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Title: RC kinase: A novel kinase expressed by alveolar macrophages that may play a role in COPD and IPF

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Body: We have characterized a novel serine/threonine protein kinase, called RC kinase, whose expression is upregulated in COPD patients. Examination of RC kinase mRNA tissue distribution showed a limited expression pattern restricted mainly to the lungs and trachea. Immunohistochemical analysis with a monoclonal antibody revealed expression in CD68+ alveolar macrophage and bronchial epithelial cells. Various cell lines upregulated RC kinase expression upon exposure to cigarette smoke extract, or conditions of oxidative or endoplasmic reticulum stress, and this correlated with the production of IL-8. In acute (4 day) and sub-chronic (14 day) cigarette smoke-induced murine models of COPD, treatment with either intra-tracheally delivered RC kinase siRNA or orally administered novel and specific small molecule inhibitors caused a significant reduction in BAL neutrophilia, as well as decreased levels of KC and CCL-20. There was also a marked reduction in the amount of pulmonary inflammation. In a murine adoptive transfer model of idiopathic pulmonary fibrosis, both siRNA and small molecule antagonist treatment significantly inhibited hydroxyproline production, inflammation and cellular and biochemical markers of fibrosis. Taken together, these results strongly suggest that inhibition of RC kinase may provide a novel therapeutic approach for the treatment of COPD and IPF.