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Roles for ADAM Proteinases In COPD.

Abstract:

Background: Cigarette smoke induces chronic lung inflammation which increases the lung proteinase burden leading to extracellular matrix destruction and pulmonary emphysema. However, little is known about the pathways that dampen inflammation and promote repair in emphysema. ADAM15 is a member of the ADAM family of transmembrane proteinases (transmembrane proteinases with a disintegrin and a metalloproteinase domain). ADAMs have the potential to regulate inflammation, cell death and proliferation, cell adhesion and migration, and fibrosis, but little is know about their activities in lung health or disease.

Preliminary studies: Cigarette smoke potently up-regulates ADAM15 expression on the surface of wild type (WT) macrophages in vitro and in vivo. When WT and ADAM15$^{-/-}$ mice were exposed to smoke from 4 cigarettes/day, smoke-exposed ADAM15$^{-/-}$ mice had 2-3 fold more alveolar macrophages and lymphocytes, greater airspace enlargement, and greater increases in lung compliance than smoke-exposed WT mice. Smoke-exposed ADAM15$^{-/-}$ macrophages had decreased rates of apoptosis than smoke-exposed WT cells. Thus, ADAM15 has potent anti-inflammatory and protective activities in the smoke-exposed murine lung likely by decreasing the half life of macrophages thereby reducing the total lung burden of matrix-degrading proteinases. ADAM15 is expressed by human neutrophils, monocytes, and lymphocytes and pro-inflammatory mediators generated in COPD lungs potently up-regulate surface ADAM15 levels on human leukocytes in vitro.

Hypotheses and proposed studies: Little is known about the roles of ADAM15 in human leukocytes, in human lung biology or human COPD. We propose to study lung samples from human COPD patients to address these unknowns. Based upon our results in smoke-exposed mice, we propose to test our hypotheses that: 1) ADAM15 has anti-inflammatory and protective activities in human as well as murine emphysema; and 2) dysregulated expression of ADAM15 in lung inflammatory (or lung structural cells such as alveolar or bronchiolar epithelial cells) may predispose individuals that smoke cigarettes to develop COPD. We propose to measure ADAM15 protein and mRNA levels in lung inflammatory and structural cells by performing immunohistochemistry and in situ hybridization for ADAM15 on lung sections from COPD patients (GOLD stage 1-3; n = 10 per group) and correlate ADAM15 protein expression in each cell type (using image analysis software) with GOLD stage. We will identify the cell types in which ADAM15 is expressed in the lungs by double immunostaining lung sections for markers of leukocyte subsets and structural cells. We will also quantify steady state mRNA levels for ADAM15 in total RNA extracted from lung samples from patients and controls (n = 10/group) using a SYBR-green real time RT-PCR protocol. If we find dysregulated expression of ADAM15 in lung samples from COPD patients (e.g. with GOLD stage 4 patients having decreased ADAM15 expression compared to GOLD stage 1-3), our long term goal would be to investigate the mechanisms involved (e.g. by screening for genetic variants in/around the ADAM15 gene, and analysis of transcription factors and microRNAs that regulate ADAM15 expression in relevant cell types.