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Dear Patporn Chankong:

We would like to thank for your letter and for the reviewer's comments concerning our manuscript entitled: **" Role of ferroptosis in regulating the epithelial–mesenchymal transformation in pulmonary fibrosis" (ID: biomedicines-2078725).** Those comments are all valuable and very helpful for revising and improving our paper, as well as have an important guiding significance for our researches. We have studied comments carefully and have made corrections which hope meet with approval. Revised portions are marked up using the "Track Changes" function in the paper. The main corrections in the paper and the responds to the reviewer's comments are as following:

1. The role of ferroptosis in acute lung injury should be discussed.

Response to reviewer's comment: Thank you for your comment. Acute lung damage can eventually lead to pulmonary fibrosis. Iron deposition in alveolar epithelial cells can produce acute lung damage. This part has been added in the Introduction.

Ferroptosis is a ~~newly characterized~~n iron-dependent non-apoptotic regulated cell death[12, 13]. The accumulation of excessive intracellular iron, depletion of glutathione (GSH), inactivation of glutathione peroxidase 4 (GPX4), and upregulation of lipid peroxidation are essential for the development and progression of ferroptosis[14]. Following the acute inflammation and injury, the lungs undergo repair and remodeling to restore homeostasis, accompanied by fibrosis and scar formation, which may lead to pulmonary fibrosis[15]. In the pathological process of acute lung injury, the release of various reactive oxygen species and the generation of free radicals can damage alveolar epithelial cells. Iron overload can further promote the transformation of hydrogen peroxide into free radicals through the Fenton reaction, thus increasing cytotoxicity and promoting the occurrence and development of acute lung injury[16]. ~~It~~ Meanwhile,it has been reported that there exists an 8-ferroptosis-related genes signature (including NRAS, EMP1, SLC40A1, MYC, ANGPTL4, PRKCA, MUC1, and GABARAPL1) in bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis (IPF), which is associated not only with the diagnosis of IPF, but also with the prognosis of IPF[12]. He *et al.* [17]compared IPF lung

2. The authors should discuss the role of ferroptosis in post-COVID-19 pulmonary fibrosis as it will be interesting to most of the readers.

Response to reviewer's comment: Thank you for your comment. At present, pulmonary fibrosis induced by COVID-19 is of great concern and has been added in the Introduction as a pathogenesis.

ment of interstitial fibrosis through paracrine signaling from the alveolar epithelium to potential fibroblasts[8]. The initiation and progression of pulmonary fibrosis involve many factors, which may be related to long-term smoking, viral infection, genetics, aging, and environmental factors[2]. In recent years, the impact of COVID-19 infection on lung diseases is noteworthy. SARS-CoV-2 enters the nasal epithelium and spreads to the respiratory system. ACE-2 receptors on the surface of the lung epithelium allow SARS-CoV-2 to enter the upper respiratory tract. Entry into the lower respiratory tract will infect type II alveolar epithelial cells, leading to diffuse alveolar injury[9]. After infection with SARS-CoV-2, it can lead to acute lung inflammation by mobilizing iron in the vascular space to activate the hepcidin-Fpn pathway and promote ferroptosis[10]. The formation of alveolar thrombosis and airway inflammatory viral damage further promoted the development of pulmonary fibrosis，and SARS-CoV-2 can induce pulmonary fibrosis by promoting the up-regulation of TGF-β and other pro-fibrosis signaling molecules[11].

3. If there any previous trials for inhibiting ferroptosis and its effect on the development of pulmonary fibrosis？if yes, those trials should be discussed in this review.

Response to reviewer's comment: Thank you for your reminding. Some experiments have been mentioned in the article, but more are added later.

GDF15, SLC2A12, NGB, DRD5, and GPX2). Meanwhile, increased iron levels directly increase the proliferation, proinflammatory cytokines, and ECM response of human lung fibroblasts. But deferoxamine reduces the number of Tfr1+ macrophages with an M2-like phenotype in bleomycin-induced pulmonary fibrosis. M2-like macrophages are known to play an important role in fibrosis[18]. Studies have shown that iron chelators ameliorate bleomycin-induced pulmonary fibrosis and alleviate leukocyte migration in mice. Yuan *et al.* [19] found that Dihydroquercetin plays an anti-fibrosis role by inhibiting iron death in human bronchial epithelial cells HBE[19]. Pei *et al*[20] showed that bleomycin and lipopolysaccharide directly induce iron overload and ferroptosis in lung epithelial cells in the early inflammatory period. TFRC promotes the transition from fibroblasts to myofibroblasts in advanced fibrosis through moderate intracellular accumulation of unstable ferrous iron mediated by the TGF-β-TAZ-TEAD signaling pathway[20]. This suggests that ferroptosis may be involved in the development and progression of IPF.

4.]] mark at the beginning of both lines 83 and 157 should be deleted.

Response to reviewer's comment: Thank you for your reminding. The format has been modified.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions. If you have any queries, please don't hesitate to contact us.

Yours sincerely,

Jiang Deng Prof. Jiang Deng