

LTRC Concept Sheet # 07-02-0002

Rho GTPases 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.

The Rho GTPases, Rac-1 and RhoA, are the primary regulators of efferocytosis, in that Rac-1 stimulates and RhoA inhibits the process. We and others (Chiba Y et al.) have demonstrated that RhoA activity is increased in mice and rats following exposure to cigarette smoke, and that this correlates with impaired apoptotic cell clearance. Therefore, we hypothesize that RhoA protein and activity levels are increased in COPD patients and that this contributes to the pathogenesis of disease.

To test this hypothesis we propose to measure levels of total RhoA and active RhoA 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.