

LTRC Concept Sheet # 08-99-0007

**Chemokine/Chemokine Receptor Expression by Airway Epithelial Cells in COPD**

**ABSTRACT**

Cigarette smoking which exposes the lung to high concentrations of reactive oxidant species (ROS) is the major risk factor for chronic obstructive pulmonary disease (COPD). Recent studies indicate that ROS interfere with protein folding in the endoplasmic reticulum and elicit a compensatory response termed the "unfolded protein response". The importance of the UPR lies in its ability to alter expression of a variety of genes involved in anti-oxidant defense, inflammation, energy metabolism, protein synthesis, apoptosis and cell cycle regulation. We recently demonstrated that chronic cigarette smoking induces an "unfolded protein response" (UPR) in the human lung using comparative proteomic technology [Kelsen et al. *Am J. Respir. Cell Mol. Biol.* Dec. 13, 2007, **epublication ahead of print**].

Studies were performed on lung tissue samples obtained from three groups of human subjects: non-smokers, chronic cigarette-smokers and ex-smokers. Proteomes of lung samples from chronic cigarette smokers demonstrated 26 differently expressed proteins (20 were up-regulated, 5 were down regulated and 1 was detected only in the smoking group) compared to non-smokers. Several UPR proteins were up-regulated in smokers compared to non-smokers and ex-smokers including the chaperones, glucose-regulated protein 78 [GRP78] and calreticulin; a foldase, protein disulfide isomerase [PDI]; and enzymes involved in anti-oxidant defense. In cultured human airway epithelial cells, GRP78 and the UPR-regulated basic leucine zipper, transcription factors, ATF4 and Nrf2, which enhance expression of important anti-oxidant genes, increased rapidly (<24 hrs) with cigarette smoke extract. These data indicate that cigarette smoke induces a UPR response in the human lung which is rapid in onset, concentration dependent and at least partially reversible with smoking cessation.

We speculate that activation of a UPR by cigarette smoke may protect the lung from oxidant injury and the development of COPD. Accordingly, we believe that the UPR may be a susceptibility factor for the development of COPD and hypothesize that smoking subjects with severe COPD fail to mount a UPR.