

## LTRC Concept Sheet # 08-99-0009

**Abnormality in Gene Expression of Key Mediators of Vitamin A Action in COPD****ABSTRACT**

Chronic bronchitis and emphysema are two types of chronic obstructive pulmonary disease (COPD), which are important causes of morbidity and mortality in the United States. Death rates from COPD are higher among cigarette smokers. Numerous findings suggest a possible association of vitamin A nutritional status and COPD and lifetime cigarette smoking. Vitamin A and its active metabolite retinoic acid (RA) are important for growth and differentiation of tissues. Considerable evidence demonstrates that RA is an essential signaling molecule for normal lung development. Retinoid signaling elements, such as receptors and binding proteins have been described in the adult lung. Recently, several studies have shown that RA is effective in promoting alveolization in elastase-induced emphysema in adult rats.

We have used guinea pigs subjected to forced smoking as a model system to induce emphysema. This experimental model is associated with an accumulation of retinol (combined retinol and its ester) and a decrease in lung retinoic acid (RA) content. Further, protein levels of some of the key mediators of vitamin A action (RAR<sub>1</sub>, CRABP-I, CRABP-II, CRBP-I and CYP26A1), and mRNA levels of CRBP-I, CRABP-I and RAR<sub>1</sub> are decreased. CRBP-I, RAR<sub>2</sub> and CYP26A1 are directly induced by RA. We postulate that in some types of COPD, there is an abnormality in the expression of genes for some of the key mediators of vitamin A action.

The objective of the proposed study is to test the above hypothesis by establishing a relationship between the severity of emphysema and levels of expression of the above referred genes as well as LRAT, the enzyme that catalyses the bulk of retinol esterification in the body, and STRA 6, recently shown to be responsible for internalization of retinol by the cell. Both are directly induced by RA as well. Because of the existence of several RAR<sub>1</sub> isoforms, we also will analyze the RAR<sub>1</sub> subtypes, particularly RAR<sub>2</sub> since its expression inversely correlates with lung cancer development associated with COPD. Furthermore, RAR<sub>1</sub>-promoter regions will be analyzed for changes in methylation patterns known to result in the silencing of the RAR<sub>1</sub> gene in certain human cancers.

Fixed and frozen lung tissues from COPD patients with mild, moderate and severe emphysema as well as normal individuals will be obtained from the Lung Tissue Research Consortium (LTRC). We have developed all of the tools required for this study, including immunohistochemistry, Western blot analysis, and Real-Time PCR.

If successful in establishing that there is a relationship between expression of the genes of the mediators of vitamin A action and COPD, it will help us in designing potentially therapeutic drugs targeting some of these genes.