The Airway Battlefield: Implications for lung cancer and COPD

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Recent advances in the fields of airway genomics and transcriptomics offer potential new approaches for personalizing the management of COPD and lung cancer. Based on the concept that cigarette smoke creates a molecular “field of injury” throughout the epithelial cells that line the respiratory tract, this presentation will describe how airway gene-expression can be used for early lung cancer detection and for guiding therapeutic strategies in COPD patients.

Our group and others have characterized the reversible and permanent impact of tobacco smoke on gene-expression and microRNA profiles in the epithelial cells that line the bronchial airway1-2. Importantly, our group demonstrated that heterogeneity in the transcriptomic response to smoking can be leveraged to develop a gene-expression signature in the cytologically-normal bronchial epithelium that can detect the presence of lung cancer among smokers undergoing bronchoscopy for suspect disease4. Our gene-expression biomarker has high sensitivity and negative predictive value for lung cancer when combined with the routine cytology collected at bronchoscopy. As the next step towards moving into the clinic, this lung cancer biomarker is being validated in two prospective multi-center clinical trials of smokers undergoing bronchoscopy for suspect lung cancer. In the first trial, the biomarker has been reported to have high sensitivity for diagnosing lung cancer among smokers whose bronchoscopy was nondiagnostic, which could help spare smokers without lung cancer from undergoing unnecessary invasive diagnostic procedures5. We are also expanding these studies to identify airway microRNA expression alterations that may regulate these cancer-specific gene-expression alterations and potentially serve as novel therapeutic targets6.

We have recently extended this “field of injury” paradigm to COPD, developing a gene-expression signature in the bronchial airway epithelium of smokers that associates with COPD and airflow obstruction7. These gene-expression alterations were similar to alterations in the small-airway epithelium and lung parenchyma of individuals with COPD, suggesting that transcriptomic alterations in the proximal airway epithelium reflect molecular events found at more distal sites of disease activity. We further demonstrate the dynamic nature of this “field of injury” by showing the reversal of these COPD-associated alterations with inhaled corticosteroids. Importantly, we found that the gene-expression alterations in the airway in response to corticosteroids, in an independent cohort, are associated with improvement in lung function and respiratory symptoms8. These data suggest that gene expression profiling of relatively accessible bronchial airway epithelium may serve as a surrogate biomarker of disease activity and may ultimately yield markers of molecular subtypes, prognosis and response to therapy.

We are currently in the process of moving these disease-associated airway gene-expression signatures to more accessible epithelial cells that we can obtain from the nasal epithelium. We have demonstrated that the nasal gene-expression response to smoking is similar to that seen in matched bronchial airway samples, suggesting the potential for nasal gene-expression to serve as a surrogate for the molecular changes that occur more deeply within the airway9. This would allow for less invasive biomarkers that could be developed in population-based studies for measuring the physiological response to inhaled environmental exposures as well as personalizing approaches to the management of COPD and lung cancer.
Bibliography


