# Bronchial Epithelial Cell Transcriptomics: A Tool to Monitor and Predict Chronic Obstructive Pulmonary Disease Progression?

It is well known that chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. Globally, 300 to 400 million people live with COPD (1), which occurs because of smoking, household and ambient air pollution, and genetic predisposition (e.g., alpha-1 antitrypsin deficiency). COPD ranks as the fourth leading cause of death, resulting in up to 3 million deaths each year (2).

The airway epithelium in COPD is characterized by dysfunctional repair and remodeling (3). Structural modifications of the COPD epithelium include basal and goblet cell hyperplasia, squamous metaplasia, decreased apical junction barrier integrity, and epithelial shedding (4, 5). Dedifferentiation of the COPD epithelium as a result of abnormal regeneration mechanisms underpins the aberrant physical structure of the epithelium and its inappropriate immune response to inhaled particles and microbes. Coupled with epithelial cell activation by cigarette smoke (CS) and other inhaled irritants, this leads to chronic airway inflammation. Furthermore, cumulative airway epithelial damage is associated with extracellular matrix deposition and airway fibrosis (6). So, although much is known about many aspects of the COPD lung that drive disease progression, the exact pathophysiological processes that underpin progression of the disease remain incompletely understood.

In this issue of the *Journal*, Samaha and colleagues (pp. 441–452) attempt to address this gap using transcriptomic analysis of transbronchial biopsies from patients with COPD at different stages of the disease (7). They performed a prospective observational study based on a 3-year longitudinal Affymetrix gene chip analysis of transbronchial samples from 104 individuals with chronic bronchitis (CB) and 16 healthy control individuals, wherein they correlated gene expression with bronchial obstruction. The observed validated gene expression patterns identified 52 genes indicative of CB, 174 for Global Initiative for Chronic Obstructive Lung Disease (GOLD) I/II, and 268 for GOLD III/IV, with interesting subsets of genes showing similar expression patterns across the various groupings. An elaborate, classical, and well-executed bioinformatics analysis was performed on the various gene sets, and, overall, the complex and comprehensive data suggested that loss of surface integrity and decreased regenerative repair processes are implicated in COPD pathophysiology. The authors conclude from their data that the actin cytoskeleton is involved in the transition from CB to GOLD I and that subsequent disease progression steps involve decreased repair, increased bronchial inflammation, hyaluronidase-mediated destruction of the bronchial matrix, and, finally, matrix accumulation and organ fibrosis. This worthwhile study provides new data on *in vivo* transcriptional changes in transbronchial biopsies from patients with COPD over a 3-year period.

The interpretation that the actin cytoskeleton is involved in the transition from CB to GOLD I is supported by previous mechanistic studies that examined the effect of CS on the epithelial barrier. For example, Nishida and colleagues reported impaired integrity associated with increasing cell contractility and decreasing cell adhesion in COPD and CS-exposed epithelia. That work demonstrated increased actin polymerization as a functional event in the process (8).

Here, increased expression of KIAA1177/CEMIB, a major activator of matrix hyaluronidases, was evident from GOLD stage II and peaked at GOLD IV. When "change of gene expression as a function of deterioration" versus "improvement during GOLD development" was considered, KIAA1177/CEMIB was the only gene demonstrating a significant increase of expression in deteriorating COPD. This later disease progression step implicated by the transcriptomic and bioinformatics analyses has functional precedence in the published literature. Hyaluronic acid (HA) and its degradation products generated by the activity of hyaluronidase are known to play an important role in lung pathophysiology and airway remodeling in COPD. Acute exacerbations of COPD are associated with increased hyaluronidase activity in BAL fluid and subsequent degradation of HA, which may contribute to airway inflammation and lung function decline during exacerbations (9). Similar observations in animal models of COPD have also been reported (10), wherein an experimental CS exposure model of COPD showed enhanced deposition of HA fragments in alveolar and bronchial walls owing to altered expression of HA-modulating enzymes.

One of the major transcriptional signatures identified in this work was related to CB/GOLD I, where the intensity of bronchitis correlated with progressive downregulation of TMSB15A, D886, and NUDT11 genes. Upregulated transcripts associated with GOLD III (FGG [fibrinogen]) and bronchial inflammation (AHRR [aryl hydrocarbon receptor repressor] and KIAA1177/CEMI8) were also clearly discriminated.

Although the risk of COPD is strongly influenced by cigarette smoking, genetic factors are also important, and many genomic regions that influence COPD susceptibility have been identified in genome-wide association studies (11). Unusually, perhaps, of the transcripts of interest noted here, there was no overlap with 82 COPD susceptibility loci identified in a recent COPD genome-wide association study (12).

As the authors point out, it is worth mentioning that one limitation of the study is the small number of patients in some of the groups (e.g., GOLD IV, $n = 2$; GOLD I, $n = 9$). In addition, the longitudinal nature of the study led to the expectation that it might be possible to observe some patients transitioning through grades over the 3-year period; however, this was not the case, as the



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signatures remained quite stable over time, suggesting that it requires longer than 3 years to clearly detect a shift in gene expression. Although the bioinformatics analysis represents a powerful tool to link otherwise unrelated lists of genes, importantly, this data only bears weight when functionally validated and/or linked to other genes through gene ontology.

The use of transcriptomics coupled with bioinformatics to dissect COPD disease progression is novel. Longitudinal analysis of the changing transcriptome in bronchial epithelial cells (BECs) represents a powerful method to assist in understanding the steps involved in the progression of a healthy lung to a profoundly damaged one. This approach has the potential to reveal previously unrecognized molecules and networks involved in disease progression and for which new or repurposed therapeutics can be considered. The bronchial epithelium is the site where much of the damage happens in COPD, and this paper very nicely shows gene signatures associated with the development of COPD in BECs. For these reasons, the use of BECs, albeit requiring a more difficult sampling method, may be a better alternative to the use of peripheral blood cells as a tool to establish the incidence of COPD in presymptomatic stages before significant end organ damage, such as in Vrbica et al. (13). Yet, for this reason, it is also more difficult to use BEC signatures as a disease progression tool in the clinic. Nonetheless, this approach has identified interesting molecular signatures that could be useful for monitoring disease progression in patients with COPD. ■

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