predicting CHP progression and survival will be of major interest. Such findings could also be in the context of extrapulmonary (e.g., hematological) abnormalities of short-telomere syndrome. Whether telomeropathy and short telomeres represent the inciting events of immune deregulation of CHP or simply exacerbate the disease process remains to be determined.

There is ongoing disagreement about what constitutes HP. In a previous study, agreement across multidisciplinary teams about an HP diagnosis was fair ($\kappa = 0.24$), whereas agreement about IPF ($\kappa = 0.60$) or connective tissue disease–associated interstitial lung disease ($\kappa = 0.64$) was moderate to good (14).

Large, prospective, collaborative studies in well-defined patients with CHP are sorely needed to overcome these limitations and allow firm conclusions to be drawn. ■

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Mechanistic Insights into Lethal Lung Developmental Disorders

The Rare Informs the Common

At birth, the lung circulation undergoes a remarkable transition from a high-resistance vascular bed with low blood flow *in utero* to a low-resistance and high-flow state immediately after birth. This dramatic physiologic response allows the fetus to successfully navigate from its prenatal dependence on the placenta for gas exchange to successful postnatal adaptation for air breathing as the lung assumes its essential role as the organ of gas exchange. This singular event represents the culmination of a successful sequence of tightly orchestrated maturational changes that occur throughout normal lung growth, which ultimately lead to the development of a mature epithelium–vascular interface that is essential for normal gas exchange. Precise coordination of lung growth involving the airways and parenchyma, especially as related to vascular development, depends on diverse and highly interactive signaling pathways whose regulation remains incompletely understood (1, 2).

In some infants, the lung circulation fails to achieve or sustain the normal decrease in pulmonary vascular resistance, leading to hypoxemic respiratory failure with pulmonary hypertension, which is known as persistent pulmonary hypertension of the newborn. Despite advances in care, however, a subgroup of term or near-term infants present with persistent pulmonary hypertension of the newborn physiology that is poorly responsive to these interventions, and die in the first days of life with evidence of lethal congenital lung disease (3–6). In this highly fatal subgroup, lung biopsy or autopsy

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findings often reveal a striking disruption of distal lung development, including signs of decreased alveolar architecture, reduced vascular density, signature hypertensive remodeling of arteries and microvasculature, and other features (3–9).

Over the past 5 decades, there has been a growing appreciation of clinical and pathologic features of lethal lung developmental disorders (3). These disorders generally include histopathologic features characteristic of alveolar capillary dysplasia (ACD), acinar dysplasia, congenital alveolar dysplasia, and other forms of lung hypoplasia (3–9). Recent advances have led to discoveries of the genetic basis underlying these disorders, including mutations or variants of FOXF-1, TBX4, and other genes, which have enabled clinicians to better discriminate these disorders by identifying factors beyond clinical and histopathologic features alone (8–10). The most prominent of these was the discovery of FOXF1 mutations as the genetic basis for ACD, which rapidly led to an explosion of novel information regarding enhanced diagnostic approaches for neonates with severe congenital lung disease (8).

In their most recent paper in this issue of the *Journal*, Ren and colleagues (pp. 1164–1176) continue to enhance our understanding of the role of FOXF-1 function during development and how disruption of this critical transcription-to-signaling pathway contributes to aberrant vascular and airspace structure, especially in neonates with ACD (11–13). FOX proteins constitute a family of winged-helix transcription factors that act in concert with or downstream from critical signaling pathways, including through induction and stimulation of VEGF (vascular endothelial growth factor) signaling. Genetic deletion of FOXF1 reduces pulmonary endothelial cell (EC) growth and capillary numbers during development and increases susceptibility to lung injury in mice (12, 13). Previous studies in other experimental settings have demonstrated that disruption of angiogenesis, including mechanisms related to impaired VEGF signaling, impairs airspace development (14, 15).

Ren and colleagues extend their previous work by studying how disruption of FOXF-1 function decreases the number of c-KIT$^+$ EC progenitors and aberrant alveologenesis. c-KIT is expressed in EC progenitors that differentiate into mature ECs in many tissues. Using a combination of antibody staining, fluorescence-activated cell sorting, and single-cell RNA sequencing, the authors demonstrate the presence of c-KIT$^+$ ECs in the mouse and human neonatal lung, and that cell abundance declines in the adult. These cells do not express markers for arteries, veins, or lymphatics, and thus are likely a subset of the capillary ECs. In comparison with c-KIT$^-$ cells, c-KIT$^+$ cells show higher *Foxf1* expression and their transcriptomic profile is enhanced with FOXF-1–regulated transcriptional targets. To demonstrate the functional significance of the FOXF1-cKIT$^+$ population linkage, the authors show that haploinsufficiency and endothelial-specific deletion of *Foxf1* or *cKit* led to similar phenotypes of increased EC death, reduced endothelial growth, and disrupted alveologenesis. Extending their investigation from ACD to bronchopulmonary dysplasia (BPD), the authors show that c-KIT$^+$ EC progenitors were reduced in a neonatal mouse model of hyperoxia-induced reduction of alveolar and vascular growth, and that lung FOXF-1 and c-KIT expression was reduced in the lungs of infants who died of BPD. Remarkably, the investigators found that adoptive transfer of c-KIT$^+$ ECs, but not c-KIT$^-$ cells, through facial vein injection after hyperoxia exposure led to the integration of donor cells into host vessels and preserved distal lung architecture. This result offers a landmark demonstration of the exciting therapeutic potential of c-KIT$^+$ ECs for preventing BPD, which, like ACD, is characterized by impaired vessel growth and alveolar simplification.

Overall, these innovative findings remind us that the pathogenesis of ACD and other rare but lethal congenital lung disorders in term neonates is highly relevant to more common multifactorial disorders of impaired lung growth in preterm infants, such as BPD. BPD has long been recognized as a disease involving various components of parenchymal, vascular, and conducting airways, and there is a growing recognition that the vascular component of BPD exerts a major impact on disease pathobiology and severity. In addition to exposure to antenatal stress with ongoing postnatal lung injury, premature birth disrupts both vascular growth and distal airspace, which are required for effective gas exchange. In fact, inhibition of angiogenesis was shown to impair alveolar development in rodent models (14), and lung VEGF-A and PECAM-1 expression was decreased in the lungs of infants who died of severe BPD (16). Findings from this study provide further evidence that pulmonary vascular growth is a critical driver of lung maturation, and they suggest that therapeutic interventions to preserve the survival and function of ECs—in particular, c-KIT$^+$ ECs with progenitor properties—may effectively stimulate lung vascular growth, improve alveolarization, and reduce the risk of pulmonary hypertension in preterm infants. Therefore, alternative strategies to improve postnatal lung angiogenesis warrant more extensive investigation.

This outstanding work convincingly demonstrates the theme that "the rare informs the common." This is exemplified in the setting of other rare lung vascular diseases, such as heritable pulmonary arterial hypertension, in which the discovery of genetic aberrations related to BMPR2 signaling led to extensive insights into the pathobiology and potential treatment of idiopathic and more common forms of pulmonary arterial hypertension. Similarly, the exciting inroads made by the Ren laboratory not only enhance our understanding of the genetic underpinnings of lethal lung developmental disorders but also contribute to a greater understanding of more common forms of lung hypoplasia, such as observed in preterm infants with BPD, and provide exciting new leads for future therapeutic interventions. ■

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The 2018 Diagnosis of Idiopathic Pulmonary Fibrosis Guidelines: Surgical Lung Biopsy for Radiological Pattern of Probable Usual Interstitial Pneumonia Is Not Mandatory

Clinical practice guidelines advise clinicians on the management of patients based on evidence and evolving knowledge. Questions that are important to patients and clinicians are posed by an expert panel, and a full systematic review of the evidence is performed by methodologists who have neither financial nor intellectual conflicts of interest. The synthesized evidence is discussed by content experts whose potential conflicts of interest are managed, and then recommendations are formulated after considering the balance of benefits versus harms and burdens, quality of evidence, patient values and preferences, cost, and feasibility.

In 2018, the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT) published a clinical practice guideline on the diagnosis of idiopathic pulmonary fibrosis (IPF), updating guidelines from 2011 (1, 2). The new guidelines *1*) used systematic reviews to inform each recommendation in strict accordance with the Institute of Medicine Standards for Trustworthy Guidelines (3), *2*) eliminated the radiological categories of "possible UIP pattern" and "inconsistent for UIP pattern" and the pathological categories of "possible UIP" and "nonclassifiable fibrosis," and *3*) refined the radiological and pathological patterns of "UIP" and defined "probable UIP" and "indeterminate for UIP." The overriding goal of the guidelines was to help clinicians diagnose IPF more accurately, thereby facilitating appropriate treatment, as described in the 2015 guidelines for the treatment of IPF (4).

The radiological patterns of usual interstitial pneumonia (UIP) described in the ATS/ERS/JRS/ALAT guidelines are like those described in a statement from the Fleischner Society (5); however, the two documents make seemingly different recommendations about whether to perform surgical lung biopsy (SLB) in patients with the radiological probable UIP pattern by high-resolution computed tomography (HRCT) (6). Specifically, the ATS/ERS/JRS/ALAT guidelines make a conditional recommendation for SLB after multidisciplinary discussions (MDDs), whereas the Fleischner Society statement indicates that a confident diagnosis of IPF can be made without SLB in the right clinical context. This reflects differences in methodology and terminology rather than any substantive difference in principles and recommended practices.

It is apparent that the recommendations in the ATS/ERS/JRS/ALAT guidelines are subject to misinterpretation as a mandate for SLB in patients with probable UIP. Avoiding this misinterpretation is precisely why the ATS/ERS/JRS/ALAT recommendation was assigned a strength

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