferroptosis inhibitors and GPX4 agonists may help further develop treatment options for COVID-19 (Figures 5 and 3).

4.3. Parasite Infection

4.3.1. Leishmania spp Infection. Leishmania spp is a parasite that parasitizes the macrophages of humans and other mammals and causes leishmaniasis in the host [145]. Leishmaniasis is widely distributed all over the world, and large numbers of people are at risk of infection, so leishmaniasis is considered a priority disease by the World Health Organization [146, 147]. Leishmaniasis has two clinical forms, visceral leishmaniasis and cutaneous leishmaniasis [148]. Pulmonary leishmaniasis is a common leishmaniasis [145]. It is suggested that GPX4-deficient T lymphocytes rapidly accumulate LPO and induce ferroptosis in vitro after leishmaniasis infection and then, GPX4-deficient T lymphocytes have difficulty resisting pulmonary infections caused by leishmaniasis [149] (Table 2). Although a definite relationship between pulmonary infection caused by Leishmania and ferroptosis has not been found so far, ferroptosis inhibitors and GPX4-related agonists deserve to be researched in the treatment of pulmonary leishmaniasis in the future (Figure 3).

4.4. The Pulmonary Infections in Other Pulmonary Diseases. Chronic obstructive pulmonary disease (COPD) is a chronic pulmonary disease, and pulmonary infection may occur during acute exacerbation of COPD (AECOPD) [150]. It is reported that ferroptosis is involved in AECOPD with unstable iron accumulation and increased lipid peroxidation [151]. Bacterial or viral infections often cause AECOPD [152]. PA is the main cause of AECOPD [153], while PA can cause ferroptosis in bronchial epithelium [71]. In addition, ferroptosis is related to asthma and may occur in airway epithelial cells of asthma [154]. The pathogen infections commonly cause the acute exacerbation of asthma [155]. However, no researches have presented the changes of ferroptosis in AECOPD or asthma with pathogen infection so far. It is reported that ferroptosis is also involved in pulmonary fibrosis (PF) [156]. PF is easily secondary to

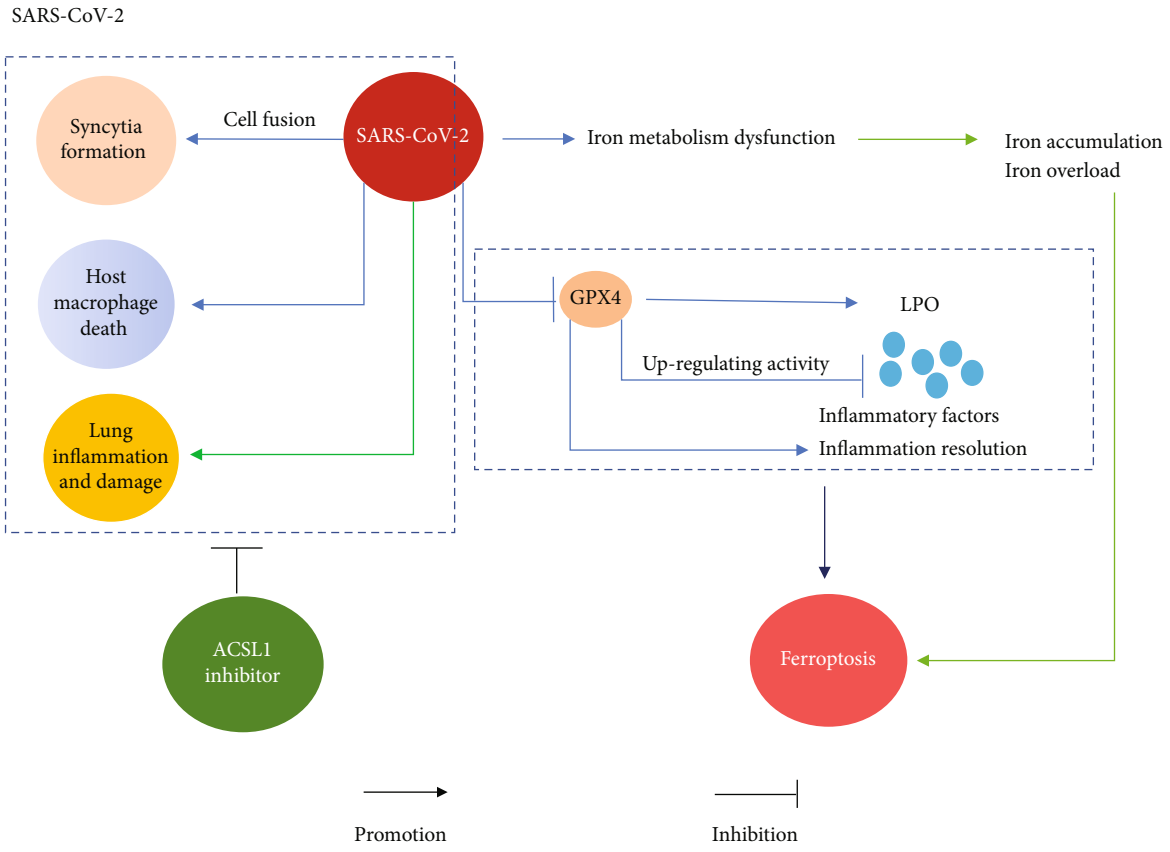

Figure 5: Ferroptosis and pulmonary infection caused by SARS-CoV-2. SARS-CoV-2 inhibits the expression of GPX4 and then promotes ferroptosis. GPX4 reduces LPO in biofilms, so upregulation of GPX4 activity reduces inflammatory factors and promotes inflammation regression. A ferroptosis inducer, ACSL1, inhibits syncytial formation and viral transmission in primary macrophages, while reducing lung inflammation and injury in the mouse model of coronavirus infection. SARS-CoV-2: severe acute respiratory syndrome coronavirus type 2; GPX4: glutathione peroxidase 4.

Table 3: The inhibitors of ferroptosis.

Compounds	Mechanisms	Special effect
DFO	Inhibit accumulation of iron	DFO completely blocks IL-6 production after SIRS, delaying SIRS and circulatory collapse
CPX	Inhibit accumulation of iron	NA
2,2′-pyridine	Inhibit accumulation of iron	NA
Fer-1	Remove ROS, inhibit lipid peroxidation	Fer-1 inhibits the process of host macrophage death induced by MTB in acute lung necrosis
Lip-1	Remove ROS, inhibit lipid peroxidation	Lip-1 can synergize with rifampicin to enhance its antibacterial effect against Klebsiella pneumoniae
Vitamin E	Compensate GPX4 loss	Vitamin E supplementation has been shown to increase resistance to respiratory infections
Curcumin	Prevent GSH depletion and lipid peroxidation	NA
EGCG	Prevent GSH depletion and lipid peroxidation	NA
Baicalein	Prevent GSH depletion and lipid peroxidation	NA
NDGA	Prevent GSH depletion and lipid peroxidation	NA

CPX: ciclopirox; DFO: deferoxamine; EGCG: (-)-epigallocatechin-3-gallate; Fer-1: ferrostatin 1; GSH: glutathione; GPX4: glutathione peroxidase 4; Lip-1: liproxstatin-1; NDGA: nordihydroguaiaretic acid; IL-6: interleukin-6; SIRS: systemic inflammatory response syndrome; ROS: reactive oxygen species.

SARS-CoV-2 infection [157]. Although SARS-CoV-2 infection leads to ferroptosis [63], whether ferroptosis is related to PF secondary to SARS-CoV-2 infection remains unclear. Ferroptosis contributes to the occurrence and development of acute lung injury (ALI) [156]. PA infection leads to severe ALI which may be related to ferroptosis in bronchial

epithelium [71]. However, the role of ferroptosis in ALI caused by PA infection needs more studies to be confirmed.

4.5. Pulmonary Infections and Ferroptosis Inhibitors. Since ferroptosis is associated with pulmonary infections, the inhibitors of ferroptosis are important for the treatment of pulmonary infections. There are four kinds of ferroptosis inhibitors according to different effects. One kind of ferroptosis inhibitor includes DFO, ciclopirox (CPX), and 2,2′ -pyridine, which inhibit iron accumulation [158]. In addition, DFO completely blocks IL-6 production after SIRS, which delays SIRS and circulatory collapse. The second kind of inhibitor includes Fer-1 and Lip-1 which remove ROS and inhibit lipid peroxidation [159, 160]. Additionally, Fer-1 inhibits the process of host macrophage death induced by MTB, while Lip-1 synergizes with rifampicin to enhance its antibacterial effect against Klebsiella pneumoniae [62, 116]. Another inhibitor includes mainly vitamin E which compensates for loss of GPX4. It is reported that supplementation of vitamin E increases resistance to respiratory infections [126]. The fourth inhibitors include curcumin, (-)-epigallocatechin-3-gallate (EGCG), baicalein, and nordihydroguaiaretic acid (NDGA) which prevent glutathione depletion and lipid peroxidation. However, no researches on the role of the fourth inhibitors in pulmonary infection were found [161] (Table 3).

5. Summary

Ferroptosis, as a new type of cell death, is closely related to the occurrence of various pulmonary infectious diseases. The mechanisms of both most pulmonary infections and ferroptosis involve features such as dysregulation of iron metabolism, the accumulation of LPO, and the inactivation and consumption of GPX4. Among pulmonary infectious diseases, PA infection, MTB infection, and SARS-CoV-2 infection are associated with ferroptosis, which may provide a potential therapeutic target for the treatment of pulmonary infections. However, the mechanisms by which these infections are involved in ferroptosis are unclear. In addition, it is unclear whether Staphylococcus aureus infection, Klebsiella pneumoniae infection, and Leishmania spp infection are involved in ferroptosis. Accordingly, more researches are required further.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Yurong Zhang and Dianlun Qian are the co-first authors.

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