

Research Progress on the Regulatory Role of Ferroptosis in the Progression of Idiopathic Pulmonary Fibrosis

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Abstract: *Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease with unknown etiology, rapid progression and extremely poor prognosis. Its core pathological manifestations include usual interstitial pneumonia lesions in lung tissue, abnormal proliferation of fibroblasts and excessive deposition of extracellular matrix (ECM). The median survival time of patients after diagnosis is only 2–3 years, and there is still no radical cure at present. Ferroptosis is a novel iron-dependent programmed cell death driven by lipid peroxidation, which is fundamentally different from traditional cell death modes such as apoptosis and autophagy. Its core biological characteristics include intracellular iron overload, massive accumulation of lipid reactive oxygen species (lipid ROS), and functional failure of antioxidant defense systems. In recent years, accumulating studies have confirmed that ferroptosis exerts a pivotal regulatory role in the initiation and progression of IPF by modulating iron metabolic homeostasis, lipid peroxidation and intercellular signal crosstalk. This paper systematically reviews the core regulatory network of ferroptosis, cell-specific regulatory mechanisms of ferroptosis during IPF progression, research breakthroughs of related biomarkers, and advances in targeted ferroptosis therapeutic strategies, aiming to provide novel theoretical basis and research directions for the investigation of IPF pathogenesis and clinical precision treatment.*

Keywords: Idiopathic pulmonary fibrosis, Ferroptosis, Regulatory mechanism, Biomarker, Targeted therapy, Iron metabolism, Lipid peroxidation.

1. Introduction

As the most prevalent interstitial lung disease with the worst prognosis, the annual global incidence of idiopathic pulmonary fibrosis keeps rising. It mainly affects middle-aged and elderly people over 50 years old, and heavy smoking is a major risk factor. Clinically, IPF patients manifest progressive exertional dyspnea, dry cough and digital clubbing, and most patients die of respiratory failure, pulmonary hypertension or concurrent lung cancer in the advanced stage [3]. Recent epidemiological surveys reveal a close correlation between pulmonary fibrosis and age; the incidence increases year by year amid population aging. Its pathological hallmark is usual interstitial pneumonia (UIP), characterized by patchy fibrotic lesions, fibroblastic foci formation, excessive ECM deposition and irreversible destruction of alveolar structure. The pathogenesis of pulmonary fibrosis is generally associated with environmental exposure, genetic factors and maladaptive tissue repair. A growing body of evidence indicates that ferroptosis is a critical modulator of pulmonary fibrosis [4]. Current clinical management merely relies on pirfenidone and nintedanib to slow disease progression, with no curative therapies available. Lung transplantation remains the only effective treatment for end-stage patients.

Ferroptosis was first named by Dixon et al. in 2012 [5]. Its occurrence depends on intracellular free iron ions, which catalyze the chain reaction of lipid peroxidation via the Fenton reaction, leading to the destruction of lipid bilayers and cell death. Distinct from apoptosis and necrosis, ferroptosis lacks typical morphological features including apoptotic body formation and chromatin condensation, and is mainly characterized by shrunken mitochondria, increased membrane density and reduced or vanished mitochondrial cristae. In recent years, molecular biological studies have observed prominent iron accumulation, elevated lipid

peroxidation products and abnormal expression of ferroptosis-related regulatory molecules in lung tissues of IPF patients, suggesting that ferroptosis acts as a core pathological regulator in IPF pathogenesis. In-depth exploration of ferroptosis regulatory mechanisms in IPF may uncover novel therapeutic targets and provide important theoretical support for developing new drugs.

2. Core Regulatory Network of Ferroptosis

The initiation and progression of ferroptosis are governed by an intricate molecular network mainly consisting of four interrelated modules: iron metabolic homeostasis, lipid peroxidation, antioxidant defense systems and related signaling pathways, which coordinate or antagonize each other to control ferroptosis activation [7].

2.1 Regulation of Iron Metabolic Homeostasis

Iron ions are an indispensable prerequisite for ferroptosis, and disrupted intracellular iron homeostasis serves as a critical trigger. Disorders in iron uptake, transport, storage and efflux lead to accumulation of free ferrous iron (Fe^{2+}), which generates abundant reactive oxygen species through the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^-$) and subsequently initiates lipid peroxidation [8–10]. Cheng et al. [11] detected significant iron deposition in lung tissues of pulmonary fibrosis patients, and observed ferritinophagy in alveolar type II (ATII) cells of bleomycin (BLM)-induced pulmonary fibrosis mice. BLM elevates iron levels, induces collagen deposition, pathological injury and ATII cell ferroptosis, thereby driving fibrotic progression. The iron chelator deferoxamine (DFO) alleviates iron overload and ferroptosis, reversing the profibrotic effect of BLM. Meanwhile, BLM dysregulates iron metabolism-related genes, triggering iron deposition, mitochondrial dysfunction and

ferroptosis in MLE12 lung epithelial cells, which can be rescued by DFO. Jiang et al. [12] reported severe lung injury and fibrotic features in COVID-19 patients, with prominent iron deposition in CD11c⁺ monocytes and CD68⁺ macrophages from COVID-19 and systemic sclerosis-associated pulmonary fibrosis (SSc-PF) patients.

Iron uptake is primarily mediated by transferrin receptor 1 (TfR1). Transferrin-bound Fe³⁺ is transported into cells, reduced to Fe²⁺ by STEAP3, and released into the cytoplasm via divalent metal transporter 1 (DMT1). Cytoplasmic Fe²⁺ is partially stored in ferritin, while the rest participates in physiological processes such as hemoglobin synthesis and mitochondrial respiratory chain function. Ferritin comprises heavy chain 1 (FTH1) and light chain (FTL); FTH1 exerts ferroxidase activity to convert toxic Fe²⁺ into inert Fe³⁺ for storage, mitigating iron-mediated cytotoxicity. Iron efflux relies on nuclear receptor coactivator 4 (NCOA4)-dependent ferritinophagy: NCOA4 recognizes and binds ferritin, transports it to autophagosomes for degradation, and releases Fe²⁺ for cellular utilization or extracellular excretion.

Under IPF pathological conditions, dysregulated expression of iron metabolism molecules results in intracellular iron overload. In BLM-induced IPF mouse models, lung tissues exhibit upregulated TfR1 and downregulated ferritin, causing Fe²⁺ accumulation and ferroptosis. In addition, a 2024 study published in Xuzhou Medical University Journal demonstrated that silencing the TfR1 gene prevents ferroptosis induced by ferroptotic agonists, while deficiency of hepcidin regulatory protein 1 increases cellular susceptibility to ferroptosis. Multiple iron metabolism proteins including heat shock protein β 1 and ceruloplasmin modulate ferroptosis severity in IPF by regulating iron uptake and transport.

2.2 Regulation of Lipid Peroxidation

Lipid peroxidation is the core biochemical event of ferroptosis, predominantly occurring on phospholipids enriched with polyunsaturated fatty acids (PUFAs) on cell membranes [13]. First proposed by Dixon in 2012, ferroptosis is defined as dysregulated iron-dependent lipid peroxidation and has attracted extensive research attention [14]. PUFAs contain multiple carbon-carbon double bonds, rendering them chemically unstable and vulnerable to attack by hydroxyl radicals ($\cdot$ OH) generated by iron ions. This initiates a chain peroxidation cascade that produces massive lipid peroxides such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), ultimately disrupting membrane structure and inducing cell death. Noguchi et al. [15] systematically illustrated PUFA oxidation pathways generating lipid hydroperoxides, confirming radical-mediated non-enzymatic oxidation as the primary endogenous source of lipid peroxides.

Regulation of lipid peroxidation involves PUFA synthesis/metabolism and lipoxygenase activation. Acyl-CoA synthetase long-chain family member 4 (ACSL4) catalyzes the conjugation of PUFAs with coenzyme A to form acyl-CoA, which integrates into membrane phospholipids and increases cellular susceptibility to lipid peroxidation [16–18]. Lipoxygenases (LOXs) including 5-LOX and 12-LOX are key enzymes catalyzing PUFA double bond oxidation to

generate lipid hydroperoxides and promote ferroptosis [19]. Yang et al. [20] identified that PHKG2-dependent iron pool-mediated LOX-catalyzed PUFA peroxidation is a prerequisite for ferroptosis, while covalent inhibition of catalytic selenocysteine in GPX4 blocks lipid peroxide clearance. Cytochrome P450 oxidoreductase (POR) also participates in lipid peroxidation to facilitate ferroptosis [21]. Zou et al. [22] validated POR as an essential driver of ferroptosis in cancer cells with inherent or inducible ferroptotic vulnerability.

Dysregulated expression of lipid metabolism proteins such as ACSL4 in lung tissues of IPF patients accelerates PUFA oxidation, triggers alveolar epithelial ferroptosis and drives lung fibrotic remodeling [23]. Li et al. [24] confirmed ACSL4 upregulation in BLM-induced pulmonary fibrosis models and IPF cell lines; TFEB-mediated ACSL4 inhibition alleviates alveolar epithelial ferroptosis and mitigates pulmonary fibrosis, establishing a direct linkage between ACSL4 and ferroptosis regulation in IPF.

2.3 Regulation of Antioxidant Defense Systems

Intracellular antioxidant defense mechanisms eliminate excess reactive oxygen species and lipid peroxides to maintain redox homeostasis and counteract ferroptosis. The glutathione peroxidase 4 (GPX4)-glutathione (GSH) axis serves as the core anti-ferroptotic pathway [25,26].

GPX4 is the sole peroxidase capable of directly degrading lipid peroxides, and its enzymatic activity depends on GSH as a cofactor. GSH is synthesized from glutamate, cysteine and glycine; cysteine acts as the rate-limiting substrate, which is imported extracellularly as cystine via the cystine/glutamate antiporter system Xc⁻ and subsequently reduced [27–29]. System Xc⁻ is a heterodimer composed of solute carrier family 7 member 11 (SLC7A11) and solute carrier family 3 member 2 (SLC3A2) [29,30]. SLC7A11 mediates cystine transport [31,32] and functions as a master regulator of GSH synthesis [33]. Downregulated or inhibited SLC7A11 reduces intracellular cystine uptake, limits GSH production, impairs GPX4 activity, abolishes lipid peroxide clearance and eventually induces ferroptosis [34]. Yang et al. [35] uncovered the RELA-SLC7A11 axis as a critical metabolic checkpoint determining macrophage ferroptotic sensitivity.

Beyond the GPX4-GSH system, multiple auxiliary antioxidant pathways cooperate to suppress ferroptosis, including the ferroptosis suppressor protein 1 (FSP1)-coenzyme Q (CoQ) system [36,37], dihydroorotate dehydrogenase (DHODH)-CoQ system [38], and GTP cyclohydrolase 1 (GCH1)-tetrahydrobiopterin (BH4) system [39]. FSP1 reduces CoQ to ubiquinol to scavenge membrane lipid radicals and inhibit lipid peroxidation [40,41]. DHODH participates in pyrimidine biosynthesis while exerting antioxidant effects via CoQ reduction [42,43]. GCH1 catalyzes BH4 generation; BH4 functions as a lipophilic antioxidant to directly neutralize lipid radicals and balance LOX activity, thereby restraining ferroptosis [44]. These antioxidant pathways synergistically maintain cellular redox balance and resist ferroptotic stimuli.

2.4 Regulation of Ferroptosis-Related Signaling Pathways

Ferroptosis is modulated by multiple signaling cascades, among which the transforming growth factor- β (TGF- β)/Smad axis, PI3K-Akt-FoxO axis and Nrf2 axis dominate ferroptosis regulation in IPF.

TGF- β 1 is the central profibrotic cytokine in IPF and regulates ferroptosis through multiple mechanisms [45]. Shao et al. [45] demonstrated that activated TGF- β 1/Smad signaling correlates with iron overload and ferroptosis, while STEAP3 overexpression suppresses this pathway to attenuate pulmonary fibrosis. On one hand, TGF- β 1 activates Smad signaling to downregulate SLC7A11 and GPX4, impair GSH synthesis, reduce antioxidant capacity and promote ferroptosis [46,47]. On the other hand, TGF- β 1 upregulates TfR1 expression via the TAZ/TEAD4 pathway to augment cellular iron intake, supplying the necessary substrate for ferroptosis [48]. Aberrant activation of the PI3K-Akt-FoxO pathway is also tightly linked to IPF-associated ferroptosis; electroacupuncture ameliorates lung function and fibrotic lesions in IPF rats by inhibiting this pathway to suppress ferroptosis [49].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is the master transcription factor governing cellular oxidative stress responses [50,51]. It transcriptionally activates SLC7A11, GPX4, ferritin and other antioxidant genes [52] to enhance anti-ferroptotic capacity, and its dysfunction contributes to excessive ferroptosis activation in IPF [53].

3. Cell-Specific Regulatory Mechanisms of Ferroptosis in IPF Progression

Ferroptosis targets multiple key pulmonary cell populations including alveolar epithelial cells, fibroblasts and macrophages, regulating cellular injury, activation, inflammatory response and ECM deposition to exert pleiotropic effects throughout IPF pathogenesis.

3.1 Regulation of Alveolar Epithelial Cell Injury and Epithelial-Mesenchymal Transition (EMT)

Alveolar epithelial cells (AECs), consisting of type I (AECI) and type II (AECII) subsets, maintain pulmonary gas exchange and barrier integrity. Persistent AEC injury is the initiating event of IPF, and ferroptosis represents a major driver of AEC damage. Multiple IPF risk factors such as BLM, lipopolysaccharide (LPS) and cigarette smoke induce AEC ferroptosis. Pei [54] first verified that BLM and LPS trigger ferroptosis in lung epithelial cells. Takahashi et al. [55] confirmed mitochondrial iron deposition in alveolar epithelial cells induced by smoking. BLM and LPS treatment significantly elevate intracellular Fe²⁺ and lipid ROS, reduce GPX4 activity and initiate ferroptosis in BEAS-2B human alveolar epithelial cells, whereas ferroptosis inhibitors (Ferrostatin-1/Fer-1, Liproxstatin-1/Lip-1) or iron chelators (DFO) markedly alleviate BLM/LPS-mediated AEC injury [57].

Ferroptotic AECs release damage-associated molecular patterns (DAMPs) including high-mobility group box 1 (HMGB1) and ATP upon death [58]. DAMPs recruit macrophages and other immune cells to trigger local inflammation, simultaneously activating fibroblasts to

accelerate fibrotic progression [59].

Furthermore, ferroptosis drives EMT in AECs to exacerbate fibrosis [60]. EMT describes the phenotypic shift of epithelial cells characterized by decreased E-cadherin and elevated mesenchymal markers (α -smooth muscle actin/ α -SMA, vimentin), serving as a primary source of myofibroblasts in IPF. Willis et al. first validated EMT induction in AECs under long-term TGF- β 1 exposure, with downregulated epithelial markers (TTF-1, AQP5, ZO-1, cytokeratins) and upregulated mesenchymal markers (α -SMA, vimentin, desmin, type I collagen). Ferroptotic agonists activate the TGF- β 1/Smad pathway to promote AEC EMT, while ferroptosis inhibition suppresses EMT-related molecular expression and alleviates pulmonary fibrosis. A 2025 study by Yang et al. [64] identified abnormally activated signal transducer and activator of transcription 6 (STAT6) in IPF airway epithelial cells. STAT6 directly binds the parkin (PRKN) promoter to repress PRKN-mediated mitophagy, aggravating epithelial ferroptosis; STAT6 knockout markedly reduces epithelial ferroptosis and pulmonary fibrosis, revealing a novel STAT6-mitophagy-ferroptosis regulatory axis.

3.2 Regulation of Fibroblast Activation and Proliferation

Fibroblasts are the primary ECM-synthesizing cells in lung tissue, and their aberrant activation, proliferation and differentiation into myofibroblasts constitute the core driver of excessive ECM deposition in IPF. Unlike AECs, fibroblasts exhibit intrinsic ferroptosis resistance via coordinated iron metabolism and antioxidant defense maintenance. Meanwhile, ferroptosis-related signaling cascades facilitate fibroblast activation and proliferation to promote fibrosis.

TGF- β 1, the canonical profibrotic cytokine in IPF, upregulates fibroblast TfR1 expression through the TAZ/TEAD4 pathway to boost intracellular Fe²⁺ uptake [63]. However, fibroblasts evade ferroptosis by enhancing iron efflux and remodeling lipid metabolism. Excess Fe²⁺ activates downstream profibrotic signaling to drive fibroblast-myofibroblast transition and upregulate synthesis/secretion of α -SMA and collagens. In BLM-induced IPF mouse models, fibroblast-specific TfR1 knockout significantly suppresses fibroblast activation and ECM deposition, mitigating fibrotic lesions and confirming the regulatory role of iron metabolic dysregulation in fibroblast function.

Ferroptosis also modulates fibroblast activity via autophagy. Ferritinophagy, a specialized autophagic subtype, mediates ferritin degradation through NCOA4 to release free Fe²⁺ and regulate ferroptosis. Yan et al. reported elevated expression of ferritinophagy markers NCOA4 and Beclin1 in lung tissues of IPF patients and BLM model mice. Traditional Chinese herbal complex Shengxian Decoction suppresses ferritinophagy-mediated ferroptosis, reduces expression of fibrotic markers α -SMA and vimentin, and improves pulmonary function. These findings indicate the ferritinophagy-ferroptosis pathway as a promising target for regulating fibroblast activation in IPF treatment.

3.3 Remodeling of Pulmonary Inflammatory Microenvironment

Imbalanced pulmonary inflammatory microenvironment is a pivotal component of IPF pathogenesis. Immune cell infiltration (macrophages, lymphocytes) and pro-inflammatory cytokine release accelerate fibrotic progression. Ferroptosis reshapes pulmonary inflammatory microenvironment by modulating immune cell function and cytokine secretion to influence IPF development.

Macrophages, the dominant pulmonary immune cells, are categorized into pro-inflammatory M1 and anti-inflammatory reparative M2 subtypes. Macrophage polarization imbalance is tightly associated with IPF progression. Ferroptosis drives macrophage polarization toward the M1 phenotype; M1 macrophages secrete tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and IL-1 β , which further induce AEC ferroptosis and injury while activating fibroblasts, forming a vicious cycle of “inflammation-ferroptosis-fibrosis”. Macrophages themselves also undergo ferroptosis; released inflammatory factors and iron ions post cell death amplify local tissue injury and fibrosis.

Ferroptosis additionally modulates the function of other immune cells such as lymphocytes. Chen et al. detected abnormal expression of ferroptosis-related ATM in peripheral blood and lung tissues of IPF patients, correlated with infiltration of CD4⁺ T cells, CD8⁺ T cells and macrophages, suggesting ferroptosis-mediated immune cell infiltration disrupts pulmonary immune homeostasis in IPF. Inflammatory cytokines including IFN- γ alter expression of ferroptosis regulatory molecules to mediate crosstalk between inflammation and fibrosis, though detailed mechanisms require further elucidation.

4. Research Advances in Ferroptosis-Related Biomarkers for IPF

Early diagnosis of IPF remains challenging due to the lack of specific biomarkers; current diagnostic approaches rely primarily on high-resolution computed tomography (HRCT), pulmonary function testing and lung biopsy. Ferroptosis-related molecules represent promising candidate biomarkers for early diagnosis, disease stratification and prognosis evaluation of IPF.

4.1 Iron Metabolism-Related Biomarkers

Iron metabolic disturbance is a prerequisite for ferroptosis initiation, and aberrant expression of associated molecules serves as potential IPF biomarkers. TfR1, the master iron uptake mediator, is significantly upregulated in lung tissues of IPF patients and model mice, with expression levels positively correlated with fibrotic severity, reflecting iron overload status. Ferritin, the primary iron storage protein, exhibits reduced serum levels and dysregulated tissue expression in IPF patients, indirectly indicating disrupted intracellular iron homeostasis.

NCOA4, the key ferritinophagy regulator, is overexpressed in IPF lung tissues. It promotes ferritin degradation and iron release to exacerbate ferroptosis and fibrosis, with expression levels linked to disease progression. Serum iron concentration and iron metabolism enzymes (STEAP3, DMT1) also show biomarker potential, yet relevant clinical research remains

limited and requires further verification.

4.2 Lipid Peroxidation-Related Biomarkers

Accumulation of lipid peroxidation products is the core hallmark of ferroptosis, and their levels directly reflect ferroptosis activity, making them potential biomarkers for IPF diagnosis and severity assessment. Malondialdehyde (MDA), a terminal lipid peroxidation product, is markedly elevated in serum and lung tissues of IPF patients, positively correlated with fibrotic degree, and can quantify oxidative injury induced by ferroptosis. 4-hydroxynonenal (4-HNE), another vital lipid peroxidation metabolite, binds biomacromolecules such as proteins and nucleic acids to impair cellular function, and its expression is significantly upregulated in IPF lung tissues to participate in fibrotic regulation.

Moreover, abnormal expression of lipid peroxidation enzymes (ACSL4, LOXs) can act as auxiliary biomarkers. ACSL4, which promotes PUFA integration into cell membranes, is overexpressed in IPF lung tissues and increases cellular ferroptosis susceptibility. LOX family members (5-LOX, 12-LOX), core enzymes driving lipid peroxidation, correlate closely with IPF fibrotic severity and serve as auxiliary indicators for disease evaluation.

4.3 Antioxidant Defense System-Related Biomarkers

Functional failure of antioxidant defense systems is a key trigger of ferroptosis, and abnormal expression of related molecules can be used as IPF candidate biomarkers. GPX4, the central anti-ferroptotic effector, is significantly downregulated in IPF lung tissues, and its expression negatively correlates with fibrosis severity, representing impaired cellular antioxidant capacity. SLC7A11, a critical mediator of GSH synthesis, is abnormally suppressed in IPF lung tissues; its downregulation limits GSH production and facilitates ferroptosis, making it a potential diagnostic marker.

Glutathione (GSH), a core intracellular antioxidant, declines in serum of IPF patients, indicating impaired antioxidant defense and supporting auxiliary disease evaluation. Other antioxidant pathway molecules (FSP1, DHODH, GCH1) are also correlated with IPF, but their biomarker value awaits more clinical validation.

4.4 Hub Genes Associated with Ferroptosis

With the development of high-throughput sequencing, multiple ferroptosis-related hub genes have been identified as potential IPF biomarkers. A March 2025 PMC study screened 10 differentially expressed ferroptosis-related genes from peripheral blood and lung tissues of IPF patients via gene sequencing and protein interaction analysis, and confirmed ATM as the core hub gene. ELISA results demonstrated lower serum ATM but higher lung tissue ATM in IPF patients versus healthy controls, and its expression level correlates with pulmonary immune cell infiltration, providing a novel target for early IPF diagnosis.

In addition, He et al. identified multiple differentially expressed ferroptosis genes (CAV1, NOS2, etc.) in IPF lung tissues: NOS2 and GDF15 are upregulated in fibrotic lesions,

while CAV1 and CDKN2A are downregulated. The expression spectrum of these genes effectively reflects disease progression stage and provides molecular evidence for condition monitoring. Gene-based ferroptosis biomarkers can be detected via peripheral blood with non-invasive and convenient advantages, which are promising for early IPF screening. However, large-sample clinical trials are still lacking to verify their specificity and sensitivity, and further optimization is needed.

5. Research Progress of Targeted Ferroptosis Therapeutic Strategies for IPF

Given the critical regulatory role of ferroptosis in IPF, therapies targeting ferroptosis have become a hot research field, mainly including iron chelators, ferroptosis inhibitors, antioxidants, traditional Chinese medicine compounds, and novel targeted delivery systems, offering new ideas for IPF treatment.

5.1 Iron Chelators

Iron chelators specifically bind intracellular free Fe^{2+} to mitigate iron overload, block Fenton reaction and lipid peroxidation, thereby halting ferroptosis progression. Deferoxamine (DFO), a classic iron chelator, forms stable complexes with Fe^{2+} for extracellular excretion and alleviates iron-mediated oxidative damage. Pei et al. [48] found that DFO significantly alleviates BLM/LPS-induced pulmonary fibrosis in mice, reduces pulmonary Fe^{2+} and MDA levels, elevates SOD and GSH-Px activity, and inhibits fibroblast activation and ECM deposition.

Besides DFO, novel iron chelators including deferiprone (DFP) and deferasirox (DFX) exhibit anti-fibrotic effects. They feature high oral bioavailability and strong tissue penetration, with promising prospects for IPF treatment. Nevertheless, clinical application of iron chelators faces obstacles: long-term administration may cause iron deficiency and gastrointestinal adverse reactions, requiring optimized dosage and treatment courses.

5.2 Ferroptosis Inhibitors

Ferroptosis inhibitors directly suppress key ferroptotic links such as lipid peroxidation and GPX4 inactivation to block cell death. Ferrostatin-1 (Fer-1) and Lipoxstatin-1 (Lip-1) are classic ferroptosis inhibitors, which eliminate lipid free radicals and inhibit LOX activity to protect AECs from ferroptosis. Studies confirm that Fer-1 and Lip-1 markedly alleviate BLM-induced pulmonary fibrosis in mice, downregulate fibrotic markers α -SMA and collagens, and improve lung function.

In addition, GPX4 activators serve as indirect ferroptosis inhibitors by boosting antioxidant capacity. A 2025 study by Yang et al. conducted virtual screening and identified rifabutin as a STAT6 inhibitor. In vivo and in vitro experiments verified that rifabutin activates PRKN-mediated mitophagy to suppress airway epithelial ferroptosis and relieve IPF symptoms, providing a new candidate drug for IPF therapy. Ferroptosis inhibitors feature high target specificity

to directly interfere with ferroptosis, yet poor bioavailability and rapid metabolism limit their clinical transformation.

5.3 Antioxidants

Antioxidants eliminate reactive oxygen species and enhance cellular antioxidant capacity to suppress ferroptosis and fibrosis. Classic antioxidants such as vitamin E and N-acetylcysteine (NAC) have been applied as adjuvant IPF therapies. Chang et al. verified that vitamin E reduces BLM-induced ferritin expression in fibrotic lung tissue. As a precursor of GSH synthesis, NAC elevates intracellular GSH concentration to enhance GPX4 activity, inhibit lipid peroxidation and mitigate ferroptosis-mediated pulmonary injury.

Novel antioxidants including idebenone and coenzyme Q10 also exert anti-fibrotic effects by improving mitochondrial function and clearing reactive oxygen species. Natural products such as curcumin and resveratrol possess dual antioxidant and anti-ferroptosis activities, with great therapeutic potential for IPF worthy of further exploration. Despite massive research investment in antioxidants, the clinical efficacy of synthetic antioxidants remains ambiguous due to mixed mechanisms, insufficient dosage, low bioavailability and toxicity. A few compounds (edaravone, ebselen) show promising effects, and NOX enzyme inhibition emerges as an emerging strategy. However, only a small number of drugs have obtained official approval; no new drugs are expected to launch in the near future due to insufficient precise molecular definition and updated testing systems.

5.4 Regulatory Strategies of Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) presents unique advantages for IPF treatment. Its multi-component and multi-target characteristics match the complex pathogenesis of IPF, which involves inflammation, oxidative stress, EMT, fibroblast activation, ECM deposition and crosstalk among multiple signaling pathways (TGF- β 1/Smad, PI3K-AKT, Wnt/ β -catenin, etc.). Single-target western medicine fails to comprehensively intervene this complex pathological network, while TCM compounds and active ingredients can intervene multiple pathways to exert synergistic anti-fibrotic effects. Accumulating studies confirm that TCM formulas and monomers relieve IPF by regulating ferroptosis. As a novel regulated cell death mode characterized by iron-dependent lipid peroxidation and ROS accumulation, ferroptosis participates in the progression of pulmonary, hepatic and renal fibrosis. TCM compounds and active ingredients can precisely modulate ferroptosis via correcting iron metabolic disorder, inhibiting lipid peroxidation and regulating core signaling pathways to alleviate fibrosis.

Shengxian Decoction, a classic TCM formula based on the "great qi theory", suppresses ferritinophagy-mediated ferroptosis, reduces pulmonary Fe^{2+} and MDA levels, increases SOD and GSH-Px activity, upregulates anti-ferroptosis molecules SLC7A11, GPX4 and FTH1, and downregulates ferritinophagy markers NCOA4, AMPK and Beclin1. It therefore improves lung function and alleviates fibrosis in IPF rats.

Electroacupuncture, an important TCM intervention, also ameliorates IPF by regulating ferroptosis. Research shows electroacupuncture reduces pulmonary Fe^{3+} , Fe^{2+} , lipid peroxides (LPO) and MDA in IPF rats, elevates GSH and SOD levels, relieves mitochondrial swelling in alveolar epithelial cells, and inhibits p-Akt and p-FoxO3 expression. It suppresses ferroptosis via modulating the PI3K-Akt-FoxO pathway to reduce pulmonary fibrosis. In addition, TCM active monomers such as tanshinone IIA, astragaloside IV and lycium barbarum polysaccharide alleviate IPF by regulating ferroptosis-related molecules. Tanshinone IIA upregulates GPX4 and SLC7A11 to inhibit lipid peroxidation and reduce AEC ferroptosis; astragaloside IV suppresses iron overload and lipid peroxidation to block fibroblast activation and pulmonary fibrosis.

5.5 Novel Targeted Delivery Systems and Combination Therapy

To enhance therapeutic efficacy and reduce adverse reactions of ferroptosis-targeted drugs, research on novel targeted delivery systems has become a hotspot. Nano delivery carriers including liposomes, nanoparticles and polymer micelles can deliver drugs precisely to pulmonary lesions via passive or active targeting, increasing local pulmonary drug concentration and improving curative effects. Studies show that encapsulating Fer-1 into liposomes significantly enhances its pulmonary enrichment, prolongs drug action time, strengthens anti-fibrotic efficacy and reduces systemic side effects. Moreover, combining TCM active ingredients with nano carriers improves their water solubility and bioavailability to boost ferroptosis regulatory effects.

Given the complicated pathogenesis of IPF, single ferroptosis-targeted therapy often yields limited efficacy, and combination therapy has become a major trend. Combined administration of ferroptosis inhibitors and classic anti-fibrotic drugs (nintedanib, pirfenidone) may generate synergistic effects. Research indicates that combined use of ferroptosis inhibitors and nintedanib exerts stronger inhibition on fibroblast activation and ECM deposition than monotherapy, possibly through crosstalk regulation between ferroptosis and TGF- β 1 signaling. In addition, combinations of ferroptosis inhibitors with antioxidants or immunomodulators can improve overall therapeutic outcomes. Combination therapy intervenes multi-pathological processes of IPF through multiple targets, breaking the limitations of single-drug treatment. Nevertheless, relevant research is still at the preclinical experimental stage, and clinical efficacy and safety require further verification.

6. Research Challenges and Future Perspectives

Although remarkable progress has been made in research on ferroptosis regulation in IPF, multiple challenges remain. Firstly, the complete regulatory network of ferroptosis in IPF has not been fully clarified, including the interaction mechanisms between ferroptosis and other cell death modes (autophagy, apoptosis), as well as cell-type-specific ferroptosis regulatory mechanisms in AECs, fibroblasts and macrophages. Secondly, clinical application of ferroptosis-related biomarkers has limitations. Currently identified

single-molecule biomarkers lack sufficient specificity and sensitivity, which need validation through large-sample clinical trials. Developing combined multi-biomarker detection panels may improve the accuracy of IPF diagnosis.

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