

LTRC Concept Sheet # 07-99-0008

Evaluation of MicroRNA Expression Patterns in COPD

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, affecting over 16 million people. This disease is reaching worldwide epidemic proportions and its incidence is rising, particularly in women. More than 85% of COPD in the United States is due to smoking tobacco, and nearly one-quarter of Americans continue to smoke. COPD is a group of diseases that includes chronic bronchitis and emphysema and the severity of disease may be classified by the GOLD criteria. COPD is recognized as a heterogeneous disease and thus, survival of patients with disease is variable. In addition to tobacco cessation, personalizing our approach to COPD through early detection, advancing understanding of biologically distinct types of disease, and identification of new targets for treatment will be important to improving overall survival.

MicroRNAs (MiRNAs or mirs) are a family of small noncoding RNAs (approximately 21-25 nt long) expressed in many organisms including animals, plants, and viruses. MiRNAs are integral to gene regulation, apoptosis, hematopoietic development and the maintenance of cell differentiation. Researchers identified abnormal expression of miRNAs in several types of malignancies including: chronic lymphocytic leukemia (CLL), colorectal neoplasia, Burkett's lymphoma, large cell lymphoma, glioblastoma, breast cancer, lung cancer, and hepatocellular carcinoma. Our knowledge of miRNA expression patterns and biological relevance in diseases other than cancer is minimal. In fact, we are not able to find any published reports investigating miRNAs in COPD.

In the proposed study, we hypothesize that distinct expression patterns of miRNAs exist in COPD. Such patterns may prove useful in increasing our understanding of molecular heterogeneity within this disease and in identifying biological pathways that may be relevant to disease pathogenesis. We will compare lung tissue from subjects with GOLD stage I, II, and III disease to smokers without disease and never smokers. We propose to use Lung Tissue Research Consortium tissue samples and their clinical correlates in this investigation. This pilot study would involve ten samples in each of the GOLD stages, five samples from smokers without disease, and five samples from nonsmokers. Our initial evaluation would be complimented by the use of in situ hybridization, to localize key miRNAs and both immunohistochemistry and protein expression of select biological targets. Secondly, through a series of in vitro and in vivo study, we propose to study a panel of miRNAs and determine their biological function in the development of COPD. We believe that select miRNAs that are biologically relevant to COPD may then be applied as biomarkers in less invasive studies such as sputum or peripheral blood.