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Cut from the Same Cloth: Similarities between Hypersensitivity Pneumonitis and Idiopathic Pulmonary Fibrosis

Hypersensitivity pneumonitis (HP) is a clinically and molecularly heterogeneous immune-mediated interstitial lung disease (ILD). Although newer classification of HP into fibrotic HP (fHP) and nonfibrotic HP has simplified diagnostic objectivity (1), the molecular pathways driving fHP have yet to be fully defined. This is important, as fHP is associated with worse outcomes compared with nonfibrotic HP (2). Furthermore, although fHP and idiopathic pulmonary fibrosis (IPF) are believed to be pathologically distinct, recent reports suggest they may have clinical and pathophysiologic similarities (3–5). Further insight of shared mechanisms between these ILDs may have practice implications for fHP as well as other inflammatory or fibrotic ILDs.

In this issue of the *Journal*, De Sadeleer and colleagues (pp. 60–74) sought to characterize the molecular determinants of fHP and whether they are shared with IPF (6). To achieve this goal, lung transcriptomic data were compared between control, IPF, and multiple samples within the same fHP lung to account for heterogeneity in regions of disease severity. Novel micro–computed tomography technology was used to stratify fHP samples by disease severity into mild, moderate, and severe groups as a proxy for morphological disease progression. Gene expression profiles were validated using publicly available data and BAL and computed tomography data from a separate fHP cohort. Distinct patterns of differential gene expression were defined, including those with an overall increase in fHP compared with controls but decreasing with local severity (degressive increase), an increase in fHP and increase with local severity (progressive increase), or an overall decrease in expression in fHP but further decrease with local severity (progressive decrease). These distinctions identified pathways implicated in fHP (disease specific) as well as implicated in the progression of fibrosis (disease severity specific).

Six molecular traits were associated with fHP. There was a degressive increase in extracellular matrix (ECM) genes and collagen functions, which have been previously implicated in HP as well as fibrotic lung diseases (7, 8). A similar pattern was seen in T cell signatures, including increased antigen presentation and T

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cell–mediated sensitization, primarily in the regions of mild disease. The authors argue this may be an early transgressor of disease, as studies have reported T cell–associated genes to be uniquely upregulated in mild fHP compared with IPF (9). There was a progressive increase in B cell functions, including more cluster of differentiation 20 + cells and in honeycombing associated signatures, which aligns with increasing fibrotic severity. A progressive decrease of cell adhesion and endothelial functions as well as intracellular homeostasis functions were identified in fHP lungs. When comparing with IPF, although there were disease-specific signals, the six molecular traits of the fHP transcriptome were active in IPF as well.

This study advances understanding of the molecular mechanisms of fHP especially as they pertain to evolving morphologic severity of fibrosis. Elucidating early disease mechanisms is of particular importance as they are optimal targets for therapeutic intervention to prevent disease progression. This manuscript highlights two predominantly active pathways in early disease: ECM remodeling and T cell activation. Although aberrant ECM is a well-established feature of fHP (10), the presence of early ECM accumulation suggests it may be an early driver of fibrosis rather than exclusively a consequential outcome (8). Similarly, the presence of early T cell activation suggests immune-mediated pathways continue to be active despite transition to a fibrotic phase of disease (9). Collectively, these findings support the idea that fHP progression may involve both inflammatory and epithelial drivers of disease; however, how the relative contribution of these mechanisms interact and whether they impact other cellular pathways over time to cause progressive lung remodeling requires further clarification.

Although recognizing fHP as a separate clinical entity, this study demonstrates converging pathways between IPF and fHP suggesting shared mechanisms in lung remodeling and fibrosis, especially as fHP progresses. The findings in this study echo those of Furusawa and colleagues, who found that of 730 differentially expressed genes in fHP, 471 shared genes with IPF, including epithelial cell pathways, ECM, and collagen organization (10). Notably, many pathways highlighted in this paper are also implicated in other forms of ILD. Systemic sclerosis (SSc)–associated ILD has been shown to have activation of collagen formation and ECM organization as well as enhanced B cell activation and infiltration in diseased tissue (11). Although the initial insult is believed to be immune-mediated, the fibrotic lung remodeling in fHP, SSc-ILD, and other progressive fibrosing ILDs appears to eventually proceed through common profibrotic molecular pathways. It raises the possibility that molecular differences may be more due to disease severity rather than disease etiology.

As data are gathered about lung fibrosis, there appear to be more similarities than differences between IPF and other fibrotic ILDs, including fHP. Clinically, the INBUILD study, of which fHP made up about a quarter of patients and included SSc-ILD and other connective tissue disease–ILDs, noted similar rate of FVC decline between progressive fibrosing (PF) ILDs and similar responses to nintedanib therapy, further supporting commonalities between IPF and PF-ILDs (12). Treatment implications are important as they expand the treatment repertoire, although the optimal timing to initiate interventions remains to be defined. Another shared mechanism between IPF and PF-ILDs is the influence of aging on fibrosis progression. In this study, the authors found lung telomere length was shorter in fHP and associated with disease severity. This is consistent with data implicating telomere dysfunction and senescence reprogramming as molecular drivers of lung remodeling and fibrosis in many clinical contexts, including IPF, fHP, and SSc-ILD (5, 13–15).

Another impactful finding from this paper is the role lung heterogeneity may play in the study of lung remodeling. Although uncertainty of whether spatial heterogeneity is synonymous with disease progression is a study limitation, the disparate findings within local disease severity, as well as those previously demonstrated in IPF (16), suggest that investigating different morphologic states, even when taken at a single time-point, may yield insights into the trajectory of disease pathogenesis. This approach may be especially useful in diseases where lung sampling only occurs at transplantation.

The pathogenesis of fHP among other progressive fibrosing ILDs remains elusive and difficult to target therapeutically. The findings of this well-designed study further understanding of the disease mechanisms underlying fHP through using a novel methodology applied to a well-characterized cohort. This study, although focused on fHP, strengthens the evolving concept that there are common threads underlying lung remodeling and the development of fibrosis distinct of the underlying etiology. Future studies should leverage more granular technology to validate and refine disease pathways on a cellular level, which will allow for further clarity and guide therapeutic development and intervention. ■

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The Future of Outcome Prediction for Preterm Infants in the Neonatal ICU

Outcome prediction for prognosis or risk stratification is particularly important in the neonatal ICU as critically ill neonates are at high risk of mortality or long-term morbidity. There are several commonly used outcome prediction tools in neonatology. The majority of these tools use static measures such as data available at birth or within 24 hours of birth to predict the risk of subsequent mortality or neurodevelopmental impairment (1–3). Gestational age and birth weight are among the best predictor variables (4), such that clinical trials in preterm infants frequently use one or both of these variables for stratification to ensure balanced allocation. As early predictors do not take into account risk factors and complications that become apparent later during the hospitalization, tools incorporating respiratory support and selected postnatal morbidities were developed to better predict mortality, bronchopulmonary dysplasia, and neurodevelopmental impairment (5, 6). The use of prediction tools in neonatology to guide clinical decisions has not been tracked formally, and the impact on clinical care is unknown. A limitation of most of the currently available prediction models in neonatology is their reliance on data available at birth with limited or no sequential clinical and/or laboratory data.

In this issue of the *Journal*, Lavilla and colleagues (pp. 75–87) examined the discriminatory power of hourly changes in neonatal sequential organ failure assessment (nSOFA) scores from birth to predict death among 436 extremely preterm and extremely low-birth-weight infants. Hourly kinetics of the nSOFA score were strong predictors of mortality before discharge and within 24 hours after birth (7). The average score over the first 28 days was also associated with hospital mortality and major morbidities. Although mortality is rightly considered the most important outcome in neonatology, it is imperative to acknowledge that neurodevelopmental assessment at a later age was not addressed in the current prediction study. Neurodevelopmental impairment may be as important or more than some of the outcomes reported, including severe intraventricular hemorrhage, bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, and retinopathy of prematurity.

The nSOFA scoring system is based on the presence of mechanical ventilation and oxygen saturation as measured by pulse oximetry:F_{IO_2} ratio for respiratory dysfunction, presence of vasoactive medications and/or corticosteroids for cardiovascular dysfunction, and platelet count for hematologic dysfunction. These measures may be dependent on clinical practice. For example, the nSOFA scores may be artificially lower in a clinical setting where hypotension is managed more conservatively (8). Similarly, in centers with more use of mechanical ventilation rather than continuous positive airway pressure, use of lower rather than higher oxygen saturation targets (9), or avoidance of higher F_{IO_2} in favor of higher mean airway pressures, the model may not be as applicable. Thus, the generalizability of the results of this study may be limited and center-specific and may need to be validated externally.

The study by Lavilla and colleagues does not define if these are the best variables or weighting to predict the risk of adverse outcomes. It is possible that prediction might be improved using optimization of cutoff values or more granular continuous respiratory

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