

LTRC Concept Sheet # 06-02-0001

Arginase Activity in COPD

ABSTRACT:

It has been shown that macrophages are a major contributor to the inflammation found in COPD. Studies by Oflue and Ko 2002 have shown that macrophage depletion prevented cigarette smoke induce emphysema. Further recent work by Morris et al 2004, and Shapiro 2002 et al with $\alpha v\beta 6$, and MMP-12 knockout mice have shown the critical role of the macrophage in initiating the process of inflammation, maintaining lung homeostasis, and repair. Similarly, Hodges et al 2002 have shown that there is lack of appropriate clearance of apoptotic cells (efferocytosis), by macrophages, and that this leads to the persistence of chronic airway inflammation.

Alternatively activated macrophages (AAM) have been implicated in multiple lung diseases including fibrosing lung diseases, and asthma. They have also been implicated as tumor associated macrophages, and found in relationship to many adenocarcinoma tumors. The principle products of AAM release, including RELM- β and CCL-18 are linked to airway hyper-reactivity, and fibrosis. To this end we have investigated the presence of AAM in samples of COPD tissue, by measuring arginase I (Proc Am Thorac Soc. 2006 Aug;3(6):546b-547), RELM- β , and CCL-18, by activity assay, immunoblot, RT-PCR, and immunohistochemistry (IHC). We have found the presence of alternatively activated macrophage markers in COPD tissue, as well as positive staining of macrophages by IHC. We have further found that there is impaired efferocytosis in IL-4, or IL-4+TGF- β stimulated macrophages, and this points to the likely role of airway AAM's in promoting localized inflammation.

We hypothesize that the presence of AAM's in COPD may contribute significantly to the process of small airway fibrosis, airway hyper-reactivity, and may eventually lead to tumor development. To this end we hypothesize that AAM's and their markers are present increasingly in later stages of COPD, and may provide markers of disease severity.