complex directly could improve antiviral responses and reduce the impact of exacerbations in debilitating diseases such as COPD. ■

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Recognizing the Many Faces of Chronic Obstructive Pulmonary Disease

The clinical heterogeneity of chronic obstructive pulmonary disease (COPD) is readily appreciated. Although identification of meaningful disease subtypes in COPD may lead to improved understanding of COPD pathophysiology and its important prognostic or therapeutic characteristics (1), it is challenging to reduce this heterogeneity to precisely defined groups of patients with COPD. Although our understanding of specific subtypes remains limited (2), two clearly recognizable dimensions of COPD heterogeneity are airways disease and pulmonary emphysema.

In this issue of the *Journal*, Faner and colleagues (pp. 1242–1253) seek to determine whether these two dimensions of COPD are associated with distinct biological processes (3). The authors treat emphysema and airway disease as separate entities, defining nonoverlapping populations of "emphysema" and "bronchiolitis" based on diffusing capacity of the lung for carbon monoxide thresholds (<60% and >80% of predicted) and computed tomographic evidence of emphysema. Through differential gene expression and correlation network analyses, the authors implicate inflammatory pathways and B cell–specific processes with emphysema, as opposed to bronchiolitis.

Hogg and colleagues demonstrated evidence of innate and adaptive immunity in the small airways in COPD, characterized by the presence of neutrophils, macrophages, CD4, CD8, and B-cells within the airway walls and lumen (4). These observations, combined with the presence of lymphoid follicles in the small airways, make a compelling case for the role of adaptive immunity in the pathogenesis of COPD. At first glance, the finding by Faner and colleagues that B cell–associated inflammation is linked to emphysema, rather than bronchiolitis, seems at odds with the observation of peribronchiolar inflammation in COPD by Hogg and colleagues. However, this is consistent with findings in a subsequent study demonstrating higher expression of B-cell signaling genes from lung regions with more severe emphysema (5).

This apparent contradiction becomes less problematic if emphysema and airways disease are viewed as distinct but related dimensions of COPD. In Roman mythology, the god Janus is represented as having two faces. Although the two-faced Janus sometimes represents mendacity and duplicity, he was originally meant to represent change and transition from one state to a qualitatively different one. In this sense, the two faces of Janus are an apt metaphor for airways disease and emphysema, two faces of COPD that are either completely separate or intimately intertwined, depending on perspective.

Similar to the mendacious Janus, the two faces of COPD complicate and confound our understanding of this disease. On one hand, emphysema is correlated with many measures of airways disease, including FEV_1 and computed tomography–based assessments of airway wall thickening. On the other hand, clinical experience and clustering analyses tell us there are subgroups of patients with COPD in which airflow obstruction or emphysema clearly predominate (6). Ultimately, it may be more useful to view the two faces of COPD like the Janus of transitions. From this perspective, airways disease and emphysema are related processes that are temporally connected, as suggested by the observation that small airway inflammation and dropout precede the development of emphysema (7).

Faner and colleagues view the two faces of COPD from a molecular perspective and ask whether emphysema and bronchiolitis arise from different biological processes, and the answer appears to be "yes." The authors construct co-expression networks for emphysema and bronchiolitis based on pairwise Pearson correlation between gene expression levels, focusing on genes with known immune function. When the emphysema and bronchiolitis networks were compared, roughly half of their genes were shared, but analysis of the nonoverlapping genes indicated enrichment of B- and T-cell

pathways in emphysema and proliferation pathways in bronchiolitis. Certain aspects of network topology were altered between the groups, with B cell–associated genes seeming to play a more central role in the emphysema network.

Visualization and analysis of data as networks is an increasingly common approach to the analysis of high-dimensional data. Although its use here provides a novel view of COPD biology, network analysis is still in an early stage of evolution, and uncertainty remains regarding the optimal approaches for making biological inferences from these complex data representations (8). One of the strengths of the current analysis is the exploration of various thresholds for constructing the correlation networks to assess the sensitivity of their network analysis to this critical parameter.

Some limitations of this work include the relatively small sample size of the study subgroups, the mixed cellular composition of the lung tissue samples, and the possibility that tissue samples were not obtained from lung regions most representative of emphysema or bronchiolitis. Although the use of Pearson correlation in coexpression networks is a commonly used approach, other approaches including partial correlations or weighted correlation networks (9) can be used and may be more informative for certain applications. The expression differences observed between the emphysema and bronchiolitis groups provide compelling evidence of the molecular heterogeneity of COPD, but it is not clear whether these differences reflect alterations in the transcriptional state of distinct cell subpopulations or rather reflect changes in the overall proportions of distinct cell types between the emphysema and bronchiolitis groups. In addition to genomic analyses of whole-lung expression data, cell type–specific genomic analyses are needed to provide a more detailed view of the molecular networks within specific cell types.

Although the association of adaptive immunity with COPD is well supported, additional work is needed to understand the chain of causality connecting inflammation, small airways disease, and emphysema. Other investigations have also identified a role for adaptive immunity in advanced COPD (10) with implications for targeted therapy (11). However, it is not clear whether adaptive immunity is an early driver of COPD or a sequela of advanced disease (12), and extrinsic factors such as altered microbial colonization appear to contribute to the dynamic inflammatory processes associated with COPD progression (13).

By focusing on groups at opposite ends of the phenotypic spectrum, the authors improved their ability to identify distinct molecular patterns of airways disease and emphysema. However, important questions remain about the middle ground between airway-predominant and emphysema-predominant COPD. Instead of defining subtypes first and discovering biology later, it will also be useful to perform this process in reverse and use genomic data to better define COPD heterogeneity. In the same way that deeper biologic understanding of COPD requires appreciation of the two faces of airways disease and emphysema, the phenotypic complexity of COPD will be easier to understand as we view the molecular faces of COPD with increasing resolution. ■

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