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Host–Microbial Interactions: Idiopathic Pulmonary Fibrosis in Technicolor

Idiopathic pulmonary fibrosis (IPF) is a complex disease that is characterized by progressive declines in lung mechanics and gas exchange, which ultimately lead to respiratory failure and death. The complexity of IPF is exemplified by genetic and environmental contributions that are thought to culminate in recurrent "microinjuries" to alveolar epithelial cells, which lead to epithelial exhaustion and chronic disrepair. To date, the origins of this unremitting injury have remained elusive. Several recent studies proposed a role for impaired or dysregulated host defense and immune signaling in IPF pathogenesis (1–7). Exogenous stimuli, including microbes, are plausible environmental factors that contribute to organ fibrosis (8, 9). Specific microbiota in the lungs of patients with IPF predict disease progression, and the fibrotic environment of the IPF lung harbors a significantly greater burden of bacteria than chronic obstructive pulmonary disease and healthy lungs (10, 11). The stage is therefore set to determine whether the microbes residing in the lower airways conceivably drive recurrent injury and disrepair in the lungs of patients with IPF, particularly in the context of dysregulated host defense.

It is in this context that Molyneaux and colleagues (pp. 1640–1650) in this issue of the *Journal* (12) build on their previous novel contributions to the field of respiratory microbiota in IPF (11). This group applied 16S ribosomal RNA gene sequencing to baseline-acquired bronchoalveolar lavage (BAL) fluid from 60 patients with IPF and 20 matched control subjects to describe the respiratory microbiome. They reported significant differences in the total abundance and relative abundance of certain microbial species, including a *Haemophilus* sp., a *Neisseria* sp., a *Streptococcus* sp., and a *Veillonella* sp. compared with age-matched control subjects. Although these results are not novel to the field, the authors also acquired corresponding peripheral blood samples prospectively at 1, 3, 6, and 12 months from patients with IPF and control subjects to explore potential associated host responses. More than 1,300 transcript clusters were differentially expressed in IPF compared with controls, and the most enriched biological processes in these clusters were "host defense" and "stress" related (based on gene ontology). Host gene expression in peripheral blood cells was examined in a weighted gene coexpression network analysis, and five gene clusters (or modules) were reported. Gene expression modules, assigned arbitrary colors, which predicted poor prognosis, were enriched for innate defense transcripts, and were associated with peripheral neutrophil counts (brown and blue). However, a module that predicted favorable outcomes (turquoise) was enriched for lymphocytic transcripts and was associated with increased

lymphocyte counts in the peripheral blood. Increased expression of the blue module transcripts was associated with worse survival, greater decline in lung function, a higher bacterial burden, and lower abundance of a *Neisseria* sp. and BAL neutrophilia in patients with IPF. Unlike previous work (10), no association was found between this module and disease progression and/or *Staphylococcus* or *Streptococcus* loads. This blue module contained several overexpressed host defense genes and enriched biological processes, including "defense response," "response to bacterium," and "immune response." The green module was strongly associated with BAL neutrophilia, peripheral blood neutrophilia, and a higher abundance of *Veillonella* operational taxonomic units in BAL. The most enriched biological process within the green module was "response to bacterium." The turquoise module, enriched for T-cell–associated transcripts, was associated with longer survival, reduced pulmonary function decline, and death, a finding that agreed with the observation that T-cell costimulatory protein expression in IPF correlates with prognosis (5). However, there was no association between the mucin 5B rs35705950 and toll-interacting protein rs3750920 and rs5743890 single-nucleotide polymorphisms and host gene expression in the current study. The other two modules reported interesting findings, but contributed less to the main hypothesis of the paper.

As a notable strength, this was the first study to postulate and integrate links between host gene transcription and respiratory microbiota in a well-characterized cohort of patients with IPF with serial follow-up and acquisition of large volumes of data. This cohort was enriched for disease progression, with 24 deaths on follow-up and another 13 patients with IPF who experienced declines in lung function that met the standard criteria for progression. Although the authors accounted for comorbidities within their statistical modeling and excluded patients with acute infection, there were caveats and limitations to this study. These included: patient numbers were limited and without validation; integration of large data sets was fraught with difficulty and might be subject to overinterpretation; and lack of longitudinal surveillance data on respiratory microbiota might weaken the results of the study.

The current paradigm of IPF centers on the alveolar epithelium, which is subject to recurrent unknown microinjuries. In conjunction with recent clinical observations of reduced mortality in patients treated with antimicrobials (13) and the known deleterious clinical outcomes of patients with IPF who are treated with immunosuppression (14), the findings of this study are provocative. Although this study provides further evidence for dysregulated host defense responses in IPF and novel associations between host response and lower airway microbiota, key questions remain. Could it be that altered microbial cues, in the setting of dysregulated alveolar epithelial repair, drive recurrent pattern recognition receptor activation and signaling? Could the fibrotic lung environment be responsible for physiological changes that promote dysbiosis, which, in turn, drives a dysregulated host response and bystander injury? Could a dysregulated host response predispose to recurrent pulmonary infection, which generates dysbiotic lower airways and contributes to disease progression through yet unknown mechanisms? Specifically, it is perplexing to note that several potent antimicrobial factors were up-regulated in IPF concomitant with dysbiosis in this disease, which suggests that these factors disproportionately target probiotic species, thereby favoring pathogenic species. Alternatively, it remains plausible that inhaled particulates and/or refluxed gastric acid might also contribute to epithelial injury in the lung. Further work is needed to address these exciting questions.

IPF remains an irreversible and devastating disease that portends a dismal prognosis. This intriguing work by Molyneaux and colleagues adds to other seminal studies and sheds additional light on the putative role of the respiratory microbiota in IPF pathogenesis. If future work strengthens the putative mechanistic links between respiratory dysbiosis and disease progression in IPF, then we may usher in an era of precision medicine for the respiratory microbiome. ■

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Invasive Mediastinal Staging in Lung Cancer
Use a Prediction Model or Just Do It?

Clinicians are faced with innumerable medical decisions affecting patient care and outcomes daily. In the diagnostic setting, some decisions are relatively straightforward, whereas others involve probabilistic reasoning that is often complex and, by definition, uncertain. The probability of a given condition is typically influenced by a number of factors that, when considered jointly, impact the decision to pursue additional testing, proceed straight to treatment, or provide reassurance. Now that clinical prediction models are increasingly available to assist physicians and patients in estimating the likelihood of disease with the potential to influence decision-making, they are increasingly being incorporated into practice guidelines across a number of medical specialties. In some diseases there is an abundance of prediction models for the same outcome (for example, there are 20 models to predict the likelihood of prolonged intensive care unit stay after cardiac surgery [1]), whereas in other conditions, novel models are still being developed and validated to improve decision-making.

One such decision in the field of thoracic oncology is whether (or in whom) to perform preoperative invasive mediastinal staging. Invasive staging can help avoid unnecessary thoracotomy among patients with lung cancer with locally advanced disease and, perhaps even more importantly, avoid missed opportunities for surgical cure among patients with evidence of suspicious mediastinal (N2/N3) lymph node enlargement or hypermetabolism on positron emission tomography (PET) imaging. In this issue of the *Journal*, O'Connell and colleagues (pp. 1651–1660) describe a new prediction model for determining the presence of N2/N3 nodal disease by endobronchial ultrasound (EBUS) (2). In the 18 years since its introduction as a new pulmonary technology, EBUS has revolutionized and redefined the role of pulmonologists in the staging and diagnosis of lung cancer. The evolution of EBUS as a diagnostic and staging tool can be seen in the progressive iterations of the American College of Chest Physicians (ACCP) guidelines for lung cancer; where EBUS was once considered a novel technology and mediastinoscopy the gold standard, minimally invasive, needle-based techniques are now recommended as the initial procedure of choice for the staging and diagnosis of those with suspected lung cancer (3, 4). The guidelines do not recommend invasive mediastinal staging for all patients with non–small-cell lung cancer (NSCLC); if the probability of nodal disease is sufficiently low (for example, among those with a small peripheral cancer without radiographic evidence of nodal disease), referral for surgical resection (with intraoperative staging) is a reasonable management strategy (4). Although in some cases locally advanced disease is quite apparent on the basis of the presence of large bulky adenopathy on noninvasive imaging, in other cases the presence of locally advanced disease is not as clear. The authors argue that using a prediction model with the ability to provide a more precise estimate of detecting N2/3 disease by EBUS would be of value by informing the next step in the management algorithm for lung cancer.

The prediction model to Help with the Assessment of Adenopathy in Lung Cancer (HAL) was developed by using information from 633 consecutive patients with treatment-naive NSCLC undergoing EBUS for staging from the ACCP Quality Improvement Registry, Evaluation, and Education (AQuIRE) registry (2). Those with small-cell lung cancer, disease recurrence, extrathoracic metastases, and T4 tumors were appropriately excluded. Because prior work indicated that PET sensitivity for mediastinal lymph node involvement depends on the size of the node on computed tomography (CT) scan (5), the authors examined the interaction between CT N stage and PET N stage and modeled N stage using this interaction. In the development cohort, the prevalence of N2/3 disease was 25%. Factors associated with positive N2/N3 disease identified by EBUS included younger age, central tumor location, adenocarcinoma histology, and higher PET-CT N stage. Many of these variables were identified as independent predictors of mediastinal metastasis in a previously developed model (6). However, with the addition of PET-CT N stage, the HAL model was considerably more accurate, with an area under the receiver operating curve (AUC) of 0.85 (95% confidence interval, 0.82–0.89). Data from three centers and 722 patients were then used to validate the HAL model externally. The pooled AUC in the external validation was 0.88 (95% confidence interval, 0.85–0.91); however, this varied depending on the institution, with site-specific AUC values ranging from 0.82 to 0.92. The authors maintain that the variation was likely due to between-site differences in N2/3 prevalence. They subsequently used statistical methods to calibrate the model for better performance. In addition, they developed and validated similar prediction models for use when PET results and/or histologic diagnosis were unavailable, making the utility of the prediction model more broadly applicable (2).