Redox-based Regulation of Cell Death as Therapeutic Target for COPD & IPF

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Overview

Chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) are debilitating, progressive disorders that result in a permanent loss of lung function. COPD, which is primarily caused by smoking, is characterized by chronic inflammation of airways as well as a loss of elasticity of lung tissue. It is estimated to afflict 65 million people worldwide and is projected to become the third leading cause of death by 2030. Though less common than COPD, the disease burden of IPF is also significant, affecting 5 million people worldwide. IPF reduces lung capacity due to the formation of scar tissue in the lungs. In both COPD and IPF, death of epithelial cells represents a key event in the development of disease.

Yvonne Janssen-Heininger of the University of Vermont has identified a redox-based protein Modification as an Important regulator of Pulmonary cell death. By modulating factors that control this redox-based modification, Janssen-Heininger has successfully prevented pathological changes to lung tissue.

Invention

Oxidative stress has been associated with a variety of pulmonary disorders, including COPD and IPF. While inhaled oxidants and those produced by inflammatory cells can directly cause cellular damage, redox-based changes can also be important regulators of cellular processes like programmed cell death, or apoptosis. In particular, one such redox-based change is the addition of glutathione to protein, a modification known as S-glutathionylation.

Elevated levels of S-glutathionylated proteins have been detected in murine fibrotic lung tissue and in cigarette smoke extract (CSE)-treated human pulmonary cells. This increased S-glutathionylation amplifies apoptosis. By investigating factors involved in regulating apoptosis through S-glutathionylation of protein, Janssen-Heininger unveiled three therapeutic targets for COPD and IPF. Intriguingly, cell death induced by CSE can be prevented by overexpression of Grx-1. Two proteins, GSTP and ERp57, promote S-glutathionylation. Reducing the levels of these two proteins has been shown to prevent fibrotic changes in mouse models of pulmonary fibrosis. Notably, pharmacological inhibition of GSTP and ERp57 can be accomplished with thiomuscimol and TLK199, respectively.

Advantages

- Potential application to several pulmonary diseases, including COPD and IPF.
- Aimed at disease modification and is capable of reversing fibrotic changes.
- Could make use of a pharmacological agent already evaluated in a Phase II clinical trial.

Applications

- Offers a new disease-modifying approach to the treatment of COPD and IPF.
- Targets factors that regulate apoptosis **of epithelial cells,** an important step in the pathogenesis of COPD and IPF.
- Can prevent the restructuring of lung tissue that occurs in pulmonary disease.

Patent Status

US, EPO and Worldwide Rights Available

Learn more about Dr. Janssen-Heininger's research at:
http://bit.ly/1ddr4lW

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