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# Biomarkers for Interstitial Lung Abnormalities: A Stepping-stone Toward Idiopathic Pulmonary Fibrosis Prevention?

Interstitial lung abnormality (ILA), defined broadly as the presence of nondependent radiographic abnormalities on computed tomography (CT) scan occurring in an individual in whom interstitial lung disease is not suspected, appears to be a precursor to idiopathic pulmonary fibrosis (IPF) and other forms of progressive pulmonary fibrosis (PPF) (1). ILAs are frequently found in asymptomatic individuals with a strong family history of pulmonary fibrosis (2, 3). In the nonfamilial setting, ILAs are more common with advancing age, in those with the rs35705950 MUC5B polymorphism, and occur in 4–9% of smokers and 2–7% of nonsmokers over the age of 60 (4). Almost half of ILAs progress over the subsequent 5 years, and risk of mortality for those with ILAs is considerably higher than for age-matched populations (5).

Given the significant morbidity and mortality associated with IPF and PFF (6), the identification of individuals prior to the development of irreversible fibrosis and onset of symptoms affords a window of opportunity for genuinely disease-modifying therapeutic intervention. Understanding of the natural history of ILAs has come a



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long way in the last 5 years; however, there are still barriers to overcome before it is possible to consider running clinical trials in this area. First, it is not yet clear how best to target screening for ILAs. To date, populations in whom ILAs have been studied have been opportunistic; that is to say CT scans were performed as part of studies designed to screen individuals at high risk for diseases other than ILD, for example, lung cancer, chronic obstructive pulmonary disease (COPD), or cardiovascular disease. Second, not all ILAs appear to confer equal risk for development of ILD. Certain imaging features such as honeycombing seem to be more often associated with progressive disease; however, accurate prediction of which individuals will develop IPF or PFF remains limited (1, 7). Third, an important prerequisite to running clinical trials in individuals with ILA is the development of appropriate endpoints. Physiological endpoints that are used in IPF trials (such as FVC) are unlikely to be usable in studies of ILA. To avoid the need for large and lengthy studies it will be important to identify surrogate measures which, based on short-term change, will predict the long-term likelihood that ILA will transform in to IPF.

Blood biomarkers have the potential to be a simple, minimally invasive way of identifying individuals at risk of developing ILA and for assessing likelihood of ILA progression. A wide range of circulating proteins have been shown to identify risk of progression of IPF and PFF (8, 9). Several studies of specific biomarkers have been performed in individuals with ILA. Serum levels of galectin-3, sICAM-1, blood monocytes, and a number of aging-related proteins (including GDF15, TNFR, CRP, and IL-6) have been associated with an increased likelihood of ILA (10–13). Increased levels of matrix metalloprotease-7 have been shown to predict progression of ILA (14).

In the current issue of the *Journal* Axelsson and colleagues (pp. 337–346) present data from an unbiased proteomic analysis, utilizing an aptamer-based platform, performed in two independent prospective cohorts; the AGES (Age, Gene/Environment Susceptibility)-Reykjavik study and the Genetic Epidemiology of COPD (COPDgene) study (15). In total, the authors measured >4000 proteins in baseline blood samples from >10,000 individuals. To make sense of such big numbers, the authors employed a technique called LASSO (least absolute shrinkage and selection operator). This approach, which is commonly used in machine learning algorithms, is helpful in interpreting large datasets but does so at the cost of potentially important measures being overlooked. In the AGES-Reykjavik cohort ($n = 5259$), 287 proteins were associated with risk of ILA; the three with the greatest odds ratios were SFTB (surfactant protein B), SCGB3A1 (secretoglobin-3A member-1), and WFDC2 (WAP four-disulfide core domain protein-2). These markers also formed part of an 8-protein LASSO model with a c-statistic on receiver operator curve analysis of 0.880 (which compared with 0.670 for a model consisting of demographic factors alone). In replication, in the COPDgene cohort ($n = 4899$) the same proteins were associated with an increased odds ratio of ILA and the LASSO model generated a c-statistic of 0.826. Furthermore, the identified proteins tended to associate with ILA imaging patterns, which correlate most strongly with unfavorable long-term outcomes.

In the AGES-Reykjavik cohort, 223 participants had progression of ILA at follow-up. Of the measured proteins, 121 associated with ILA progression. SFTB and WFDC2 together with growth differentiation factor-15 (GDF15) and cathepsin H (CTSH) were the proteins that identified the greatest odds for ILA progression. An adaptive LASSO model generated a c-statistic of 0.824. Unfortunately, progression data is not available for the COPDgene cohort and these observations could not be validated.

Axelsson and colleagues are to be congratulated for undertaking such a large-scale proteomic study in two well-defined patient populations. Their findings suggest that blood protein signatures can be used to identify individuals at risk for ILA (thus opening the door to targeted use of CT screening in high-risk individuals) and for determining which individuals with ILA are most likely to have progressive disease (information which could be used to enrich future clinical trials). Aptamer-based proteomic assays only generate semiquantitative data. If the findings from the current study are to be translated into clinical practice, it will be necessary to develop quantitative assays for the proteins identified and for these to be tested prospectively to validate specific thresholds that define individual risk more precisely. Nonetheless, Axelsson and colleagues have taken the critical step of demonstrating a role for blood-based biomarkers in the identification and assessment of ILAs.

ILAs appear to be an important precursor to IPF and PFF. Thus, successful implementation of secondary prevention strategies should be a highly effective approach for averting the development of deadly fibrotic lung disease (in much the same way that treatment of hypercholesterolaemia and the use of antiplatelet drugs have dramatically improved cardiac outcomes in the 21st century). The demonstration that blood biomarkers can be used both to identify individuals at risk for ILA and to predict subsequent risk of progression once an ILA has been confirmed represents an important stepping-stone toward the goal of making IPF and PFF preventable conditions. ■

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