Found in Translation: Multi-omics Assessment of the Chronic Obstructive Pulmonary Disease–Lung Cancer Interaction

Smoking is indisputably the major cause of chronic obstructive pulmonary disease (COPD) and lung cancer. However, COPD is independently associated with lung cancer risk, even after adjusting for smoking history, suggesting common pathologies beyond smoke exposure (1–4). Elucidating the key mechanisms linking the two diseases may lead to identification of modalities for lung cancer chemoprevention and the development of biomarkers to better ascertain lung cancer risk.

Although the study of mechanisms shared between COPD and lung cancer is evolving, several general theories are emerging. Hypotheses include genetic predisposition, enhanced oxidative stress and chronic inflammation, accelerated cellular aging, and extracellular matrix (ECM) pathology, among others. Genome-wide association studies have shown a handful of risk regions associated with both diseases (5, 6). Cigarette smoking leads to the accumulation of reactive oxygen and nitrogen species in the lung. COPD-associated airway and parenchymal damage, mucus alterations, mitochondrial dysfunction, and inflammation may enhance this accumulation, supporting an environment that cannot appropriately expel carcinogens or respond to damaged cells (7–10). The resultant oxidative stress leads to irreversible cellular and DNA damage, activating both inflammatory pathways that contribute to COPD-associated chronic inflammation and proliferative pathways that contribute to tumorigenesis and cancer progression (8, 10). Furthermore, the chronic inflammation that is a hallmark of COPD is increasingly recognized as a contributor to lung cancer pathogenesis, with immune checkpoint inhibitors transforming lung cancer therapeutics (11, 12). Both lung cancer and COPD also primarily affect an aging population. As this clinical observation suggests, accelerated cellular aging as a result of telomere shortening, oxidative stress-induced DNA damage, and arrested cell growth (senescence) is common to both of these diseases (13, 14).

Another potential area of COPD–cancer overlap is the stroma. The stroma is composed of ECM and connective tissue cells such as fibroblasts and mesenchymal stromal cells, and serves mainly to support the structural stability and functionality of tissues (15). The stroma and associated cells in the stromal and tumor microenvironment (e.g., immune and endothelial cells) are now recognized as being intimately involved in tumor development, progression, and therapeutic responses (15, 16). The stromal compartment is also a key contributor to COPD pathogenesis, in that altered and excessive ECM production and degradation contribute to emphysema.

In a study presented in this issue of the *Journal*, Sandri and colleagues (pp. 348–358) used a multi-omics approach to examine how differences in lung function affect stromal signaling in lung cancer (17). They examined gene expression by total mRNA sequencing, gene translational efficiency by polysome profiling, and protein expression by mass spectrometry–based proteomics in tumor-adjacent lung tissue (primarily stromal) samples and matched samples from participants without cancer. Samples from patients with and without cancer were matched based on lung function ranging from normal to severe airflow obstruction. They first show that cancer-associated alterations in the proteome are dependent on lung function. They then suggest that these proteome alterations are predominantly due to changes in mRNA translational efficiency. They found an enrichment in differentially translated, but not expressed, mRNA levels for the interaction between lung function and cancer across all genes and secondarily in the genes with altered proteins. Based on a series of pathway analyses, they go on to suggest that different cancer-associated mechanisms are important in participants with different degrees of lung function. For instance, they show that a fibrotic ECM pathway is associated with declining lung function and translational efficiency, whereas a senescence pathway is associated with better lung function and overall gene expression.

The agreement between the results from proteomic and polysome RNA sequencing shows a strength of using multi-omics datasets derived from the same subjects, which is becoming more common in genomics studies (18, 19). They used two methods to validate the omics results, including Western blotting of two proteins, CAV1 and SFXN3, although they do not specify how they chose these two proteins. In addition, immunofluorescence in lung tissue highlighted IL-6 and BMP-1, which were selected to represent two identified gene ontologies.

In this study, the authors used advanced genomics technologies, and they should be commended for their detailed reporting of the laboratory and analysis methods used. To make such reporting easier in the future, the American Thoracic Society's Section on Genetics and Genomics recently published a workshop report on high-throughput sequencing research, including a list of best practices, that can serve as a checklist for readers and journal reviewers (20). The datasets generated in the current study will be made publicly available, to allow further exploration of the results.

The major limitation of this paper is the small sample size (58 subjects with proteomics data and 32 with RNA sequencing). It is not clear how these sample sizes were selected out of the much larger Lung Tissue Research Consortium. Small sample sizes may be prone to both false-negative and false-positive results. Current RNA-sequencing and proteomics studies in lung disease now include hundreds or thousands of subjects (21, 22), which is still small compared with genome-wide association studies, which include hundreds of thousands of subjects (23, 24).

Testing for gene expression-by-environment interactions is difficult, as currently available RNA-sequencing analysis methods, such as DESeq2 and limma/voom, do not allow for such assessment (25, 26). To overcome this limitation, Sandri and colleagues tested for interactions between FEV_1 and cancer, not interactions between

Originally Published in Press as DOI: 10.1164/rccm.201901-0156ED on February 12, 2019

FEV_1 and gene expression differences between cancer and controls. Direct testing of interactions in RNA-sequencing data is an active area of methods development.

Despite the findings that gene expression patterns differed based on FEV_1, it is unlikely that the physiologic impairment in lung function leads to changes in the biologic mechanisms. FEV_1 is more likely a surrogate for emphysema or pathologic changes in the airway, both of which have been proposed to affect lung cancer development (8). Future studies should directly assess emphysema and airway disease based on preoperative chest computed tomography imaging.

Sandri and colleagues have added to a growing body of work interrogating the COPD–lung cancer connection. As the authors have demonstrated, high-throughput technologies provide ever-improving avenues to investigate pathologies associated with important clinical questions. In future studies, multi-omics data could be exploited to ascertain the contribution of COPD-related pathology to premalignant and tumor microenvironments in many ways. For example, pharmacogenomics approaches could be used to identify pathologic pathways (e.g., immune responses) that may be directly modifiable by available therapeutics. Alternatively, machine learning and classification approaches could be used to identify COPD-relevant cancer risk biomarkers. As the costs of high-throughput technologies continue to decrease, we are likely to see an explosion of data available to address these and other critical issues related to the care of patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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