Pulmonary research in 2013 and beyond: a National Heart, Lung, and Blood Institute perspective

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Predicting the future is always perilous, particularly regarding trends in biomedical research. With no scientific analog of a crystal ball, we probably prognosticcate best by simply observing trends — noting areas of research and approaches that have recently developed or are moving forward rapidly. Several general predictions follow immediately from such an approach. Studies on pulmonary health and disease will be increasingly multidisciplinary, involving experts in fields beyond the lung and even beyond the biological sciences, including engineering, physics, informatics, and other physical sciences. Partnerships among academia, government, industry, and patient advocacy organizations will be essential to provide the needed expertise and support and to maximize efficiency. Research teams will be bigger and less defined by geography. And, very importantly, data will be increasingly abundant as a result of the burgeoning of “omics,” making data analysis, informatics, and computational methods a challenge for the research community.

Predictions can also be made regarding specific areas of research that are likely to expand and be fruitful over the next 5–10 years. This perspective identifies a number of these promising areas. It is written from the viewpoint of the Division of Lung Diseases (DLD) of National Heart, Lung, and Blood Institute (NHLBI), which supports a wide range of basic, clinical, and applied research in pulmonary, critical care, and sleep, most of which is investigator initiated. The DLD portfolio encompasses research on the fundamental mechanisms of how the lungs work in health and common lung conditions — chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, and acute lung injury — and less frequent conditions, such as cystic fibrosis, pulmonary arterial hypertension, primary ciliary dyskinesia, and lymphangiomyomatosis (LAM), as well as lung disease secondary to systemic diseases such as sickle cell anemia and human immunodeficiency virus (HIV) infection. The research is supported through single-site awards and multisite clinical projects to evaluate questions such as the role of statins in attenuating acute lung injury or COPD exacerbations, and the characterization of diseases such as sarcoidosis. The portfolio also includes the development of research resources, such as repositories of biological samples obtained from human subjects and production of rodents with genetic alterations to help model human diseases. In addition, DLD is engaged with voluntary, professional, and private sector organizations to leverage its resources and avoid duplication. From this broad perspective, we highlight a number of topics in pulmonary research and several areas of investigation that show promise for advancing the prevention, treatment, and cure of lung diseases.

Innovations in Disease Prevention

Avoidance of tobacco products, known occupational respiratory hazards, and contagious pulmonary infections and vaccination for influenza and Streptococcus pneumoniae, are currently the principal means of preserving lung health. On a worldwide scale, obstructive lung disease secondary to indoor air pollution is a major problem (19). Accordingly, prevention of this COPD-like disease should be a goal of lung researchers. Simple stoves that replace open indoor fires in developing countries can reduce indoor air pollution, but so far the reductions achieved do not appear to be enough to reduce disease (7).

Much has been learned about early origins of lung disease (13, 26), which opens the opportunity to study the developing lung in the context of both primary prevention strategies and promotion of healthy lungs, similar to what is underway for cardiovascular disease (18, 33). Looking beyond the traditional exposures and risk factors for lung disease, has progress been sufficient to identify lung diseases for which there are near-term opportunities for testing primary preventative interventions? If not, what resources are required to accelerate development and testing of such interventions?

The extent to which viral infections are a precursor of chronic lung disease is an area that merits further study. The possibility that viruses alter lung biology permanently has experimental support (2, 11, 16). Indeed, the repertoire of respiratory viruses keeps increasing. Human rhinovirus C exemplifies discovery of a new human viral pathogen whose late consequences, if any, are not known (4). An important related, but poorly understood, issue is the interplay between viruses and cigarette smoke (15). The relationship of viral infections to asthma has long been a challenge that continues (27). The role of viruses, including HIV, in pathogenesis of pulmonary arterial hypertension (3) or herpes viruses in pulmonary fibrosis (28) is not understood. Finding connections between viruses and lung disease should stimulate development of new vaccines and other forms of antiviral therapy. The role of the microbiome in disease prevention, development, progression, and treatment is new territory just now being explored.

Innovations in Understanding Lung Disease Pathogenesis

Alpha-1 antitrypsin (A1AT) deficiency exemplifies the complexity of understanding the pathogenetic mechanisms of chronic lung diseases. In A1AT the genetic defect and princi-
pal function of the deficient protein are known, but it remains a mystery why some individuals with the deficiency develop COPD and others do not. Clearly, chronic lung diseases such as COPD have complex pathogenesis. As such, gene-gene, gene-epigene, and gene-environment analyses, along with improved phenotypic, molecular, and genomic characterization, will be necessary to unravel the pathogenesis of these conditions.

Despite impressive steps forward, molecular characterization of lung diseases has only moved description of these conditions to a more sophisticated level. Still missing in the discoveries are mechanisms linking these findings to function and disease etiology; how abnormalities of the MUC5B gene (25) relate to idiopathic pulmonary fibrosis (IPF) is an example. Another is understanding how penetrance and expression of BMPR2 are dysregulated in pulmonary arterial hypertension. An important impediment to progress on mechanisms of chronic lung conditions is lack of good animal models of human conditions. Studies of individuals and families with heritable, uncommon forms of lung disease may yield opportunities for biological samples from which subtle abnormalities of physical properties and function can be investigated. For example, studying individuals with familial pulmonary fibrosis due to a mutation in surfactant protein C may provide valuable insights into early events in pulmonary fibrosis pathogenesis (29). Recent findings about effects of nicotine on vascular remodeling point to the importance of continuously integrating new and emerging concepts (30).

Innovations in Early Disease Detection

The goal of detecting a disease at an early stage is to begin treatment to prevent progression and ideally to achieve cure. Successful early detection occurs before symptoms or obvious physical manifestations, and, in the case of infections, before the infectious agent spreads to other individuals. Tuberculosis (TB) skin testing and chest radiographs to identify TB infections are the classic examples of tests for early detection of a lung disease. A recent example is low-dose chest computed tomography scans to detect lesions suspicious for lung cancer among middle-aged smokers (1). Early detection may not benefit everyone for every condition. Early detection is rational only selectively, when applied to individuals at increased risk for a treatable or preventable pulmonary condition or disorder. Increased risk may be suspected from personal habit (cigarette smoking), familial association (A1AT deficiency, idiopathic pulmonary fibrosis), environmental circumstances (premature birth, coal mining), use of medication with pulmonary side effects (amiodarone), and body size (massive obesity). So-called subclinical interstitial pneumonias are an example of a recently described condition detectable without clinical disease (8). The implications of identifying this condition and whether it is a precursor of clinical disease need to be determined.

Classically, biomarkers of lung diseases for identification of disease or as prognosticators have been nonspecific, such as arterial blood gases and indicators of inflammation like the erythrocyte sedimentation rate. Use of diagnostic panels of multiple factors already identified may be an innovative approach to monitor disease activity and generate prognoses. For example, coupling the BODE index for COPD with a battery of factors associated with inflammation, especially IL-6 levels, appears to improve the prognostication strength of BODE alone (6). An index derived from clinical data and serum MMP7 concentration can predict mortality in IPF patients (23). Prognostication tools may influence clinical decisions, such as early referral for lung transplant consideration.

In recent years, measurable factors linking to specific lung conditions have been reported: for example, serum VEGF D for LAM (34), and pulmonary vascular endothelial microparticles for emphysema (10). What makes these recent tests exciting is they derived from insights into disease pathogenesis. Circulating lymphocytes may carry molecular signatures of inflammatory conditions. Accelerated efforts are needed to discover other relevant origins/preclinical markers of lung disease susceptibility in peripheral blood leukocytes and lung cells that reflect the activity and prognosis of pulmonary diseases.

With rapid whole genome sequencing on the immediate horizon, identifying individuals with risk for a particular lung condition may become available. Using existing diagnostic tools with advanced molecular profiling of the lung may provide new paradigms to understand the earliest manifestations of lung pathology that will lead to more precise tailored interventions. At the same time, it remains critical to heighten awareness of lung conditions and the importance of early diagnosis using tools already available.

Innovations in Therapy

Except for the skin, the lungs are the only directly accessible organ. Accordingly, lung cells can be reached without passage through the circulation or by a surgical procedure. Although such access has enabled direct instillation into the lungs of medications such as surfactant replacement for neonatal respiratory distress syndrome, bronchodilators for COPD, and asthma and antibiotics for cystic fibrosis, recent studies demonstrate the possibility of altering lung gene expression by safely putting reagents into the lungs via the airways. An example of this approach is instilling vectors into the airways of mice designed to infect lung macrophages with the human A1AT gene, leading to production of human A1AT by mouse alveolar macrophages (32).

The capacity of the gut microbiome to process ingested molecules into bioactive forms might be an intriguing way to treat the lungs and to determine differences between individuals in the efficacy of drugs. A gut cardiovascular axis has been identified by which small molecules ingested are modified by gut organisms into agents that affect the development of atherosclerosis (14, 31). Ingestion of microbial products alters respiratory inflammatory cells consistent with the idea that the gut microbiome affects the lung (22). The relationship of the gut microbiome to the lung will be an exciting area for investigation to be developed along with studies of the lung microbiome itself. Clearly, as with the cardiovascular system, there is a lung-gut microbiome axis that has broad effects on the lung, including the response to drugs for lung diseases. This nascent area of research as it applies to lung health and disease needs further study.

Lung regeneration and stem cell therapy are the holy grail of treatment for advanced forms of lung disease. If this is going to happen much needs to be learned about populating the lungs with proliferative cells capable of differentiating into the vari-
etity of epithelial, vascular, and mesenchymal cell types in the normal lung including vascular and epithelial, for these cells to establish the lung architecture for gas exchange and for ways to deliver these cells to the lungs (17). Developing strategies for lung regeneration and repair will undoubtedly be an important direction for future lung research.

Acute lung injury affecting alveolar epithelial cells may be susceptible to reparative effects from bone marrow-derived mesenchymal cells. The mechanism appears to involve direct mitochondrial transfer from mesenchymal cells via channels connecting these cells to alveolar type 1 cells (12). Studies such as these and others with fat stem cells that reduce the effects of smoke on alveolar remodeling suggest the possibility that nonpulmonary cells and factors from extrapulmonary cells may be a source of therapeutics for lung injury (24).

Research to identify therapeutic targets in critical gene pathways is another strategy that can be used to develop new treatments for lung diseases. Translation of the results from the laboratory to clinical practice can be done rapidly if the targets are amenable to therapeutic agents that are already FDA approved for other purposes. For example, the chain of events that led from the discovery that mutations causing dysfunction of the TSC2 gene underlie the molecular defect in LAM, to the identification of mTOR as a key factor in regulating LAM cell growth, to proof-of-concept testing in an animal model, to clinical trials, to demonstrating that sirolimus (rapamycin) could slow progression of loss of pulmonary function in LAM patients took about 13 years (5, 9, 20). Efforts to identify both novel and repurposed agents show promise for the future but need to move at a more rapid pace.

Conclusions

We are in an era of remarkable advances in diagnosis, understanding, and treatment of lung diseases and conditions. Areas ripe for research now include development of molecular signatures for risk and monitoring lung diseases such as sarcoidosis, techniques of safely altering gene expression by lung cells in vivo, uncovering the late consequences of lung infections, especially viral, on lung immunity and inflammatory responses, and the interplay between the lungs and other parts of the human body such as the gut microbiome. The explosion of knowledge in recent years has shown that attaining better lung health for the country is possible and desirable given the very high prevalence and burden of lung disease (21). Progress has also taught us that the lungs and the respiratory system overall have incredible complexity, so the potential for generating new knowledge about the respiratory system appears inexhaustible. Our goal at NHLBI is to facilitate research and press the frontier of this exciting science to improve public health. At the same time, an important priority is to train the next generation of clinician/scientists to discover more about human lung biology in health and disease.

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