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Role for fibroblasts in the chronic immune response in COPD

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Chronic Obstructive Lung Disease (COPD) is caused by loss of the walls of air sacs and by narrowing of the airways due to scarring. Currently, there are no effective therapies to treat COPD. While the loss of alveoli is unlikely to be reversible, the narrowing of the airways represents a possible therapeutic target.

TGF-β is a potent molecule that causes scarring and there is ample evidence that it plays a role in airway wall narrowing. However, TGF- β must be made active before it can function. Our published and preliminary data suggest that in COPD, enhanced TGF- β activation is cause by molecules, called integrins, located on the surface of airway cell types. Our published studies demonstrate that integrin-mediated TGF- β activation in airway cell types correlates with worsening airway obstruction. Our pilot experiments using genetic deletion of a particular integrin, α v β 8 blocks airway inflammation and fibrosis in a mouse COPD model. This data suggests that the integrin α v β 8 might be novel therapeutic targets in COPD.

The roles of the various airway cell types (i.e. epithelium, immune cells and fibroblasts) that are implicated in airway narrowing in COPD are not completely understood. Our work proposed here is the first to directly implicate the fibroblast in contributing to the abnormal persistent inflammatory response that characterizes COPD. We propose experiments that characterize the mechanisms involved in fibroblast regulation of pathologic inflammation. This work identifies several unique targets to block both inflammation and fibrosis in COPD.

This new work represents three entirely new directions for our laboratory 1) developing mouse models of airway disease; 2) studying pathologic immunity; 3) studying the in vivo effects of tobacco smoke. The successful completion of the proposed experiments will allow our laboratory to establish the facility, methodology and expertise to study tobacco related lung disease in mice. In this proposal we test the hypothesis that the integrin α v β 8 contributes pathologic inflammation and fibrosis in airway remodeling in COPD.We will use genetic deletion models combined with the use of biospecimens to maximize the application of our findings to human COPD. The successful completion of this project will be a crucial translation step in establishing the role and mechanism of integrin-mediated TGF- β activation in small airways disease in COPD