The Role of Ferroptosis and Its Inhibition in Chronic Obstructive Pulmonary Disease (COPD)

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RATIONALE
Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the lung, mainly caused by cigarette smoke (CS) and characterized by obstructive bronchiolitis and pulmonary emphysema. Ferroptosis, an iron-dependent form of regulated necrosis, is characterized by lipid peroxidation that leads to oxidative stress and cell death. Glutathione peroxidase 4 (GPX4) is a regulatory molecule able to convert toxic lipid peroxides into non-toxic lipid alcohols, thereby limiting the overwhelming iron-dependent production of reactive oxygen species (ROS). E06 is a naturally occurring monoclonal antibody that binds oxidized phosphatidylcholine with high affinity, reflecting the extent of lipid peroxidation during ferroptosis. This study aimed to evaluate the presence of ferroptosis markers in lungs of COPD patients and investigate the therapeutic potential of inhibiting ferroptosis in experimental COPD models using the specific ferroptosis inhibitor UAMC-3203.
METHODS
mRNA expression and protein levels of GPX4 were quantified in lung tissue from individuals with and without COPD using RT-qPCR and immunohistochemistry. Lipid peroxidation in lung macrophages was evaluated through E06 staining. In addition, lipid peroxidation was also measured by C11-BODIPY in vitro cultured primary human bronchial epithelial cells (pHBECs), stimulated with increasing percentages of cigarette smoke extract (CSE) or the ferroptosis inducer RSL3. C57BL/6 were either exposed to air or CS for 4 weeks to examine pulmonary inflammation or subjected to oropharyngeal elastase instillation to model the development of pulmonary emphysema. The animals were treated daily with increasing doses of UAMC-3203 or placebo via intranasal instillation.
RESULTS
Results showed that GPX4 mRNA expression in lung tissue and GPX4 protein levels in airway epithelium were significantly higher in patients with severe COPD. E06 staining revealed significantly higher lipid peroxidation in lung macrophages of current smokers both with and without COPD. In the in vitro study, CSE and RSL3 significantly induced lipid peroxidation in human bronchial epithelial cells. Pharmacological inhibition of ferroptosis using UAMC-3203 dose-dependently attenuated inflammation in bronchoalveolar lavage in CS-exposed mice and significantly protected against elastase-induced emphysema.
CONCLUSION
These findings suggest that ferroptosis is increased in lungs of COPD patients and contributes to the pathogenesis of the disease, with ferroptosis inhibition representing a potential therapeutic approach for managing COPD.

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