

LTRC Concept Sheet # 07-99-0001

Role of RTP801 and NRF-2 in Cigarette  
Smoke-Induced Emphysema

Abstract: Given the importance of the alveolar structural maintenance program and the increased prevalence of COPD in older smokers, we proposed that alveolar destruction in emphysema might be related to organismal aging, which would reset the organ's threshold to injury by cigarette smoke or pollutants. The accumulation of lung cellular injuries would then trigger oxidative stress, inflammation, and excessive extracellular matrix proteolysis, which have been also linked to age-dependent organ damage. This proposal seeks to validate this overall paradigm with human lung tissue studies aimed at the cellular stress response genes NRF-2 and RTP801 in cigarette smoke-induced inflammation, alveolar cell apoptosis, and emphysema. Specifically, *RTP801 functions as a sensor of cellular stress, causing cell growth arrest, as means to increase the chances of cellular survival. Oxidative stress, largely dependent on the activity of the master anti-oxidant transcription factor NRF-2, is critically involved in the upregulation and pathological effects of RTP801. Indeed, in situations of cellular stress such as due to exposure to cigarette smoke, RTP801 signaling may cause cellular damage and inflammation, and most importantly by oxidative stress.* The aims of the present proposal are to provide evidence that abnormalities in the RTP801/, NRF-2, and mTOR signaling pathways are present in the smoker's lungs with or without emphysema, when compared with non-smoker controls. Smokers will include lung samples from patients with a positive cigarette smoke history but no or minimal COPD (Gold 0 and 1). These groups will be compared with a large number of samples of patients with advanced emphysema already banked in our lab, who show upregulation of RTP801 expression when compared with normal lungs.