

Remarkable contribution of particulate matter-induced macrophage ferroptosis to the pathology of pulmonary fibrosis

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Abstract

Occupational exposure to particulate matter (PM) induced pulmonary fibrosis has aroused broad public concern. Pulmonary interstitial fibrosis is a central pathologic process of pneumoconiosis. Meanwhile, ferroptosis is a newly defined iron-dependent programmed cell death (PCD) that features increased intracellular labile iron and lethal accumulation of lipid peroxidation. Ferroptosis has been found to involve particulate-induced cytotoxicity. Recent studies have suggested that ferroptosis is closely associated with the occurrence and progression of pulmonary fibrosis. Here, we present a mini review to summarize the main mechanisms responsible for PM-induced pulmonary fibrosis via inducing macrophage ferroptosis to provide new insights into basic and clinical research of pulmonary fibrosis.

Introduction

Particulate matter (PM) is a type of environmental air pollutants. Once inhaled into the human airway, it will trigger a series of disorders of the respiratory system, including pulmonary fibrosis through inflammation¹⁻³. After crossing the air-blood barrier, PMs can even elicit harmful effects on distant organs through blood circulation, including joint injury and nervous system impairment⁴⁻⁶. Recently, it has been recognized that macrophage damage caused by inhalation exposure of PMs is closely associated with fibrogenesis *via* multiple fibrogenic cytokines, such as transforming growth factor β (TGF- β), tumor necrosis factor α (TNF- α), interleukin (IL) 1 β , IL-4, IL-6, IL-10 and IL-13^{3,7-11}. Remarkably, inhalation exposure to PMs could induce alveolar macrophage damage as well as different programmed cell death such as apoptosis, necroptosis, autophagy, pyroptosis and ferroptosis¹¹⁻¹⁴. Especially, ferroptosis is a type of programmed cell death (PCD) characterized by overloading intracellular labile iron and accumulation of lipid peroxide caused by ferrous ion-mediated Fenton reaction^{15,16}, which differs from other PCDs in the sense of biochemical characteristics¹⁷. Some studies have revealed that PM-induced macrophage ferroptosis is associated with various pulmonary diseases, including pulmonary fibrosis^{7,9,14,18}. This mini review will focus on how PM-induced macrophage ferroptosis further triggers pulmonary interstitial fibrosis and provide a new perspective for the study of pathogenesis and clinical treatment of fibrosis.

PMs and pulmonary fibrosis

Pneumoconiosis is one of a family of interstitial lung diseases caused by the inhalation and deposition of PMs, including silica particles, asbestos fibers, coal dust and other mineral dust, characterized by chronic pulmonary inflammation and progressive pulmonary fibrosis¹⁹. Pneumoconiosis patients suffer from a significantly increased risk of pulmonary functions^{20,21}. Recent epidemiologic studies in humans have indicated that pulmonary fibrosis is closely correlated with PMs^{21,22}.

Experimental data in animals have indicated that pulmonary fibrosis is closely associated with PM exposure^{23,24}. Previous studies have revealed that diffuse interstitial pulmonary fibrosis causes compromised pulmonary compliance and capillary bed, leading to severe respiratory dysfunction^{25,26}.

Silicosis is the most typical and common PM-induced pulmonary fibrosis-related disease, which is mainly induced by occupational exposure to SiO₂ dust^{2,27}. SiO₂ is often used to develop pulmonary fibrosis animal models by inhalation exposure²⁸⁻³¹. In addition to silicon-based PMs, Xu et al. established a pulmonary fibrosis model in mice *via* multiple intranasal instillations of urban PM_{2.5}, evidenced by reduced pulmonary function, chronic pulmonary inflammation, and otherwise increased histological fibrosis scores²³. Jacobsen et al. recognized a dose-dependent increased collagen accumulation in the mouse pulmonary system upon exposure to zinc oxide nanoparticles³². Besides, carbon-based PMs have also been found to be important inducers of pulmonary fibrosis in rats and mice^{33,34}. Overall, PMs are closely implicated in the development of pulmonary fibrosis.

It is a generally accepted mechanism that inhaled PMs in the alveoli interact with alveolar macrophages and then cause pulmonary fibrosis through the activation of pro-inflammatory reactions². Inhaled PMs enter the alveoli and associate with alveolar macrophages and epithelial cells⁶. As shown in Figure 1, alveolar macrophages play a crucial role in the pathological process of pulmonary fibrosis. According to previous studies, overall, in the lung injury stage, macrophages are polarized into the M1 state to play a pro-inflammatory and pro-injury role³⁵. And in the lung repair process, M2 macrophages are responsible for the regulation of fibrogenesis, which aggravates the progression of pulmonary fibrosis^{35,36}. M2 macrophages can secrete excess TGF-β to enhance the proliferation and differentiation of lung fibroblasts and thus facilitate the progression of pulmonary fibrosis³⁷. Moreover, a previous study has revealed that PM exposure could trigger epithelial-mesenchymal transition (EMT) in alveolar epithelial cells³⁸. And epithelial cells are also verified to contribute to pulmonary fibrosis *via* EMT³⁸⁻⁴⁰. Persistent chronic inflammation is one of the preconditions for progressive fibrosis⁴¹. It has been reported that macrophage-mediated inflammation is vital in forming PM-induced pulmonary fibrosis⁴². Once PMs cause alveolar macrophage damage, cytokines, such as TGF-β, TNF-α, IL-1β and IL-6 are released from macrophages. These cytokines will further promote more fibroblasts' activation and transformation into myofibroblasts^{13,43-45}. Then accompanied by the deposition of collagen leads to excessive accumulation of extracellular matrix in the alveolus and interstitium, leading to pulmonary fibrosis⁴³.

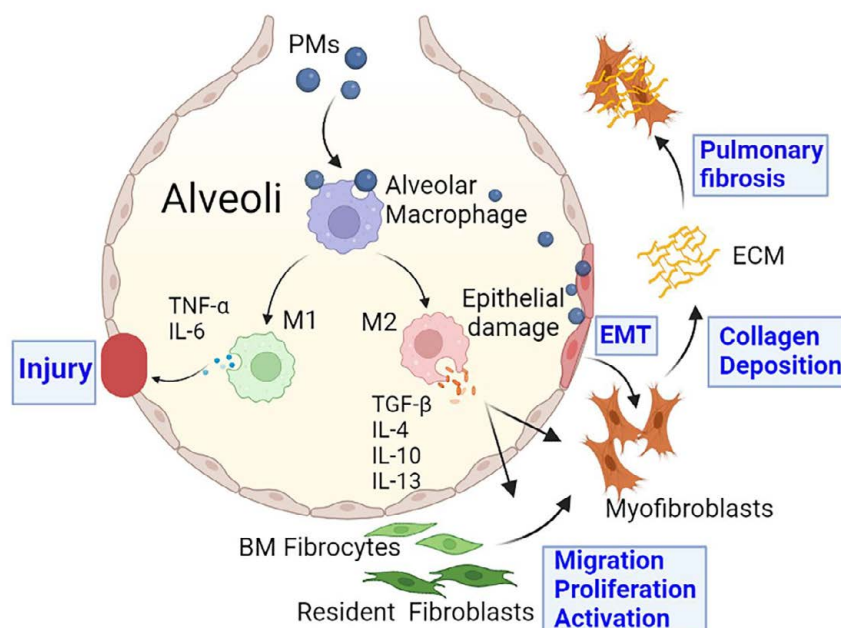


Figure 1: Inhaled PMs trigger fibroblast activation and fibrosis via cytokine release by alveolar macrophages

Macrophage ferroptosis upon PM exposure

Ferroptosis is, per se, a kind of oxidative stress-induced cell death¹⁶. The labile iron pool (LIP) provides active Fe^{2+} to initiate the Fenton reaction, associated with excess reactive oxygen species (ROS) production and increased sensitization of cells to ferroptosis¹⁷. And lipid oxidation (LPO) is a key process and an outcome of ferroptosis⁴⁶. The generation of LPO involves iron-catalyzed enzymatic (ALOXs) and non-enzymatic (the Fenton chemistry-aided) processes⁴⁷. Moreover, repressed glutathione peroxidase 4 (GPX4) and reduced glutathione (GSH) account for the initiation of ferroptosis^{16,48}. As a newly defined PCD, ferroptosis was recognized to be implicated in diverse diseases, including neurodegeneration⁴⁹, cerebrovascular diseases^{50, 51} and pulmonary diseases. For example, iron overload, decreased GSH and GPX4 were found in pulmonary tissue in oleic acid-induced acute lung injury (ALI)⁵². Besides, Ghio et al. found that the iron and ferritin contents in BALF, serum ferritin levels and nonheme iron concentrations were elevated in the rat lung tissue after exposure to cigarette smoke⁵³. This mini review focuses on the role of macrophage ferroptosis in PM-induced pulmonary diseases.

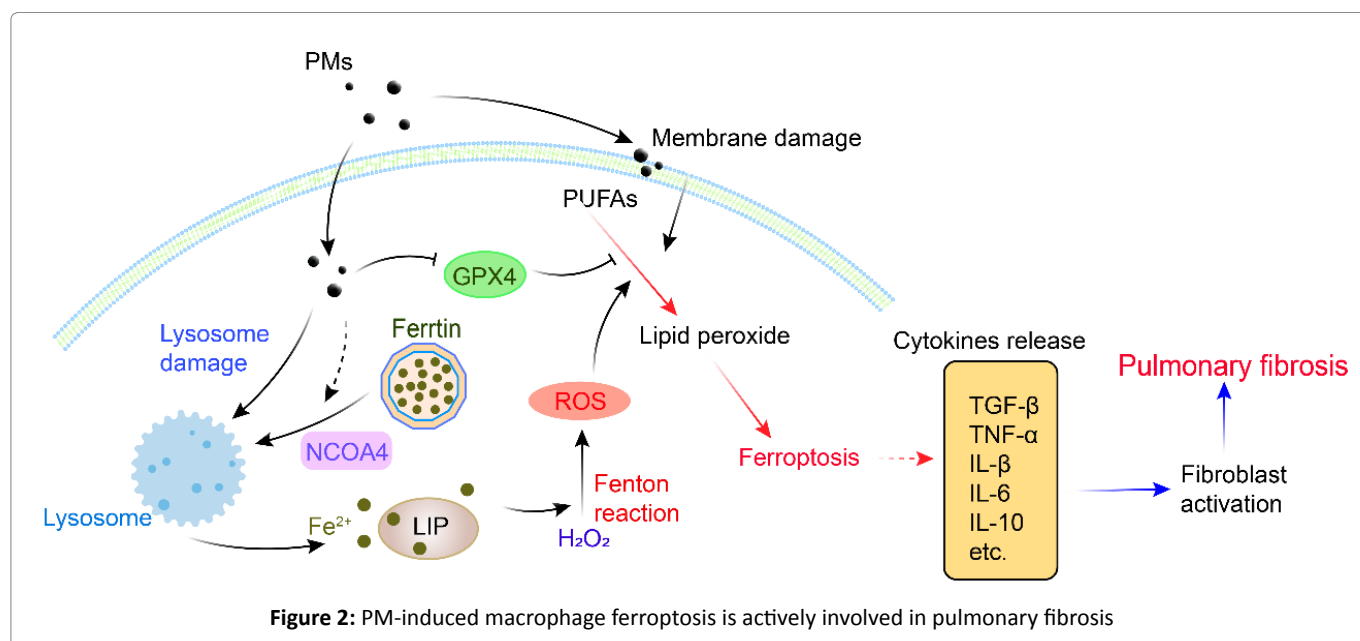
With the increasing environmental pollution problems, the health effects caused by exposure to PMs are considerably drawing people's attention. The development of industry also gave rise to occupational exposure. A growing number of studies suggest that PM exposure causes macrophage ferroptosis^{11,23,54}. The inhaled PMs invade alveoli and attack alveolar macrophages, and the cues of ferroptosis with decreased superoxide dismutase (SOD) activity and reduced glutathione (GSH) levels were observed in mice pulmonary tissues²³. Signal transducer and activator of transcription 6 (STAT6) is a key regulator in innate immune response, which mediates direct repression of inflammatory enhancers and regulates activation of alternatively polarization⁵⁵. Yang et al. found that ALI caused by crystalline silica was reversed by overexpression of STAT6 to suppress ferroptosis *via* positively regulating SLC7A11 in pulmonary epithelial cells⁵⁶. Liu et al. reported that quartz particles induced ferroptosis in macrophage cell line RAW 264.7 *in vitro* and ferroptotic effects such as suppression of GPX4 and accumulation of malondialdehyde (MDA), a lipid peroxidation product in mice lung tissue *in vivo*⁷. Since SiO_2 is an apparent inducer of pulmonary fibrosis in silicosis, there is also a correlation between ferroptosis and pulmonary fibrosis, and ferroptosis may take part in SiO_2 -induced pulmonary fibrosis. These findings suggest that ferroptosis is involved in PM-induced lung disorders.

With the widespread applications of nanoproducts, there is an increased risk of exposure to nanoparticles, scilicet nano-scaled PMs^{65,67}. Although 1-2 μm PMs are most

pathogenic in the respiratory system^{21,58}, toxicity caused by nano-scaled PMs is worth further study due to the unique properties of nanomaterials. Recently, several pieces of research focused on the ferroptotic cell death caused by nano-scaled PMs. Li et al. found that 2D-layered carbon-based materials graphene oxides (GOs), a type of nano-scaled PM, triggered significant lipid peroxidation in human macrophage THP-1 and mouse alveolar macrophages *in vivo*. Meanwhile, they also unraveled that the surface oxidation state and carbon radical content of GOs greatly dictated the generation of lipid peroxide in cells⁵⁴. In another study, they found transition metal dichalcogenides WS_2 and MoS_2 nanosheets induced macrophages and epithelial cell ferroptosis, and their nano-SAR analysis revealed that surface vacancies of the nanosheets were the real culprit in ferroptosis¹¹. The above studies have unveiled that some nanoparticles could also be considered as nano-scaled ferroptosis inducers and may cause pulmonary fibrosis *via* ferroptosis. Understanding nano-scaled particle-associated ferroptosis is extremely important for the safety design of nanoproducts. To this end, PMs as the pulmonary fibrosis inducers are also responsible for cell ferroptosis, and it is valuable to perform more in-depth studies to shed light on the connections between alveolar macrophage ferroptosis and pulmonary fibrosis.

The involvement of macrophage ferroptosis in pulmonary fibrosis

Previous studies have indicated that macrophage death plays a vital part in pulmonary fibrosis, and different cell death types give rise to diverse detrimental outcomes¹². In recent years, the action of ferroptosis in PM-induced cytotoxicity has attracted research interest. Liu et al. found that SiO_2 -induced fibroblast activation was obviously suppressed by ferrostatin-1, a specific inhibitor of ferroptosis⁷. Through a co-culture system of macrophage RAW 264.7 and mouse lung fibroblasts, they recognized that the ferroptotic damage of macrophages caused by PMs triggered the release of inflammatory factors and TGF- β , which in turn induced the activation of fibroblasts⁷. In addition, ferroptosis also plays an essential role in inflammation⁵⁹. Li et al. found WS_2 and MoS_2 nanosheets induced lung inflammation and promoted cytokine secretion, including lipopolysaccharide-induced CXC chemokine (LIX), TNF- α and IL-1 β in bronchoalveolar lavage fluid from exposed mice¹¹. These cytokines, especially TNF- α and IL-1 β , were closely related to fibrosis^{60,61}. Disrupted cellular iron homeostasis is a critical cause of ferroptosis¹⁵. Ali et al. found that iron accumulation was increased in lung tissue sections of pulmonary fibrosis patients. Their animal experiment also showed that iron accumulation localized predominantly in macrophages, and intranasal treatment with the iron chelator deferoxamine (DFO) could inhibit airway fibrosis and decline in lung function⁶². These findings suggest that ferroptosis



in macrophages has a potential causal correlation to pulmonary fibrosis. Earlier studies have showed that 4-hydroxy-2,3-nonenal (HNE), a major end product of cellular lipid peroxide and a key biological marker of ferroptosis, could further elevate TGF-β1 expression in J774. A1 macrophages⁶³. This circumstantial evidence suggests that macrophage ferroptosis may be an important motivator of fibroblast activation. Furthermore, Li et al. and Tao et al. found that liproxstatin-1, a ferroptosis inhibitor, functioned to remarkably reduce TGF-β expression and collagen accumulation in the idiopathic pulmonary fibrosis animal model^{64,65}. The implications of macrophages in this process needs further exploration. Overall, macrophage ferroptosis contributes to PM-induced pulmonary fibrosis. However, the specific causal relationship between macrophage ferroptosis and pulmonary fibrosis still requires detailed investigation, and the exact mechanisms warrant further studies (Figure 2).

Conclusions and Perspectives

In the past views, macrophage damage-associated cytokines, such as TGF-β, TNF-α, IL-1, IL-6 and IL-10, could promote fibroblast proliferation and activation and collagen accumulation, ultimately leading to pulmonary fibrosis. The contributions of macrophage death to pulmonary fibrosis are not clearly understood, which is of great importance for the pathology and therapeutics of PM-associated pulmonary fibrosis. Moreover, the role of the macrophage state in lung fibrosis is very complicated, and there are great controversies over whether a particular phenotype aggravates or improves fibrosis. Although previous studies suggest that a predominant pro-fibrotic M2 priming state is detrimental to pulmonary fibrosis, the role of ferroptosis in macrophage polarization remains to be further explored. In

this review, we exploited the contributions of PM-induced ferroptosis to macrophage damage, which then lead to pulmonary fibrosis. In short, PM-induced ferroptotic cell death in macrophages is significantly accountable for pulmonary fibrosis. Ferroptosis-associated inflammation is one of the fundamental ways to promote fibrosis, but more underlying mechanisms remain to be further explored. In fact, in the PM-induced lung injury model, PMs could induce ferroptotic effects not only in macrophages but also in other cell types. Nevertheless, identifying which cell types undergo ferroptosis in pulmonary fibrosis and their contributions to the progress of pulmonary fibrosis remains a challenge. The types of lung cell damage caused by PMs are complex, including apoptosis, necroptosis, pyroptosis and autophagy, and it is valuable to figure out their roles in PM-induced fibrosis. In terms of anti-cellular damage, since ferroptosis contributes to the pathogenesis of pulmonary fibrosis, it is hopeful to prevent and treat PM-induced pulmonary fibrosis *via* anti-ferroptosis strategies. Nevertheless, as PMs deposited in the lungs are the fundamental initiating factor of fibrosis, preventing inhalation of PMs and developing a method to remove PMs from the lung may represent the basic and essential intervention methods. As an outlook, in future clinical practice, one can try to delay the progression of PM-induced fibrosis by regulating alveolar macrophage ferroptosis and related homeostasis in pulmonary fibrosis patients.

Conflict of Interest

The authors have no conflict of interest to disclose.

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