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Salt and Fluid Transport in COPD Lung

ABSTRACT

Terminal airway occlusion is a major manifestation in chronic obstructive pulmonary disease (COPD). Airway mucus consists of two layers: the viscoelastic gel layer on the top and the watery sol layer at the bottom. To maintain functional mucociliary clearance, enough water from the sol layer is requested to hydrate mucins in the gel layer, which is over produced in inflammatory lungs. Epithelial Na channel (ENaC) governs the volume of the sol layer. In the cystic fibrosis lung, hyperactive ENaC has already been proved to be a fundamental mechanism for drying airway and lung, in turn, causes impaired mucociliary clearance. However, little is known about the expression and regulation of ENaC channels in COPD lungs.

The balance between protease and antiprotease in the airway mucus is crucial. It has been confirmed reduction of the activity of α1-antitrypsin; a very important antiprotease inhibitor plays an essential role in the pathogenesis of COPD. The deficient α1-antitrypsin is unable to inhibit elastase, an emphysema-causing enzyme released by inflammatory cells (neutrophils), eventually resulting in emphysema.

Based on our previous results, we hypothesize that ENaC expression is up-regulated in distal bronchoalveolar epithelial cells mediated by a protease-antiprotease imbalance in COPD lungs. Our three specific aims include: 1) we will investigate expression of four ENaC subunits (α, β, γ, and δ ENaC) in bronchoalveolar epithelial cells at the mRNA and protein levels using real-time RT-PCR, Western blot, and confocal miscrosope. 2) We will examine the content and distribution of α1-antitrypsin, matrix metalloproteinases, and elastase in epithelial cells and inflammatory cells. We will analyze the correlationships of ENaC and the ratio of protease/antiprotease as well as severity of COPD. 3) We will assess ENaC channel activity by examining airway potential difference in COPD mice and transepithelial ion transport across airway epithelium mounted in Ussing chamber. In addition, we will record whole-cell and single channel currents in primary bronchoalveolar epithelial cells using patch clamp techniques.

The subject matter of this research is timely and important: there is considerable interest in understanding the mechanisms underlying mucus occlusion in airway in COPD. Results of these studies may provide novel information to our understanding of the contribution of salt and fluid transport to plugged airway, and to form the molecular basis for development of new therapeutic strategies to combat COPD.