against advanced lung cancer, molecular targets are being explored. An emerging molecular target for lung cancer is the signaling molecule Akt as it is frequently activated in lung cancer. Akt is activated by a number of growth factor receptors and mediates processes such as proliferation, survival, migration, and metabolism. Three Akt isoforms (Akt1-3) exist in mammals and it remains unclear whether each isoform has distinct functions. To evaluate the function of Akt isoforms in lung cancer, a transgenic mouse model (SPC-IGFIR) where lung tumors were induced by elevated expression of IGF-IR and subsequent activation of Akt was used. SPC-IGFIR mice were mated with Akt1 -/- or Akt2 -/- mice to produce SPC-IGFIR mice lacking either Akt1 or Akt2. Lung tumorogenesis was suppressed in SPC-IGFIR/Akt1 -/- mice and enhanced in SPC-IGFIR/Akt2 -/- mice. Lung tumor cells in SPC-IGFIR/Akt2 -/- mice appeared to infiltrate the lungs to a greater extend than either SPC-IGFIR or SPC-IGFIR/Akt1 -/- tumor cells which had a more nodular appearance. RNA sequencing revealed a number of genes and transcripts differentially expressed in the SPC-IGFIR/Akt2 -/- mouse compared to SPC-IGFIR/Akt1 -/- mice. A total of 11 patient cohorts were created based on combination of cancer histology and smoking history. An emerging molecular target for lung cancer is the signaling molecule Akt as it is frequently explored. An emerging molecular target for lung cancer is the signaling molecule Akt as it is frequently activated in lung cancer. Akt is activated by a number of growth factor receptors and mediates processes such as proliferation, survival, migration, and metabolism. Three Akt isoforms (Akt1-3) exist in mammals and it remains unclear whether each isoform has distinct functions. To evaluate the function of Akt isoforms in lung cancer, a transgenic mouse model (SPC-IGFIR) where lung tumors were induced by elevated expression of IGF-IR and subsequent activation of Akt was used. SPC-IGFIR mice were mated with Akt1 -/- or Akt2 -/- mice to produce SPC-IGFIR mice lacking either Akt1 or Akt2. Lung tumorogenesis was suppressed in SPC-IGFIR/Akt1 -/- mice and enhanced in SPC-IGFIR/Akt2 -/- mice. Lung tumor cells in SPC-IGFIR/Akt2 -/- mice appeared to infiltrate the lungs to a greater extend than either SPC-IGFIR or SPC-IGFIR/Akt1 -/- tumor cells which had a more nodular appearance. RNA sequencing revealed a number of genes and transcripts differentially expressed in the SPC-IGFIR/Akt2 -/- mouse compared to SPC-IGFIR/Akt1 -/- mice. A total of 11 patient cohorts were created based on combination of cancer histology and smoking history.

Purpose: Although long-term survival rates for early stage lung cancer are high, most patients are diagnosed with advanced stage disease. The National Lung Screening Trial demonstrated a survival benefit with annual low-dose chest CT (LDCT) in patients at high risk, despite a false positive rate of 96%. Most attempts at development of blood-based early detection for lung Cancer employ panels of several biomarkers, which are susceptible to overfitting and poor reproducibility on new samples. We hypothesized that a single biomarker-based approach would be more effective.

Methods: Whole blood was collected in PAXgene tubes from 289 patients under IRB-approved protocols at four institutions. This included 231 retrospective specimens and 58 specimens collected prospectively. We collected smoking history, cancer diagnosis, age and gender for all patients. Due to the use of a single marker and low risk of overfitting, the training set consisted of only 29 patients. The validation set consisted of 133 non-small cell lung cancer, 14 small cell lung cancer and 113 cancer-free patients. A total of 11 patient cohorts were created based on combination of cancer histology and smoking history. RNA was extracted, and the expression of formyl peptide receptor 1 (FPR1) and a reference gene were quantified by an automated one-step Taqman RT-PCR assay.

Results: In the validation set, elevated levels of FPR1 mRNA in whole blood demonstrated a sensitivity of 55% and a specificity of 87% for lung cancer detection. Among prospectively collected specimens, FPR1 mRNA had a sensitivity of 68% and specificity of 89%. The sensitivity of prospective samples was significantly higher than retrospective samples (p=0.018) while the specificity was unchanged. We observed that longer times between collection and refrigeration/freezing of samples tended to yield negative results. This time was much shorter on prospective samples, and this likely explains the increased sensitivity. No significant difference in sensitivity was observed based on histology (including small cell vs. non-small cell) or cancer stage. Results from patients with benign nodules were similar to healthy volunteers. We used multiple data mining techniques and found no meaningful relationship between our test results and any clinical characteristic other than lung cancer diagnosis, including age, smoking history, and gender.

Discussion: FPR1 mRNA levels in whole blood can identify the presence of lung cancer with high accuracy. A single-marker test is less prone to overfitting of data when compared to a multi-marker test created through complex data mining algorithms, and thus is more likely to be reproducible. The use of a training/validation set strategy further increases likelihood that results will be reproduced in follow-on studies. Using FPR1 as a reflex test for suspicious lung cancer screening CT scans may have the potential to increase the positive predictive value (PPV). Future planned studies will explore the source of this biomarker and evaluate its effectiveness in augmenting CT scans for patients undergoing lung cancer screening.

Whole blood FPR1 mRNA expression identifies both non-small cell and small cell lung cancer

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