

LTRC Concept Sheet #08-99-0029

The Role of Granzyme A and B in COPD

ABSTRACT

HYPOTHESIS: GRANZYME A AN B PLAYS A MAJOR ROLE IN THE PROGRESSION OF COPD

SPECIFIC AIM: 1) characterization of GrB and GrA protein expression in specific lung tissues and plasma using enzyme-linked immunosorbent assay (ELISA) and immunohistochemistry across different severity of COPD

RATIONALE: GrB is a serine protease that is expressed by CD4+/CD25+ and CD8+ T-cells, natural killer cells, macrophages and mast cells. GrB is released into the space adjacent to the target cell. Perforin is required for GrB release and entry into the cytosol of the target cell. Upon entry into the cytosol, GrB-mediated substrate proteolysis ensues resulting in the initiation and execution of apoptosis. Additionally, GrB is capable of cleaving extracellular matrix proteins. *In vitro* assays indicate GrB can cleave ECM proteins such as fibronectin, vitronectin, laminin and aggrecan. Of particular interest is possible GrB cleavage of elastic fibres, a key ECM component whose degradation is linked to aging, atherosclerosis and COPD. Thus, we hypothesize that accumulation of GrB in the extracellular milieu during chronic inflammation in COPD could contribute to matrix degradation and remodeling, leading to emphysematous changes in the lung.