

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.

## **ABSTRACT [Addendum]**

An additional aim of our project is to examine chemokine and chemokine receptor expression in subjects with COPD. Chemokine receptors control several fundamental cellular processes in both hematopoietic and structural cells including directed cell movement i.e., chemotaxis; cell differentiation; and proliferation. We have recently demonstrated that CXCR3, the chemokine receptor expressed by Th1/Tc1 inflammatory cells in the lung, is also highly expressed by structural cells in the human lung, i.e., airway epithelial cells and alveolar type II pneumocytes [1-4]. In both types of lung epithelial cells, activation of CXCR3 by its cognate ligands, the interferon- $\gamma$ -inducible chemokines, I-TAC/CXCL11, IP-10/CXCL10, and Mig/CXCL9, induces airway epithelial cell movement and proliferation, processes which underlie lung repair. Accordingly, expression of CXCR3 by airway and alveolar epithelial cells may be important to lung tissue homeostasis in the setting of COPD in which cell apoptosis and tissue remodeling are important in the pathogenesis of this disease.

Previous studies have demonstrated that IP-10 expression by human airway epithelial cells is increased in the small airways of subjects with COPD [5, 6]. However, the effect of over-expression of IP-10 on expression of its receptor by structural cells is unstudied. This study will examine CXCR3 expression by airway and alveolar epithelial cells and its correlation with IP-10 expression in subjects with a range of COPD severity. We will test the hypothesis that expression of CXCR3 by airway and alveolar epithelial cells is diminished in COPD in proportion to expression of IP-10 and the severity of airflow obstruction. Studies will be performed using airway epithelial cells and alveolar pneumocytes obtained by laser capture microdissection, and whole lung lysates. Expression of CXCR3 and IP-10 will be assessed at the message level using Taqman real time RT-PCR and at the protein level by Western blotting.

## **REFERENCES**

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