Researchers discover new approach for identifying smokers at highest risk for developing lung cancer

April 7 2010

Researchers from Boston University School of Medicine (BUSM) in collaboration with investigators at the University of Utah, have discovered a new approach for identifying smokers at the highest risk for developing lung cancer. The findings, which appear in the April 7th issue of *Science Translational Medicine*, will allow the researchers to use a genomic approach to prevent lung cancer in these individuals and to personalize cancer chemoprophylaxis and therapy.

Cigarette smoke is the dominant cause of lung cancer in the United States, accounting for an estimated 90 percent of all cases. While only 10-20 percent of smokers develop lung cancer in their lifetime, there are currently no tools available to identify which of the approximately 90 million current and former smokers in the U.S. are at the highest risk. Unfortunately, diagnosis is most often made at a very advanced stage where treatment is largely ineffective. The damage caused by cigarette smoke, however, is not limited solely to the lung, but rather constitutes a 'field of injury' throughout the entire respiratory tract that is exposed to the toxin. Consistent with this idea, study lead author Avrum Spira, MD, MSc, chief of the section of computational biomedicine in the department of medicine at BUSM and his colleagues, previously developed a gene expression-based biomarker measured in the cytologically normal bronchial airway epithelium that reflects an individual's physiologic response to smoking and distinguishes smokers with and without lung cancer. Although this biomarker is successful at

diagnosing lung cancer, it does not identify the signaling pathways underlying these gene expression changes.

Using a novel gene-expression based approach to define oncogenic pathway signatures, the researchers, in collaboration with Dr. Andrea Bild at the University of Utah, have now discovered that the expression of genes belonging to one specific cancer-related pathway, PI3K, are activated in the cells that line the airway of smokers with lung cancer. This gene expression activity in the normal cells of the proximal airway precedes the development of lung cancer and may be reversed with a specific chemopreventive agent (myo-inositol) that targets this pathway.

"This finding is significant as these cells can be obtained in a relatively non-invasive fashion from the airway of smokers at risk for lung cancer, and does not require invasive sampling of lung tissue where lung tumors normally arise," said Spira, who is also an associate professor medicine and pathology at BUSM.

The BUSM researchers then went on to validate their findings by measuring the biochemical activity of this pathway in the airway epithelial cells from an independent group of smokers with and without lung cancer. "We found that this PI3K pathway gene expression activity is decreased in the airway of high-risk smokers who had regression (or improvement) of their premalignant lesions following treatment with a potential lung cancer chemopreventive agent known as myo-inositol, and demonstrated that myo-inositol inhibits the PI3K pathway in lung cancer cell lines," he added.

According to the researchers, the data suggests that measuring this airway gene expression activity can help determine which specific cancer pathways have been deregulated within an individual smoker, allowing one to tailor a specific drug that will target the pathway to reduce that individual's risk of lung cancer. "This represents a critical

advance in the field of lung cancer prevention as there are currently no effective strategies for lung cancer prevention among high risk smokers. Our work has the potential to help address the enormous and growing public health burden associated with lung cancer, the leading cause of cancer-related death among men and women in the US and the world," added Spira.

Provided by Boston University Medical Center