IDENTIFICATION OF PROGNOSTIC BIOMARKERS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) USING A MULTIPLEX SOMAMER™ ASSAY

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD), a progressive lung disease is the 4th leading cause of death in the US. It is associated with history of smoking and is characterized by irreversible air flow obstruction. The prevalence of COPD in the US is 13 million and another 12 million go undiagnosed. COPD patients may have stable disease for many years or progress rapidly. A non-invasive blood test to identify who will progress will enable different treatment options for COPD.

Methods: A case-control study was performed on 304 samples that had been obtained at approximately one year intervals from each of 61 COPD patients (diagnosed by GOLD score) over a period of 8 years as part of a lung cancer CT screening study at UPMC. Subjects were classified as case (progressors, N=25) if the linear regression slope was negative (specifically, $< 0.005$ FEV1/year), and control (non-progressors, N=36) if the linear regression slope was stable or improving. Subjects were >50 years old, smokers or ex-smokers with 10 or more pack year smoking history and had FEV1 predicted between 110 and 85 at baseline. Eleven patients did not have COPD at baseline. Samples were assayed using a SOMAmer™ (a Soma-Off-rate Modified Aptamer)-based proteomic assay, which measured 1001 analytes. Key demographics and clinical parameters were balanced between the two groups. A candidate list of biomarkers were identified in the following ways:

1. Using KS-statistics to identify biomarkers associated with a decrease of lung function over time
2. Comparing progressors versus non-progressors within each subject to identify proteins at baseline that related to future rate of FEV1%, (lung function decline) over time and
3. Within each subject to discover the rate of change in the protein relative to the rate of change in lung function

A random forest algorithm was applied to the candidate list resulting in a binary classification model which was evaluated via 5x internal cross validation.

Results: A marker panel using baseline samples predicted the class - progressor vs. non-progressor - with a cross-validated AUC of 0.86. This model performed similarly when tested on samples from any other time point, even though those samples were not used for training. The model was also able to correctly identify subjects who did not have COPD at baseline. Several of the identified markers have been implicated in COPD and are biologically relevant and involved in roles such as innate immune responses, and leukocyte chemoattraction.

Conclusions: Unbiased proteomic discovery using a novel multiplexed platform has revealed novel biology in COPD and a proteomic classifier that predicts the progression of COPD. Further studies are needed to validate these early findings.

SOMAmer™ Proteomics Platform for Biomarker Discovery

From Protein to DNA: A Critical Transformation

Protein Chemoattraction

Chemoattractant for blood monocytes, memory T helper cells and eotaxin. Causes the release of histamine from basophils and activates eosinophils

Periphas (PSRN)

Directs neutrophilic activity on mesenchymal stromal and motor neurons

COPD Prognosis: Study Design

Alto: To determine whether there is a protein signature which predicts the future rate of decline in FEV1% in subjects with progressive COPD

Design: This was a nested case control study from University of Pittsburgh’s lung cancer screening study of 86 subjects in each group had COPD at baseline.

25 subjects with progressive COPD and 36 with stable COPD based on FEV1% with up to 6 time points each

Subjects in the two groups were matched for age and FEV1%.

61% of the subjects in each group had COPD at baseline.

Mean Pr(progression) / subject

COPD Prognosis: Results

Prognostic Model on Baseline

The model predicted decline even in subjects who did not have COPD at baseline

Mean (progression) by class

Relevant Biology of Markers

Protein (GeneID) | Direction of Change in Disease | Biological Significance
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Static acid-binding Ig-like lectin 7 (SALL7) | Up | Natural killer cell activation – response to infectious diseases
Insulin-like growth factor-binding protein-like 1 (IGFBP11) | Up | Senesence and in regulation of lung matrix composition
Lymphotactin (melin A-like 1) | Draw | Normal development of lymphoid tissue and also acts as an indicator of the inflammatory response
Small inducible cytokine A5 (CCL15) | Up | Chemotactant for blood monocytes, memory T-helper cells and eosinophils
Periphas (PSRN) | Draw | Directs neutrophilic activity on mesenchymal stromal and motor neurons

Conclusions

- Using the SOMAmer™ proteomic technology we have discovered prognostic markers of COPD
- A 6 marker protein signature identified patients with COPD whose lung function would decline in the future (6 years out)
- The model maintained its performance in cross-validation (results not shown) and on subsequent samples that it was not trained on
- Model predicts correctly patients who will develop COPD who did not have it at baseline
- Further validation of these biomarkers is warranted
- Potential Clinical Utility: A noninvasive blood test to predict future decline in airway function (FEV1%) in smokers or ex-smokers (>10 pack yrs) with or without COPD and aid pulmonologist in treatment decisions

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