Research: Tobacco Carcinogen-Induced Transformation of Human Bronchial Epithelial Cells is Associated with Chromatin-Mediated Reprogramming of the Genome

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Disease/Condition: Lung Cancer

Lung cancer, associated with tobacco use, may soon become the leading cause of cancer-related death worldwide due to the advanced stage at detection and the ineffectiveness of chemotherapy to achieve long-term remission. To reduce mortality from lung cancer will require early detection, more effective therapeutic approaches, and the development of primary and secondary prevention approaches. Investigations using malignant tumors and premalignant lesions of lung cancers have provided insight into some of the genes and cellular pathways that contribute to the development of lung cancer. These studies have established a link between exposure to carcinogens in tobacco smoke with changes in gene expression and changes in DNA structure associated with gene silencing (DNA methylation).

Researchers at LRRI have developed a tobacco carcinogen premalignancy model using normal lung cells. The induction of premalignant changes includes the growth pattern of the cells (change in cell shape), increased growth rate, and genes turned off or on, allowing the cells to grow aggressively like cancer cells. Many of the genes silenced during the initiation of lung cancer are silenced by DNA methylation. The model has allowed LRRI scientists to systematically assess the role of individual genes silenced in the development of lung cancer; and use genes silenced by DNA methylation as a diagnostic test for the early detection of lung cancer. These studies could greatly enhance lung cancer diagnosis by identifying a biomarker panel of methylated genes that can detect individuals with preclinical lung cancer, or those at high risk for developing lung cancer who might benefit from increased lung cancer screening. This would ultimately lead to earlier lung cancer diagnosis, improved survival, and new molecular targets for intervention and prevention.

The results of this study help determine the timing of gene silencing to provide additional knowledge of the molecular origins of lung cancer. Most importantly, these findings can identify biomarkers for early detection of lung cancer.