Pulmonary fibrosis: something old, something new...still waiting for a breakthrough

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Whether idiopathic or associated with environmental triggers or rheumatic and connective tissue diseases such as systemic sclerosis (SSc), pulmonary fibrosis (PF) remains an incurable condition. Idiopathic pulmonary fibrosis (IPF) and SSC-associated PF demonstrate convergent and divergent features and gene expression profiles (7, 9, 14), suggesting that similarities exist between diseases of comparable phenotype. With the emergence of SARS-CoV-2 and the associated pulmonary fibrosis complication in some patients (5, 17), PF has garnered increased interest as efforts to mitigate the long-term consequence of the infection bring a new sense of urgency to advance research on PF. A recent survey administered by the Pulmonary Fibrosis Foundation (PFF) and described in this issue (15) showed that 86% of Americans are not aware of the symptoms of PF. In its effort to promote awareness and improve diagnosis and treatment for patients with PF, the PFF has established a Care Center Network with 68 medical centers across the United States, developed a Registry that currently tracks 2,000 patients, and launched a consortium to identify biomarkers in IPF (15). Admirable efforts to disseminate information about PF would not be possible without the support of patients, caregivers, clinicians, and investigators, in addition to the various organizations that promote awareness about PF and support research in the field.

Recent advances in PF research have included new findings as well as exploring old findings from a different angle. Much progress has been made in understanding mechanisms mediating the fibrotic phenotype and the cellular players. For example, new insights have been gained on the functional impact of matrix stiffness (16). There has been renewed interest in molecules such as members of the cellular communication network (CCN) (12) and the insulin-like growth factor (IGF) (3, 22) family of proteins and their functions in the setting of lung fibrosis. Moonlighting functions for enzymes such as sialidases (11) and phosphatases (1, 18, 21) have been identified. Research into mechanisms mediating oxidative stress and its role in lung fibrosis has continued (6). Characterization of new cell populations and subpopulations has refined our understanding of cellular heterogeneity in lung disease. These include characterization of pericytes (20) and myofibroblasts (2, 19) and their functional roles in healthy and diseased lungs. The vasculature has also been implicated in PF (4). The role of central mediators of fibrosis such as transforming growth factor (TGF)-β has continued in the form of targeted therapies, as discussed in another editorial in this issue (10).

Progress has included the identification of extracellular vesicles and their role in the pathogenesis of PF, in cell-cell communication, as potential biomarkers, and as therapeutic targets and/or carriers of therapeutic cargo (13). In the past few years, much has been learned about the potential role of epigenetic modifications such as DNA methylation in the development and progression of PF. Mechanistic insights into the role of noncoding RNAs and the regulatory network they modulate unveiled new avenues of research. Novel common and rare genetic variants have been reported in patients with PF, especially those with IPF (10), suggesting that the disease may develop in those with genetic susceptibility factors. Furthermore, development of new research tools to more closely mimic the human disease has included hydrogels, lung slices, and three-dimensional (3-D) lung cultures, among others. These, in combination with recent insights gained from single-cell RNA sequencing and integration of a variety of “omic” approaches, have provided a wealth of new leads in PF research.

Although sex differences in the prevalence of diseases characterized by PF have been identified, with male predominance in IPF and female preponderance in SSc, less is known about sex-related pathogenic mechanisms leading to PF. Sex differences in lung disease is the focus of an upcoming National Heart, Lung, and Blood Institute (NHLBI)-hosted workshop entitled “Sex/Gender-Related Autoimmune Induced Lung Disease” that will generate discussions and collaborations across diseases and institutions.

Despite extensive research, the triggers of PF have remained elusive. Therapies that slow the progress of PF have been developed; however, none of the available therapies halts the progression of fibrosis or reverses it. Thus, the need to develop effective therapies is undiminished. Identification of new potential therapies has led to several potential candidates at various stages of development in the bench-to-bedside pipeline. Such targeted approaches build on insights gained from mechanistic studies and identification of specific targets. Future therapies are likely to harness the patients’ own “blunted” antifibrotic response and should simultaneously target multiple pathways implicated in PF pathogenesis. Such therapies can be guided by a better understanding of mechanisms mediating the resolution of fibrosis and promoting matrix degradation (8).

The emergence of PF as a complication of COVID-19 is likely to garner new and renewed interest in PF research and will propel research in the field in an era when collaborations and new tools and technologies have accelerated progress and promoted new discoveries. Emerging topics of research focus in PF are likely to further advance the field with novel insights.
gained into inflammaging, senescence, metabolism, mitochondrial dysfunction, the microbiome, matrixe functions, the identification of biomarkers of disease and response to therapy, mechanisms mediating the resolution of fibrosis, and ultimately the translation of findings for the development of antifibrotic therapies. Additional emerging areas of PF research are included in recent calls for papers by the American Journal of Physiology-Lung Cellular and Molecular Physiology on “Deconstructing Organs: Single-Cell Analyses, Decellularized Organs, Organoids, and Organ-on-a-Chip Models,” “Circadian Rhythms in the Lung,” and “Extracellular Vesicles in Lung Health, Disease, and Therapy.”

September is Pulmonary Fibrosis Awareness Month. As we raise awareness about the disease and its impact on patients, their families, and our health system, we must also raise awareness about the importance of research for the identification of the cause and the cure for PF. As Mary Woodard Lasker, who advocated tirelessly for increased funding of medical research, pointedly said: “If you think research is expensive, try disease.”

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