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# Pathogenesis of Interstitial Lung Disease in Children and Adults

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Interstitial lung diseases (ILDs) occur across the lifespan, from birth to advanced age. However, the causes, clinical manifestations, histopathology, and management of ILD differ greatly among infants, older children, and adults. The historical approach of classifying childhood ILD (chILD) using adult classification schemes may therefore have done more harm than good. Nevertheless, identification of novel forms of chILD in the past decade, such as surfactant metabolism dysfunction disorders and neuroendocrine cell hyperplasia of infancy (NEHI), as well as genomic analysis of adult ILDs, has taught us that identical genotypes may result in distinct phenotypes at different ages and developmental stages, and that lung developmental pathways and cellular phenotypes are often recapitulated in adult ILDs. Thus comparison of the pathophysiology of ILD in children and adults in the context of lung development is useful in understanding the pathogenesis of these disorders, and may lead to novel therapeutic interventions for ILDs at all ages.

## Introduction

If there is any "central dogma" of chILD, it is a modification of the overarching mantra of pediatrics, that is, that chILD is "not just small adult" ILD. Largely through the work of our pioneers in the field, Dr. Hillman, Dr. Fan, and Dr. Langston, we have emphasized that shoe-horning childhood ILDs (chILDs) into adult classification systems does far more harm than good.[1] Many of the early descriptions of chILD considered it a form of idiopathic pulmonary fibrosis (IPF), which is now known to be a disease exclusively of adults. However, the child is often father of the man, as evidenced by recent resurgence of interest in developmental origins of adult disease, the hypothesis that many chronic disorders of adults arise during development.[2,3] Thus, while from a clinical perspective it makes sense to maintain a bright line between chILD and adult ILD, from a teleological perspective it is useful to consider mechanisms that might be shared between the 2, as they may have critical therapeutic implications. This brief review considers the connections between ILDs affecting children and adults, with a focus on 2 of the "novel" chILD entities, surfactant metabolism dysfunction disorders and neuroendocrine cell hyperplasia of infancy (NEHI). Some of this material has been more extensively reviewed elsewhere.[4]

### *General pathophysiology of ILD*

Most ILDs share in common structural remodeling of the distal airspaces leading to impaired gas exchange. In the past, such remodeling was felt to result from persistent inflammation; however, the more recent paradigm has been tissue injury with aberrant wound healing, often resulting in collagenous fibrosis. Wound healing and fibrosis are complex, involving numerous cellular processes and molecular pathways (eg, cell adhesion, migration, proliferation, apoptosis, extracellular matrix (ECM) biology, and phenotypic reprogramming). Fibrosis *per se* is more prominent in adult ILDs than in chILD disorders. The pathophysiology of lung fibrosis (from an adult ILD perspective) has been the subject of multiple reviews.[5–8] It is useful to start with what is known about fibrosis in considering the pathophysiologic derangements common to adult and chILDs.

Many types of ILDs follow some type of injury to the distal airspaces (eg, infection, radiation, environmental exposures), resulting in damage to the epithelial or endothelial layers and the associated basement membrane. Many authors have thus conceptualized lung fibrosis as a form of aberrant repair.[9–12] In bleomycin-induced animal models, as well as in genetic models of surfactant disorders, apoptosis of the alveolar epithelium has been shown to be a critical early

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event. Inflammation is present in many types of ILD, and many forms of ILD are triggered by inflammatory events, such as infection or hypersensitivity. However, lung inflammation does not necessarily result in fibrotic remodeling, and fibrosis can occur in the absence of inflammation; therefore, inflammation has a prominent, but not an essential, role in lung remodeling and fibrosis. ILD occurring in the setting of inflammatory or autoimmune disease occurs in both children and adults, and would seem to be where adult ILDs and chILDs are most alike, although there have been few studies comparing clinical or pathologic manifestations of immune-mediated ILD at different ages. Angiogenesis is prominent in several animal models of ILD and substantially affects outcomes. Many ILDs feature fibroblast proliferation and excessive elaboration of ECM molecules such as collagen. Fibroblasts, which normally reside in the scant interstitial spaces between alveoli and surrounding small airways and blood vessels, are critical in both lung development and remodeling. Fibroblasts also produce proteases, protease inhibitors, cytokines, and chemokines, and thus have major effects on other cell types and the overall milieu. Recent data have demonstrated alternate origins of fibroblasts, including circulating precursors such as fibrocytes and mesenchymal stem cells, and transdifferentiation of other cells, such as epithelial–mesenchymal transition (EMT). Although many of these events are essential for repair of the injured lung, excessive activation or failure of resolution of these pathways is felt to result in disabling fibrosis.

### *Role of developmental pathways*

Selman et al. had a major impact on the field by proposing reconsideration of IPF as a disorder of epithelial–fibroblast interaction.[6] Interactions between the epithelium and mesenchyme are known to be critical in developmental morphogenesis of the lung,[13] and are also prominent in lung fibrogenesis. Expression array data from both IPF and experimental models have demonstrated the recapitulation during fibrosis of expression patterns and signaling pathways critical during lung development.[14,15] Thus it seems that many of the cellular and molecular events critical to "modeling" of the lung are recapitulated during the "remodeling" following injury or during the pathogenesis of ILD. We and others have thus suggested that fibrosis and ILDs may be conceptualized as "disordered redevelopment" of the lung.[4]

### *Role of the alveolar epithelium and surfactant metabolism*

The lung alveolar epithelium is the final barrier interface between the bloodstream and the environment. The epithelium, along with alveolar macrophages, responds to environmental insults via interactions with mesenchymal and vascular cells, and thus is critical to normal alveolar homeostasis. Intrinsic or extrinsic epithelial cell stress can lead to surfactant dysfunction, epithelial apoptosis, impaired innate immunity, altered injury response, and promote abnormal epithelial–mesenchymal signaling, and a variable degree of remodeling up to and including fibrosis.[16] Genetic abnormalities of surfactant proteins are teaching us a great deal about how disturbances of alveolar homeostasis result in disease.

Genetic disorders in surfactant production and function in the lung have been demonstrated to cause significant, often severe primary lung disease in full-term infants, a variable spectrum of alveolar and interstitial alterations in older children, and fibrotic disease in adults. Recent laboratory work including studies in transgenic and knockout mice define molecular mechanisms and genotype–phenotype correlations for these disease entities, and may give clues about how age and stage of development affect the response to lung injury. The genetic basis of chILD, with an emphasis on inherited surfactant metabolic dysfunction disorders, is the subject of another review in this volume.[17] The relationship of these disorders to pathophysiology of ILD and presentation across the lifespan will be discussed here.

Hereditary surfactant protein (SP)-B deficiency is usually a severe, rapidly progressive respiratory disease in newborns, often fatal by 3–6 months of age.[18–20] However, children with partial defects in SP-B production have been reported with severe chronic lung disease in infancy,[21] and 2 children have survived beyond 2 years of age, both with chronic oxygen therapy. No disorders of SP-B have been reported in association with adult lung disease.

Age of onset of respiratory symptoms in patients with *SFTPC* mutations is highly variable including both early (newborn) and late (>70 years) presentation.[22] The 10%–15% of affected patients develop respiratory symptoms within the first month of life, while 40% develop symptoms between 1 and 6 months of life. The histopathologic appearance appears to vary with age at presentation. In infants, the most common histopathologic diagnosis is chronic pneumonitis of infancy. Other histopathology diagnoses in children with *SFTPC* mutations include neonatal pulmonary alveolar proteinosis (PAP), infantile desquamative interstitial pneumonia (DIP), and nonspecific interstitial pneumonia (NSIP). In adults with *SFTPC* mutations and chronic ILD, the most common histopathologic diagnosis is pulmonary fibrosis with either NSIP or nonspecific interstitial pneumonia (UIP).[22,23] *SFTPC* mutations rarely cause ILD in adults; in 2 recent studies of adults with sporadic UIP or NSIP, only 1 patient out of 135 was identified with an *SFTPC* mutation.[24,25] Progression of disease is variable ranging from no oxygen supplementation to need for lung transplantation. Asymptomatic individuals with *SFTPC* mutations have also been identified.[22] The wide variability in age of presentation, severity, and progression with *SFTPC* mutations suggest that additional genetic or environmental factors modify lung disease. Most of the *SFTPC* mutations are thought to cause misfolding of pro-SP-C and preclude processing of the precursor protein to the mature peptide. A primary cellular mechanism to deal with deleterious mutant proteins includes the endoplasmic reticulum (ER)-based stress response pathways that aid degradation or slow production of an offending protein. ER stress response proteins are increased in the fibrotic lung tissue of individuals with *SFTPC* mutations consistent with aberrant stress response as a component of disease.[26–28]

Expression of a common human *SFTPC* mutation specifically in the lungs of mice resulted in severe disruption of lung development.[29] This finding is consistent with the deleterious effects of the mutated pro-SP-C in human lung disease wherein the adaptive mechanisms to cope with a cytotoxic or misfolded pro-SP-C are overwhelmed. SP-C has

also been inactivated in the lung by gene targeting; SP-C null mice developed an ILD-like disease with age. The ILD histopathology in SP-C null mice was heterogeneous and dependent on the strain of mice suggesting that genetic modifiers influence the disease, consistent with the clinical variability described earlier.[30] Fibrosis was increased in the lungs of SP-C null mice exposed to bleomycin indicating that SP-C-deficient lungs are predisposed to profibrotic injury.[31] Exacerbations of disease in SP-C-deficient individuals have been linked to infections. SP-C null mice are susceptible to infection with the pulmonary pathogens *Pseudomonas aeruginosa* and respiratory syncytial virus (RSV).[32,33] The increased sensitivity of SP-C-deficient mice to RSV was linked to increased expression of a cellular innate immune receptor, TLR3 that responds to viral double-stranded RNA (dsRNA). Inflammation was more severe in the lungs of SP-C null mice exposed to synthetic dsRNA. SP-C was shown to block dsRNA stimulation of TLR3 signaling *in vitro* suggesting that SP-C may modulate early events in viral infection including receptor activity.[33] The infection susceptibility of SP-C-deficient mice and infection-related exacerbation in humans is consistent with the emerging view that SP-C is an essential component of pulmonary innate host defense.

Mutations in the *ABCA3* gene are currently the most common genetic cause of respiratory failure in full-term infants with >150 distinct mutations identified. Most infants with *ABCA3* mutations present with severe respiratory distress that requires ventilatory support in the immediate newborn period. However, a common mutation of the *ABCA3* protein has been identified in older children with chronic ILD with the onset of symptoms varying from milder neonatal disease to presentation later in childhood. Mutations in *ABCA3* have also been identified in adolescents and adults with chronic ILD with histological features of UIP.[34,35] The direct impact of an individual mutation on ABCA3 structure and function in relation to the clinical course has been determined for a small number of defined *ABCA3* mutations.[36] When mutations associated with mild disease were expressed *in vitro*, the mutant ABCA3 protein was found to retain residual transport activity and acquire a subcellular localization similar to wild-type ABCA3. These results were interpreted to indicate retention of partial catalytic and transport function accounts for the mild disease. In contrast *ABCA3* mutations located in predicted critical functional domains were devoid of any enzymatic activity, correlating with the observed poor clinical outcome. *ABCA3* may also be a modifier gene in lung disease caused by *SFTPC* mutations, as patients heterozygous for both an *ABCA3* and an *SFTPC* mutation had more severe lung disease than family members with only the *SFTPC* mutation.[37]

Inactivation of the *ABCA3* gene by gene targeting in mice causes respiratory failure and death in the immediate neonatal period.[38,39] Lungs of *ABCA3*-deficient mice had malformed lamellar bodies, and surfactant phosphatidylcholine and phosphatidylglycerol levels were decreased, similar to the disturbance of human surfactant composition. Insights into regulation of *ABCA3*-dependent surfactant production have come from *ABCA3* promoter analysis. Sterol responsive transcription factors sterol response element-binding protein-1a (SREBP-1a) and SREBP cleavage-activating protein (SCAP) affect *ABCA3* promoter activity. SREBP-1a stimulated ABCA3 promoter activity *in vitro* while SCAP deletion in the lungs of mice decreased the expression of fatty acid, cholesterol, lipid biosynthetic genes, and *ABCA3* in embryonic lung.[40,41] Expression of both SCAP and SREBP-1a are controlled by the transcription factor STAT3. When STAT3 was inactivated in lung epithelial cells, the type II cells had reduced ABCA3 expression and lacked normal lamellar bodies.[42] These findings identify a central role for lipid-sensitive factors in controlling a network of genes that sustain *ABCA3* and related lung lipid metabolism. Abnormalities in these may account for as yet undefined rare cases of ILD.

A recent study reported an association between 2 heterozygous mutations in the *SFTPA2* gene and familial pulmonary fibrosis that segregated with lung cancer in adults.[43] Preliminary studies suggested that the mutations caused misfolding and trapping of SP-A in the ER. As SP-A knockout mice have normal lung structure and function and do not develop ILD, the *SFTPA2* mutations likely exert a toxic gain-of-function effect as seen in *STFPC* mutations.

An important insight that has emerged from the study of surfactant dysfunction disorders is that mutations in a single gene can cause different disease manifestations at different ages and stages of development. This can be the result of different mutations that affect the physiology of the gene product in different ways, or perhaps an identical mutation that results in an abnormal response to an environmental insult ("second hit") that may occur at a specific developmental stage. Another example is some forms of α-1 proteinase deficiency, in which a mutation may result in toxic gain-of-function causing neonatal jaundice or later cirrhosis, and loss-of-function resulting in emphysema in response to smoke exposure. Thus in addition to genotype and phenotype, it may be useful to consider "auxotype" (Greek root *aúx(ein)* to grow; generally used to refer to microorganisms differentiated on the basis of environmental conditions required for growth) in understanding interstitial lung diseases (ILDs) in children and adults.

### *Neuroendocrine cells and diffuse lung disease*

Neurendocrine cell hyperplasia of infancy remains somewhat enigmatic since its original description by Deterding et al. in 2005.[44] As implied by the name, and by its location in the new chILD classification system,[45] this is primarily a condition of infancy. Mean age at presentation was 3.8 months. However, at the time of publication two-third of the patients, then at school age, had persistent respiratory symptoms and some showed continued evidence of air trapping and/or oxygen requirement. This cohort of patients would now be in their teens; it would be interesting to see if any remain symptomatic. There are reports and small series of a similar syndrome in adults. In a series of 19 patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNCH), cough and dyspnea were the most frequent symptoms, with an average symptom duration of 8.6 years before diagnosis. Symptomatic and asymptomatic individuals showed mainly stable disease without treatment, although one patient progressed to severe airflow obstruction and one was diagnosed at single lung transplantation. Mosaicism with nodule(s) was the typical pattern of DIPNCH on HRCT. Lung function tests showed obstructive ($n = 8$), mixed ($n = 3$), or normal ($n = 5$) physiology.[46] In another report of patients aged 49–76 years from Brazil, all

were women, underscoring the noted female predominance of DIPNCH, and all had a mosaic pattern on HRCT and mild–moderate airflow obstruction.[47] Whether there is a spectrum from NEHI to DIPNCH, or whether these represent similar but distinct processes remains to be seen. The etiology and pathogenesis of both disorders are unknown, but the childhood origins of NEHI and expanded neuroendocrine cell foci within bronchioles are consistent with the working concept that various forms of chILD in part emerge as a disordered development/redevelopment. The distinctive neuroendocrine cellular lesions in NEHI and DIPNCH are identified through immunostaining for the neuropetide bombesin. Careful co-localization studies using immunogold electron microscopy revealed that pulmonary neuroendocrine cells in infants express combinations of bombesin, calcitonin, and calcitonin gene-related peptide (CGRP).[48] These findings have an intriguing connection to studies to map mouse lung airway stem cells. Experiments to detect the origins and function of airway progenitor/stem cell in the lungs of mice have identified a population of distinct slow turnover, injury-resistant neuroepithelial cells that reside at bronchoalveolar duct junctions and repopulate injured airways.[49,50] The role of these regenerating cell foci in airway homeostasis has been tracked by their intense distinctive staining for the neuropeptide CGRP similar to the expression of CGRP in the human bronchiolar neuroendocrine cells. Despite airway anatomical differences between the species, the overlap in the role of newly identified CGRP-positive neuroendocrine cells as key airway progenitor cells and the equivalent human cell as the lesion in NEHI suggests the exciting concept that NEHI is a progenitor cell/stem cell disease due to misregulated progenitor cell growth. A search for mechanisms by which fibrillin-1 deficiency causes impaired alveolar development found that a transcription factor, Neuro-D, has major effects on neuroendocrine cell differentiation and proliferation as well as distal alveolar development, reinforcing the concept that neuroendocrine cells may have an important role in alveolar morphogenesis.[51]

## Overall Summary and Future Directions

We now know the molecular defects underlying a variety of previous idiopathic childhood interstitial diseases. Disorders of surfactant homeostasis underscore the importance of normal lung epithelial biochemistry in maintaining normal lung function. As more key target genes for alveolar homeostasis are identified, the underlying causes of additional forms of pediatric ILD will be revealed. Whether mutations cause a fundamental derangement (eg, lack of surfactant protein), induce cellular stress (protein misfolding), or affect response to an environmental agent (disordered innate immunity) is likely to affect the age at presentation. Analysis of the surfactant protein family and *ABCA3* genes have identified an extensive and growing number of transcription factors such as *NKX2.1* that when mutated can perturb cellular function or surfactant metabolism as a cause of what was idiopathic disease. Similarly incorrect regulation of progenitor cell function and growth may underlie NEHI as an early onset disease. It is possible that DIPNCH is caused by abnormal regulation of NE cell response to injury thus accounting for the later presentation. Thus completely different aspects of "disordered lung development" may result in disease phenotypes in children that are not a mechanism of ILD in the relatively "static" non-growing adult lung. Pedigrees of *SFTPC* mutations exist where the same genetic lesion elicits severe respiratory symptoms at several months of age in some individuals while others are not diagnosed until the second to fifth decade of life. Such a continuum of disease indicates that carefully defining the regulatory networks that influence gene expression, as well as the consequence of an aberrant gene product, may reveal the etiology of a subset of adult ILD that overlaps with infant disease. Thus it is critical to consider age and developmental stage, or "auxotype," in addition to genotype, in considering the phenotype of a diffuse lung disease. In addition, there are unanticipated findings such as compound heterozygous individuals for a single gene (*SPTPB* or *ABCA3*) or for 2 distinct genes in a common process that together amplify the apparent ILD (*SFTPC* and *ABCA3*). Re-creation of the genetic defects in mice and careful study of cellular phenotype alterations *in vitro*, combined with coordinated clinical assessment of genotype, phenotype, and "auxotype," will aid in discerning mechanisms and factors that modify the severity of disease as well as provide rational targets for therapeutic testing.

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## Author Disclosure Statement

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