Update in Diffuse Parenchymal Lung Disease 2013

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Abstract

The period covered by this update can be considered as the most exciting period in idiopathic pulmonary fibrosis (IPF) research. It started with the identification of genetic variants that are associated with IPF in the majority of patients and continued with discovery of molecular and genetic biomarkers that predict distinct clinical presentations of patients with IPF and potential new biological mechanisms. More importantly, the period ends with the publication of two groundbreaking studies that confirmed that two drugs, pirfenidone and nintedanib, slowed disease progression, leading to a historic approval by the FDA. In this update, we describe these key advances, their scientific and significant clinical implications, and future directions.

Keywords: IPF; ILD; genomics; personalized medicine; immunity

In this update in diffuse parenchymal lung disease for 2013, we focus on advances in the field of idiopathic pulmonary fibrosis (IPF) because of the dramatic progress in the understanding and management of this disease. To provide a better view of the scope and extent of the progress, we decided not to limit ourselves to the 2013 calendar year and instead used the broader definition of the academic year. This allowed us to review the genetic discoveries that happened in 2013 as well as the breakthrough drug studies that were published in the first half of 2014. In this review, we provide the highlights and key studies in this period that transformed our perception of IPF from a poorly understood lung disease without an effective treatment to a disease with a strong known genetic background, distinct progression patterns that can be described molecularly and genetically, and effective FDA-approved therapies.

A New Standard of Care for IPF

IPF, the most common idiopathic interstitial pneumonia, is a variably progressive disease that carries a poor prognosis. Over the last two decades, lung transplantation has extended survival and improved the quality of life for a limited number of patients who met criteria to undergo transplant. IPF had so far proven to be refractory to drug treatment; however, recent large international multicenter Phase III clinical trials testing the efficacy of pirfenidone (1) and nintedanib (2) demonstrate that antifibrotic agents can slow the decline of lung function in patients with IPF.

In a third phase III clinical trial (1) called ASCEND (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes), 555 patients with IPF were treated with pirfenidone, an antifibrotic agent that previously demonstrated promising but inconclusive results (3), or with placebo. Pirfenidone reduced the number of patients with decline in physiologic (FVC) and functional (6-min walk distance) metrics and improved progression-free survival. Although treatment did not affect survival in the ASCEND population, a prespecified pooled analysis incorporating results from the previous CAPACITY program (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes) with ASCEND demonstrated reduced death rates from IPF (or any cause) in the treatment group.

The efficacy of nintedanib, a small-molecule tyrosine kinase inhibitor, targeting vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor, was tested in two simultaneous phase III trials (IMPULSIS-1 and IMPULSIS-2). A total of 1,066 patients were treated with nintedanib or placebo; nintedanib reduced the rate of

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decline in FVC in both clinical trials. The proportion of patients with at least one acute exacerbation and the time to first acute exacerbation was lower in the treatment group in INPULSIS-2; however, this was not observed in the replicate trial. Although gastrointestinal side effects were commonly associated with pirfenidone and nintedanib, these symptoms did not lead to discontinuation of study medication in the majority of study subjects. The reductions in FVC decline were similar for pirfenidone and nintedanib.

The FDA granted both drugs fast track, priority review, orphan product, and breakthrough designations and approved both drugs on October 15, making it a date to remember for the IPF community (4). The concomitant approval of two antifibrotic drugs provides a renewed source of hope for patients and a much-anticipated evolution in the standard of care for the IPF medical community. It also marks the potential emergence of antifibrotics as a new class of therapeutics targeting a common process that underlies the end stage of many diseases and until recently was thought to be impossible to target. Although distinct and potentially overlapping mechanisms of action mediate the antifibrotic properties of pirfenidone and nintedanib in IPF, it remains unclear if subsets of patients will selectively respond to a single agent or if combination therapy will have synergistic effects and improved outcomes. In the short term, drug availability and provider or patient bias will influence the choice of therapy for patients with IPF. However, in the long term, we anticipate that efforts to characterize clinical and molecular traits in patients with IPF will enhance our ability to predict response and to personalize therapies.

IPF Genomic Studies and the Promise of Precision Medicine

Sequencing of the human genome and introduction of large-scale genomic approaches provides comprehensive assessment of susceptibility genes in multiple chronic diseases and allows us to better understand complex interactions between genetic, epigenetic, and environmental factors. Personalized or precision medicine will be one of the most important deliverables of genomic medicine; accordingly, a number of pulmonary fibrosis genomic studies in 2013 suggest that molecular and genetic information could be used to guide and personalize treatment of IPF (5, 6).

The discovery of novel susceptibility genes could facilitate the development of personalized therapies by identifying molecular pathways that contribute to pathogenesis and disease progression. Fingerlin and colleagues (7) completed a milestone association study in a large number of patients and identified multiple loci associated with IPF. This study in non-Hispanic white individuals confirmed the strong association of the *MUC5B* rs35705950 polymorphism with the risk of developing IPF. In a subsequent study by the same group, Peljto and colleagues (8) showed that the same polymorphism (rs35705950) is significantly associated with improved survival in patients with IPF. This unexpected finding suggests that patients with IPF with the rs35705950 polymorphism are at an increased risk of developing IPF, but when they develop the disease it exhibits a less progressive phenotype. Although the *MUC5B* SNP seemed to be specific to IPF but not to lung fibrosis secondary to systemic sclerosis or sarcoidosis (9), it was associated with the presence of interstitial lung abnormalities in the general population (10). Taken together with similarities in radiologic and physiologic features, these results suggest that interstitial lung abnormalities, in a subset of the general population, may represent an early stage of IPF.

Noth and colleagues performed a three-stage, genome-wide association study to identify SNPs associated with disease and mortality in patients with IPF (11). In addition to variants in MUC5B, they identified novel variants in Toll interacting protein (TOLLIP) and SPPL2C that were associated with IPF. Carriers of the TOLLIP minor allele rs5743890_G, which decreased susceptibility to IPF, experienced earlier mortality. TOLLIP expression was decreased in the lungs of patients with IPF. This study suggested that innate immunity aberrations may be involved in IPF and, together with the study by Peljto and colleagues (8), indicated that distinct clinical outcomes (i.e., survival) in IPF may be related to a patient's genetic background.

Further support for the potential role of innate immunity genes in IPF was provided by O'Dwyer and colleagues (12). They characterized the role of Toll-like receptor (TLR)3 loss of function in a murine model of pulmonary fibrosis and explored the effects of the TLR3 Leu412Phe polymorphism in fibroblasts and outcomes in two IPF cohorts. TLR3 knockout mice exhibited increased predisposition to bleomycin-induced pulmonary fibrosis compared with wild-type mice. The TLR3 L412F variant was associated with a greater risk of death and disease progression in patients with IPF in two cohorts. Fibroblasts homozygous or heterozygous for the polymorphic allele exhibited an enhanced fibroproliferative phenotype after TLR3 stimulation, an effect that was inhibited with recombinant IFN-β. These findings suggest a role for defective TLR3 function in disease progression while providing a mechanistic link between a gene variant and the development of fibrosis.

Additional evidence that distinct disease progression phenotypes could be characterized and predicted genomically was provided by Herazo-Maya and colleagues (13). Applying gene expression microarrays to peripheral blood mononuclear cells obtained from patients with IPF, they identified a 52-gene signature that was significantly predictive of increased mortality in two independent cohorts. A pathway enrichment analysis suggested that reduced expression of T cell costimulatory pathways, and in particular the genes CD28, ICOS, LCK, and ITK, was highly associated with subsequent mortality. A proportional hazards model combining expression of these genes with patient demographics and lung physiology improved the accuracy of the prediction of mortality and time to transplant. These findings suggest that immune aberrations may predict disease progression in IPF and that CD28, ICOS, LCK, and ITK are IPF biomarkers that could be used to stratify outcomes and improve the design of therapeutic trials.

Treating Lung Fibrosis by Protecting the Alveolar Epithelium and Regulating Fibroblast Differentiation

Major pathogenic determinants that drive the development of pulmonary fibrosis include alveolar epithelial cell injury, fibroblast/myofibroblast activation, and

extracellular matrix deposition. In 2013, several studies explored molecular mechanisms that regulate these biological events.

Previous studies in patients with IPF have shown up-regulation of developmental signaling pathways, including the Wnt/β-catenin (B-catenin) pathway. Murine studies have provided evidence that inhibitors of B-catenin signaling can abrogate experimental fibrosis, suggesting that alveolar B-catenin signaling promotes fibrosis. Recently, Tanjore and colleagues demonstrated that mice with selective deletion of B-catenin in alveolar epithelial cells had increased apoptosis, extracellular matrix deposition, and delayed resolution of fibrosis after bleomycin administration (14). Accordingly, the authors found that small interfering RNA knockdown of B-catenin in mouse lung epithelial cells led to decreased wound closure, proliferation, and increased bleomycin-induced cytotoxicity. The authors conclude that alveolar epithelial cell survival and wound healing are enhanced through β-catenin–dependent mechanisms. The findings also suggest that activation of select developmental pathways could contribute to alveolar epithelial repair after injury. This apparent contradiction may be explained by (*1*) the possibility that temporary activation of the B-catenin pathway is required for response to injury and healing, whereas sustained activation of the pathway may predispose to fibrosis, or (*2*) the possibility that activation of the pathway in one cell type, such as fibroblasts, may be profibrotic, whereas in epithelial cells it may be required for repair (15). The evidence for increased B-catenin in epithelial cells in IPF can be explained in this context as a failed compensatory response. A more detailed dissection of the role of the B-catenin pathway in animal models and potentially more sophisticated human models, such as tissue slices, may help to resolve this paradox.

The role of syndecans, which are abundant heparan sulfate proteoglycans that promote alveolar epithelial cell repair, inhibit fibroblast migration, and may attenuate experimental fibrosis, has not been studied in detail in lung fibrosis. Shi and colleagues describe a potential mechanism by which alveolar macrophages exert alveolar epithelial cytoprotective effects (16). The authors found significant increases of syndecan-2 in alveolar macrophages and bronchoalveolar lavage fluid of patients with IPF. Transgenic mice that overexpress human syndecan-2 in alveolar macrophages were protected from bleomycin-induced lung injury and fibrosis, and therapeutic administration of human recombinant syndecan-2 had the same effect. The authors suggest that syndecan-2 modulates transforming growth factor (TGF)-β1 signaling by promoting trafficking of the transforming growth factor β receptor I (TbRI) from a primarily plasma membrane nonraft localization to the caveolin-1–rich lipid-raft fraction and thus increases caveolin-1–dependent TGF-β1 and TbRI internalization and degradation. An intriguing aspect of this paper is that it suggests a paracrine effect by which alveolar macrophage syndecan-2 can protect alveolar epithelial cells from TGF-β1–induced cell death. Continued research into the role of proteoglycans should be very promising, considering the abundance of changes in proteoglycans in the fibrotic lung and their potential roles in modulating fibrosis.

TGF-β is a central mediator of fibrosis; therefore, the molecular pathways that regulate TGF-β activity and signaling are attractive targets for new antifibrotic treatments. TGF-β activation by the β_6 subunit of the $\alpha_v\beta_6$ integrin is a key regulatory event in tissue fibrosis, especially in the lung, but its expression is restricted to epithelial cells. To determine whether the α_v subunit plays a role in fibrosis, Henderson and colleagues used cre-recombinase, under the control of the *Pdgfrb* promoter, to inactivate the α_v integrin expressed in lung and kidney pericytes and myofibroblasts and in hepatic stellate cells (17). Deletion of the α_v integrin protected mice from experimental fibrosis by reducing TGF-β activation. In contrast, constitutive or conditional loss of myofibroblast-expressed β integrins did not abrogate lung, liver, or kidney fibrosis. CWHM 12, a small-molecule inhibitor of α_v integrins, attenuated the development and progression of organ fibrosis. Taken together, these findings suggest that modulation of the α_v integrins may affect TGF-β activation in stromal cells and should be further studied as a therapeutic intervention for pulmonary fibrosis and other fibrotic conditions.

Myofibroblast resistance to apoptosis and matrix stiffening are critical driving forces in the development and progression of human pulmonary fibrosis. Zhou and colleagues recently demonstrated that therapeutic targeting of the mechanosensitive Rho/ROCK pathway regulates myofibroblast contractility, differentiation, and survival (18). The authors demonstrate that ROCK-induced actin polymerization leads to nuclear translocation of MKL1, which further promotes differentiation and survival of myofibroblasts in response to biomechanical and/or biochemical fibrogenic stimuli. Disruption of myofibroblast contractility with fausidil, a small-molecule inhibitor of ROCK, induced lung myofibroblasts to undergo apoptosis. Additionally, ROCK inhibition depolymerizes the actin cytoskeleton, decreases myofibroblast contractility, and abrogates MKL1-induced BCL-2 expression, which activates the intrinsic apoptosis pathway. These findings suggest that the use of a pharmacologic inhibitor of ROCK is a potential therapy for lung fibrosis by preventing fibroblast differentiation and inducing myofibroblast apoptosis.

The Origin of Lung Myofibroblasts in IPF

Lung fibroblast differentiation to myofibroblasts is associated with increases in extracellular matrix deposition that contribute to aberrant alveolar remodeling and decreased gas exchange. Hence, a critical component of successfully treating pulmonary fibrosis is to determine potential sources of myofibroblasts and the biologic processes that regulate myofibroblast differentiation. Two studies published in the *AJRCCM* provided insights into potential cellular sources of lung myofibroblasts, which may have significant therapeutic implications (19).

Using genetic tools, Hung and colleagues mapped the fate of lung mesenchymal progenitors that express the Foxd1 transcription factor and differentiate into lung cells with pericyte characteristics (20). The authors describe populations of cells that contain markers for pericytes, myofibroblasts, or both. The majority of the cells, defined as pericytes, did not express α-smooth muscle actin, a protein closely associated with myofibroblasts. After bleomycin administration, Foxd1 progenitor–derived pericytes proliferated and differentiated into matrix-synthesizing

cells with a lung myofibroblast phenotype. These findings demonstrate that pericytes are fibrogenic precursors that contribute to the lung myofibroblast pool and suggest that Foxd1 progenitor–derived mesenchymal cells are potential therapeutic targets in pulmonary fibrosis.

Several human studies have demonstrated the presence of fibrocytes in patients with IPF; however, the mechanisms by which these circulating bone marrow–derived cells can contribute to the development of pulmonary fibrosis remains unclear. Using adoptive transfer, Nakashima and colleagues (21) identified a population of bone marrow–derived progenitor cells that differentiate into a distinct subpopulation of profibrotic cells that exhibit markers of dendritic cells and macrophages. After bleomycin administration, these effector cells mobilize to the lung, where they proliferate, differentiate, and enhance fibroblast chemoattractant activity. These findings suggest that the bone marrow contributes to the development of pulmonary fibrosis by generating hematopoietic progenitor cells that are recruited to the lung after injury; these cells in turn modulate myofibroblast differentiation and extracellular matrix production.

Novel Roles for Innate and Acquired Immunity in Pulmonary Fibrosis

The increased mortality in response to immunosupression in a majority of patients with IPF, the paucity of inflammatory cells in IPF lung pathological specimens, and the wealth of data from animal models of disease have led many to conclude that increased inflammation and activated immunity in their most simplistic definitions are probably not important in IPF. However, evidence for immune aberrations in patients with IPF and the association of variants in innate immunity genes with distinct outcomes mentioned above (7, 13) suggest that a more nuanced assessment of immunity in IPF is required. Below we highlight studies that explore the role of the adaptive immune system in the development of pulmonary fibrosis.

Reilkoff and colleagues (22) studied the role of Semaphrorin 7, a glycosylphosphatidylinisoto membrane anchor protein expressed on lymphocytes that is known to be involved in regulating cell migration and immune modulation in lung fibrosis. Semaphrorin 7a–expressing regulatory T cells were increased in patients with rapidly progressive lung fibrosis, and hematopoietic expression of Semaphrorin 7a was sufficient for fibrosis and lung remodeling in a TGF-β1–driven murine lung fibrosis model. A series of adoptive transfer experiments revealed that Semaphrorin 7a is expressed in a population of regulatory T cells with impaired suppressor capabilities and profibrotic inflammatory responses. Although the direct connection between the human and mouse findings is still unclear, these results again indicate that aberrations in adaptive immune signaling are frequently encountered in patients with IPF and that its role in the progression of IPF should be investigated.

In that vein, Kahloon and colleagues found that anti-HSP70 antibodies are increased in IPF and enriched in populations that experienced disease progression and/or acute exacerbations (23). Although anti-HSP70 antibodies were found only in a minority of patients with IPF, these data suggest that more detailed immunophenotyping approaches should be applied to identify the minority of patients that may benefit from immunomodulation and targeting of pathway-specific immunomodulatory interventions.

Conclusions

The most remarkable achievements in the time period covered in this update were the promising results reported out of the phase III clinical trials testing the therapeutic role of pirfenidone and nintedanib in IPF. The slowing of disease progression and the relatively benign safety profile led the FDA to approve the two new oral antifibrotic agents for IPF on October 15 of this year. This approval can be considered the climax of a decade of exponential increases in our understanding of the basic mechanisms of fibrosis as well as the molecular characteristics and genetics of IPF. Although the period covered in this update can be considered as the "season of breakthroughs" for the IPF community, this progress is occurring at a time in which the reduction in availability of research funds and the uncertainty about government funding is leading many pulmonary researchers to question the feasibility of research careers. Although the significant achievements of 2013 cannot alleviate these doubts, they should at least inspire junior investigators, demonstrating that, with persistence, significant patient-relevant insights are attainable in chronic lung disease. They should also encourage funding agencies to make significant efforts to secure funding to these areas because the strides made were big and answers are closer than they ever where, and obviously this is not the time to let go! ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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