European Respiratory Society
Annual Congress 2012

Title: Longitudinal analysis of airway epithelium of COPD subjects reveals unique inflammatory gene networks up-regulated over time

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Body: Introduction: The goal of this study was to determine temporal changes in regulatory gene networks in the small airway epithelium of subjects with COPD. Methods: Small airway epithelial (SAE) cells were collected at bronchoscopy from smokers with COPD (n=42), healthy nonsmokers (NS, n=30) and healthy smokers (HS, n=71). A subset of these subjects were subsequently sampled after 3 months (n=25 NS, n=11 HS, n=10 COPD). RNA from >95% pure populations of SAE was isolated and hybridized to Affymetrix microarrays. Weighted gene co-expression network analysis (WGCNA) was used to determine modules of correlated genes associated with clinical parameters at each timepoint, and temporal modules were compared to determine similarities. Functional categories were determined for modules using gene ontology analysis. Results: WGCNA yielded an immune signaling module (e.g. TLR signaling and inflammasome genes), correlated with decline in FEV1/FVC ratio (baseline: R=-0.28, p = 0.002; month 3: R=-0.57, p=0.007). There was a significantly high degree of overlap in the immune-signaling module generated at each timepoint (173 genes, p=0) indicating the robustness of expression of this module. Another module associated with smoke exposure included genes involved in oxidative stress response and metabolic pathways. Conclusions: Network analysis revealed a data-derived inflammation module associated with decline in lung function which is perturbed over time. This suggests that subtle induction of inflammatory signaling can be measured in the airway epithelium of COPD subjects in addition to pathways known to be induced by cigarette smoke exposure.