

**LTRC Concept Sheet # 07-02-0001**

**p120 Catenin and ABCA7 in COPD**

**ABSTRACT**

Apoptotic cell removal (termed efferocytosis) is a pivotal factor in the maintenance of homeostasis in the lung, as well as the organism as a whole. Efferocytosis removes cells before they become necrotic and pro-inflammatory, and it initiates anti-inflammatory, anti-protease and pro-growth responses that may be crucial to dampening inflammation, preventing collateral damage and repairing tissues. A growing list of systemic and lung-specific chronic inflammatory diseases have been associated with impaired efferocytosis, including cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD), suggesting a role in the pathogenesis of these diseases and potentially a novel therapeutic target.

Professional phagocytes, such as macrophages, are classically considered to be the main drivers of apoptotic cell removal. Yet, most cell-types have the capacity to ingest apoptotic cells, and many of these cells, such as the retinal and mammary gland epithelium, have the capacity to switch from “non-professional” to “professional” phagocytes in response to regulatory signals and to voraciously ingest apoptotic cells.

Previously, we, and others demonstrated that airway epithelium has the capacity to remove apoptotic cells in vitro to a degree similar to the alveolar macrophage, and that this process can be disrupted by loss of functional cystic fibrosis transmembrane regulator (CFTR) and activation of the Rho GTPase, RhoA. Recent data further suggests that airway epithelium removes apoptotic cells (or their bead surrogates) in vivo, and that proteins in the adherens junctions regulate this process.

P120 catenin is a member of a subfamily of Armadillo repeat domain proteins, like  $\beta$ -catenin, that is involved in intercellular adhesion at the adherens junctions. P120 catenin has emerged as a master regulator of cadherin stability, and an important modulator of RhoGTPase activities, NF $\kappa$ B activity, and a regulator of Tcf-targeted gene transcription. Interestingly, p120 Catenin was also first identified as a phosphorylation target of src and has been shown to correlate with malignant transformation in the gut and lung.

We hypothesize that expression of p120 catenin will be decreased in the airway and alveolar epithelium of patients with COPD and that this will result in increased epithelial cell activity of RhoA, a negative regulator of efferocytosis. Ultimately, decreased p120 catenin could lead to enhanced inflammation, tissue destruction and malignant transformation.

ABCA7 is an ATP-binding cassette protein that is highly expressed in the lung and as recently been shown to contribute to apoptotic cell phagocytosis in the lung. We have recently found that cigarette smoke decreases efferocytosis in mouse lungs and decreases ABCA7 expression. Therefore we hypothesize that ABCA7 expression will be decreased in the airway/alveolar epithelium and the alveolar macrophages of patients with COPD.

To test these hypothesis we propose to measure levels of p120 catenin and ABCA7 in lung tissues using immunohistochemistry and western blotting in COPD patients with FEV1 of <50%, 50-80% and >80%, compared to control idiopathic pulmonary fibrosis patients with an FVC >80%. We will perform these analyses on formalin-fixed, slide-mounted tissue and on flash-frozen tissue by western blot, using de-identified specimen collected by the Lung Tissue Research Consortium.