

LTRC Concept Sheet # 07-02-0003

Selected Peptidases and Pulmonary Vascular Remodeling In Chronic Obstructive Pulmonary Disease

ABSTRACT

Purpose: An elevation in pressure within blood vessels in the lung in response to low levels of oxygen (known as chronic hypoxic pulmonary hypertension [PHTN]) complicates many lung disorders, like chronic obstructive pulmonary disease (COPD). Abnormal structural change in the blood vessels of the lung (also known as pulmonary vascular remodeling) is a major contributor to the severity of the hypertension. In COPD, cigarette smoke, oxidant stress, inflammation, and hypoxia cause pulmonary vascular remodeling. These same factors may decrease activity or expression of selected vascular cell surface enzymes, called peptidases. Studies with mice suggest that one of these enzymes (called Neprilysin or NEP) may protect the lung vasculature from pulmonary vascular remodeling in response to chronic hypoxia. However, the importance of NEP versus other peptidases in human pulmonary vascular disease is unknown.

Hypothesis: NEP activity and/or expression is selectively reduced (vs other relevant peptidases, like dipeptidyl peptidase IV [DPPIV]) in de-identified lung tissue from patients with COPD compared to 'control' samples.

Approach: De-identified lysates and fixed sections are prepared from 'control' lung samples and those from patients with COPD who have undergone lung tumor/nodule resection, biopsy, transplant, or lung volume reduction surgery. Sections are blindly scored for extent of vascular remodeling and emphysema. Relevant peptidase activity and expression are measured by assays of enzymatic activity and western and immunohistochemical analyses.

Significance: If the hypothesis is correct, these studies would support the idea that levels of selected peptidases present in the lung may determine, at least in part, the severity of pulmonary vascular remodeling and hypertension observed in chronic lung conditions, like COPD. Levels of these peptidases in lung could be therapeutically manipulated to protect against the development of pulmonary vascular remodeling and hypertension.