

LTRC Concept Sheet #08-99-0034  
PLAGL2 Expression in Emphysema

**ABSTRACT**

Pleomorphic Adenoma Gene Like-2 (PLAGL2) was identified as a transactivator of surfactant protein C (SP-C). In an attempt to examine the effect of PLAGL2 expression on SP-C production *in vivo*, an inducible, a lung specific PLAGL2 transgenic mouse model was developed. Lungs from transgenic mice developed an accelerated form of centrilobular emphysema following doxycycline (Dox) induction of PLAGL2 expression in type II and bronchiolar epithelial cells. This phenotype occurred in multiple mouse founders with varying PLAGL2 gene copies, indicating little contribution from integration sites or transgene copy numbers. Airway inflammation involving macrophages, neutrophils, and CD8 lymphocytes that frequently accompanies the development of COPD in humans did not appear in this PLAGL2 transgenic mouse model. Female mice displayed a higher incidence of emphysema, suggesting that this mouse model of centrilobular emphysema might mimic recent data demonstrating an increased prevalence of chronic obstructive pulmonary disease (COPD) among women. The initial characterization of this mouse model demonstrated that both PLAGL2 and SP-C expression were upregulated in distal airway epithelial cells in the induced mouse lung. **The hypothesis of this study is that PLAGL2, which may play a role in surfactant protein homeostasis, is capable of initiating centrilobular emphysema in humans.**

This hypothesis will be tested with the supply of patient samples from LTRC. PLAGL2, TTF-1, SP-B and SP-C expression will be examined on immunohistochemistry (IHC) staining of formalin fixed and HOPE fixed tissue sections from patients with clinically identified emphysema. Relative expression levels of these genes will be evaluated using real-time PCR analysis of transcripts isolated from the tissue samples (RNA Later) or from the section samples collected within the emphysema lesion by laser capture microdissection (LCM) technique. The correlation of PLAGL2 expression and disease severity categorized by the FEV 1% predicted function (>80%, 50 – 80%, or < 50%) will be assessed and determined by scoring the cell counts from the IHC staining and measuring the gene expression value from the quantitative RT-PCR analysis. The other genes will also be evaluated and used as references for comparison. The final index of PLAGL2 expression in each lung sample will be the average of indices generated by two investigators, who will examine the slides independently unaware of clinicopathological data at the time of slide examination. Given that long term lung specific expression of PLAGL2 results in centrilobular emphysema in mice, and data suggesting that PLAGL2 may either directly induce apoptosis or cause cytotoxic changes from overproduction of misprocessed SP-C, the probability that PLAGL2 plays a role in emphysema in humans is substantial.