Using Deferiprone to Target Mitochondrial Iron for the Treatment of Pulmonary Diseases

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Technology description

This invention discloses the use of the iron chelator, deferiprone for targeting mitochondrial iron as a therapeutic target for IRP2-regulated cigarette smoke-induced bronchitis and emphysema or chronic obstructive pulmonary disease (COPD).

Technology Overview

COPD presents as a complex debilitating lung disease that encompasses a variety of clinical and pathologic phenotypes ranging from airway inflammation (chronic bronchitis) to destruction of lung tissue (emphysema) and remodeling of the small airways. The pathogenesis of COPD remains poorly understood, but involves aberrant inflammatory and dysregulated cellular responses of the lung to cigarette smoke (CS) exposure. CS exposure remains the greatest environmental risk factor for COPD; however, multiple studies have suggested that genetic factors influence COPD susceptibility.

The iron-responsive element binding proteins (IRPs) IRP1 and IRP2 regulate cellular iron homeostasis, with IRP2 serving as the major regulatory protein in mammalian cells. IRPs have important physiological roles in the duodenum, spinal cord and central nervous system, and in the pathogenesis of pulmonary hypertension and neurodegenerative diseases. The inventors previously identified IRP2 as a leading candidate COPD susceptibility gene based on genome-wide association studies (GWAS), and also demonstrated that IRP2 protein is increased in the lungs of COPD subjects. IRP2 is located within a cluster of genes on chromosome 15q25, which includes several components of the nicotinic acetylcholine receptor.

The inventors integrated human COPD expression data with experimental mouse models of COPD to show that exposure to CS raised the levels of IRP2, which in turn led to mitochondrial iron accumulation, along with aberrant activation of the enzyme cytochrome c oxidase (COX). The resultant mitochondrial dysfunction causes defective mucociliary clearance and COPD. They also show that mitochondrial iron chelation using the siderophore deferiprone alleviates established disease in a model of CS-induced pulmonary inflammation and injury (experimental COPD).

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