

**LTRC Concept Sheet # 08-99-0018**

**Expression of Regulators of Mucous cell Hyperplasia in Chronic Bronchitis**

**ABSTRACT**

Exposure to cigarette smoke (CS) increases the risk of developing chronic bronchitis, a disease associated with an increased number of mucus-producing cells in the small airways. These mucous cells can suddenly release vast quantities of mucus and obstruct the airways and contribute to cough and phlegm production that is the hallmark of chronic bronchitis. Our studies in animal models of asthma and chronic bronchitis suggest that the mechanisms to remove excess numbers of mucous cells are dysfunctional in individuals with chronic conditions that are associated with mucous hypersecretion. When screening for regulators of this removal process we identified Bcl-2 being expressed in metaplastic mucous cells. Furthermore, screening for cell death inducers showed that Bik, a pro-apoptotic Bcl-2 family member, is an important mediator of interferon gamma (IFN $\gamma$ )-induced apoptosis in airway epithelial cells. We found that a higher percentage of Bcl-2-positive cells are present in airways of smokers and that Bik mRNA levels are reduced in airway epithelial cells obtained by bronchial brushings from 11 subjects with chronic bronchitis compared to those from 11 controls. Suppressing Bcl-2 expression using antisense oligonucleotides caused reduction of inflammation-induced mucous cell metaplasia in rats. Furthermore, Bik mRNA levels were decreased in cultured primary airway epithelial cells from 5 independent donors that were exposed to CS. Exposure of primary human airway epithelial cells to CS increases the numbers of mucous cells but this increase was reversed by ectopic expression of Bik, further supporting the importance of Bik. Another regulator of CS-induced mucous cell metaplasia was found to be the GABA-receptor. To further investigate whether cigarette smoking alone or susceptibility to developing chronic bronchitis causes change in expression in these regulators, I am requesting formalin-fixed, paraffin-embedded lung tissues. In this study, I would like to compare lung tissues from never-smokers, current smokers with and without chronic bronchitis, and former smokers with and without chronic bronchitis. I would prefer to analyze lung tissues showing increased numbers of mucous cells in small airways of the lung. Expression will be monitored by carrying out quantitative real-time polymerase chain reaction (qRT-PCR) and immunohistochemistry.