Pulmonary, Sleep, and Critical Care Updates

Update in Chronic Obstructive Pulmonary Disease in 2010

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The year 2010 marked several milestones for chronic obstructive pulmonary disease (COPD). Unfortunately, COPD moved from fourth leading cause of death in the United States to third. On the other hand, the United States also celebrated the 1-year anniversary of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which led to increased regulation of tobacco marketing, and the implementation of public health strategies to reduce tobacco-related morbidity and mortality (1). Also in 2010, the editorial team of the *Journal* published an article entitled "What the Journal Would Like to Publish on Chronic Obstructive Pulmonary Disease" (2). This article challenged the scientific community to focus on issues such as understanding disease susceptibility, the mechanism of inflammation persistence after smoking exposure is withdrawn, and the multicomponent nature of the disease. The review that follows is an overview of key publications on COPD in the last year. So I invite you to be the judge: Have we risen to the challenge? The obstacles we face in understanding and treating COPD are great, but not unique. The year 2010 also marked the 5-year anniversary for the Bill & Melinda Gates Foundation Grand Challenges in Global Health initiative. In reviewing the past 5 years, Bill Gates reflected, "We were naïve when we began." The rate of discovery in medical research may seem slow relative to the exponential pace of advance in fields such as computing. Yet we are making progress. The articles that follow demonstrate progress in our understanding of host susceptibility and the inflammatory response in COPD, and also the mechanisms of currently available therapies and how biomarkers may help us better target therapies in the future.

GENOMICS

COPD clearly results from a combination of risk factor exposure and host susceptibility. Our understanding of disease susceptibility has been increased by results of several genome-wide association studies. We can now be fairly confident that the CHRNA3/5, HHIP, and FAM13A loci all appear to be associated with disease susceptibility (3). It is hoped that data from studies such as COPDGene will identify additional loci of importance. The ability of this and other such studies to provide new insights will depend on the quality of patient phenotyping with detailed clinical, biological, physiological, and radiological assessments. Other approaches, however, will also be needed to make the most use of genetic data. By identifying rare variants, whole exome sequencing may help us to better understand COPD heterogeneity. Other loci of interest associated with COPD susceptibility, including SERPINE2 and XRCC5, have emerged using linkage analyses in combination with gene expression data, in the case of SERPINE2, and fine mapping data, in the case of XRCC5 (4, 5). By contrast, prior genome-wide association study data had suggested a linkage for chromosome 8p and FEV_1, but fine mapping studies were not confirmatory. However, copy number variation of the β-defensin gene, located in this region, was demonstrated to influence β-defensin expression in airway epithelial cells and increased risk for COPD (6). Epigenetic changes are also likely important. In an analysis of lung function in a cohort of ever-smokers, wood smoke exposure in combination with aberrant promoter methylation resulted in a synergistic decrease in FEV_1 (7). Exploration of known genetic mutations in other pulmonary disorders may also inform our understanding of COPD heterogeneity. Homozygosity for a mutation in surfactant protein B leads to fatal respiratory distress syndrome in the newborn period, but heterozygosity for this mutation was identified in a subpopulation of individuals with COPD and was associated with greater risk for lower lung function (8).

IMMUNOPATHOGENESIS

Mounting evidence suggests that both innate and adaptive immune responses play a role in the pathogenesis of COPD. Innate immune cells classically thought to play a larger role in COPD include neutrophils, macrophages, and dendritic cells. Data, however, also demonstrate significant alteration in mast cell populations in the COPD lung that correlate with lung function (9). Granulocyte/macrophage colony-stimulating factor (GM-CSF) is also a component of the innate immune response, as it is a known neutrophil chemoattractant and regulator of the immune response to LPS. In a cigarette smoke–induced lung inflammation model, administration of GM-CSF antibody reduced macrophage and neutrophil numbers and decreased mRNA expression of inflammatory mediators in bronchoalveolar lavage fluid, suggesting a possible therapeutic role for this antibody (10). With respect to the adaptive immune response, B cell–activating factor expression is increased in smokers with COPD and correlates with lung function impairment and hypoxia (11). We have also learned more about the role of T cells in COPD. In an intriguing study, adoptive transfer of $CD3^+$ T cells from cigarette smoke–exposed mice into lymphocyte-deficient mice ($Rag2^{-/-}$) led to neutrophil accumulation, protease activation, alveolar epithelial cell apoptosis, and emphysema-like airspace enlargement (12).

Autoimmune responses to neoantigens generated by pulmonary protease degradation of elastin and collagen peptides have also been hypothesized to contribute to the pathogenesis of COPD. In contradiction to this hypothesis, however, an analysis of patients with COPD, $α_1$-antitrypsin deficiency, or

cystic fibrosis found no anti-elastin or anti–N-acetylated pro-line-glycine-proline autoantibodies. Furthermore, IL-32, which has been previously reported to be elevated in certain autoimmune syndromes, was also not elevated in these patients (13). These data, however, should not be interpreted as the last word on the subject, both because lack of evidence to support a hypothesis is not the same as proof against it (14), and because the study did not examine T cells, which have previously been implicated in antigen-specific autoimmunity in COPD.

INFLAMMATION AND REPAIR

COPD is a disease of inflammation, but whether the net effect leads to tissue destruction, fibrotic tissue accumulation, or repair likely depends on a complex balance of factors (15). An appropriate balance between inflammation and repair maintains alveolar integrity and prevents the development of emphysema. Several studies have identified key pathways that modulate this balance. In an elastase-induced emphysema model in mice, the administration of recombinant human keratinocyte growth factor induced proliferation of epithelium, endothelium, and fibroblasts as well as increased expression of proteins involved in alveolar maintenance pathways (16). Vascular endothelial growth factor (VEGF) is also recognized as having a role in alveolar development and maintenance; VEGF blockade in animal models leads to alveolar cell apoptosis and emphysema-like pathology (17). Activation of the sphingosine 1-phosphate signaling pathway prevents airspace enlargement induced by VEGF receptor blockade, suggesting that sphingosine 1-phosphate receptor agonists could also be tested as therapeutic agents for arresting progression of emphysema (17). The balance between tissue destruction and deposition has also been highlighted by the observation that small airway thickening frequently appears in close proximity to surrounding lung tissue undergoing emphysematous destruction (18). An analysis of tissue repair gene expression from paired small airway and emphysema tissue samples demonstrated that the overall gene expression pattern in the alveolar tissues favored lung destruction but that the gene expression pattern in the bronchial walls did not strongly support bronchiolar wall thickening (18). The authors hypothesized that perhaps thinner bronchioles are destroyed through mechanisms similar to those responsible for alveolar destruction, leaving fewer thickened bronchioles behind.

Although smoking is clearly associated with chronic inflammation, why lung inflammation persists even after smoking cessation is another aspect of COPD that is not well understood (19). Smoking induces extracellular ATP in human airways that is present even after smoking cessation (20). ATP concentration is also associated with neutrophil chemotaxis and proinflammatory mediator release. MicroRNAs may also play a role in this abnormal inflammatory response, as reduced expression of miR-146a has been demonstrated in COPD as compared with control subjects and linked to prolonged cyclooxygenase-2 mRNA half-life and increased production of prostaglandin E_2, a known inhibitor of fibroblast repair functions (21). High-mobility group box 1 (HMGB1), a DNA-binding protein, has been implicated in multiple inflammatory conditions. HMGB1 is released both from activated inflammatory cells and also passively by necrotic cells, and induces production of multiple proinflammatory mediators (22). Smokers with COPD have increased levels of HMGB1 in proximal and distal airways. HMGB1, when bound to IL-1β, also enhances synthesis of tumor necrosis factor-α, which may contribute to the tissue inflammation and remodeling seen in COPD (22).

AGING AND OXIDATIVE STRESS

That COPD might represent accelerated aging has been offered as a possible clue to its development, as many of the pathological changes seen in COPD are also present in the aging lung, independent of smoke exposure. Oxidative stress is increased both in aging and in COPD. Glutathione is an antioxidant that is either obtained from food or produced by the body; it is normally concentrated in epithelial lining fluid. Mouse models indicate that cigarette smoke exposure induces glutathione production, but also that this response is blunted with age (23). Reactive nitrogen species, found in cigarette smoke and produced endogenously, have also been implicated in COPD pathogenesis. Alveolar nitric oxide production may be particularly important as levels correlate inversely with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage (24, 25). The oxidative damage caused by cigarette smoke, however, is not isolated to the lungs and may help to explain some of the systemic effects also seen in COPD. Cigarette smoke exerts direct oxidative modifications on muscle proteins that may contribute to muscle loss and dysfunction in both smokers and patients with COPD (26). On the other hand, nicotinamide N-methyltransferase (NNMT) may help to counteract these effects. NNMT expression appears to be up-regulated in the diaphragm and quadriceps muscles of patients with COPD and is negatively correlated with COPD severity and limb muscle wasting (27). NNMT expression also promotes myoblast proliferation and reduces protein oxidation and hydrogen peroxide–induced cell death, suggesting an adaptive response that could enhance myogenesis and muscle resistance to oxidative damage.

BIOMARKERS

Perhaps one of the greatest challenges existing for COPD research is the development of more efficient ways to conduct therapeutic trials. There is a desperate need for molecular, physiological, and imaging-based biomarkers that could be used both in identifying patient phenotypes and as surrogate outcomes in clinical trials (28). Novel genomic and proteomic approaches should aid in this endeavor. A non–hypothesis-driven proteomic analysis of induced sputum from patients with COPD identified two biomarkers, apolipoprotein A1 and lipocalin-1, whose levels correlate with disease severity (29). The use of exhaled breath condensate (EBC) for studying COPD has been problematic, in part due to poor reproducibility. Because of an improvement in the methodology for analyzing pH in EBC samples via a CO_2 gas standardization, EBC pH was demonstrated to be significantly decreased in asthma but unchanged in COPD (30). It is possible that such advances in methodologies to analyze EBC will increase its utility.

The development of quantitative computed tomography (QCT) as an imaging biomarker for COPD is increasingly being established, as several articles from 2010 illustrate. QCT measures of emphysema and airway wall thickness independently correlate with dyspnea after adjustment for FEV_1% predicted (31). Wall thickness was also significantly related to cough and wheezing. Another study found that a measure of total cross-sectional area of small pulmonary vessels on QCT of patients with severe emphysema correlated to mean pulmonary arterial pressure measured by right heart catheterization (32). This technique may represent an advance in being able to noninvasively identify patients with pulmonary hypertension, an important comorbidity in COPD.

COMORBIDITIES

We have focused on the pulmonary manifestations of COPD for many years; but increasing evidence suggests that what we

really need is a true "systems" approach to this disease. Airflow obstruction and emphysema have been associated with impaired left ventricular filling (33). COPD is also known to be an independent risk factor for cardiovascular events, but the link between these two conditions is not fully understood. The generation of inflammatory mediators may play a role. While biomarkers including C-reactive protein (CRP) are elevated in both conditions, microalbuminuria, a marker of endovascular dysfunction, may be another biomarker of interest linking these two diseases. Increased microalbuminuria has been documented in patients with COPD as compared with control smokers and correlates with both Pa_{O_2} and systolic blood pressure (34). Whether microalbuminuria can identify patients at increased risk for cardiovascular disease or whether these findings suggest new possible therapeutic strategies such as renin–angiotensin system modulators is yet unknown. Further investigation into the significance of other comorbidities including lung cancer, osteoporosis, and depression may also provide insights both into disease pathogenesis and therapeutic targets.

Another comorbidity of interest in COPD is obstructive sleep apnea, and the term "overlap syndrome" has been coined to indicate patients with both conditions. Such patients are at greater risk for cardiac dysrhythmias and pulmonary hypertension as opposed to those with either condition alone. For the first time, however, a study has documented that treatment of such patients with continuous positive airway pressure results in a decrease in mortality and fewer severe COPD exacerbations leading to hospitalization as compared with untreated subjects (35). These data not only underscore the importance of diagnosing and treating this key comorbidity, but also suggest that treatment of a comorbidity can actually influence the course of COPD.

EXACERBATIONS

Exacerbations are a significant cause of morbidity and mortality in COPD and are associated with more rapid disease progression and poor quality of life (36). New insights into exacerbations were provided by the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) Study (37). Among other things, this study helped to establish that a history of two or more exacerbations in the prior year is a relatively stable phenotype and predictive of future events (37). Although infections are the most common cause of COPD exacerbations, the nature of increased susceptibility to infection is not well understood. The finding that airway epithelial cells cultured from patients with COPD produce greater levels of proinflammatory cytokines in response to rhinovirus infection suggests that altered airway epithelial cell phenotype may increase susceptibility (38). From a therapeutic standpoint, while antibiotics are frequently used to treat exacerbations, a randomized, placebo-controlled trial of doxycycline added to systemic corticosteroids in patients hospitalized for COPD exacerbation demonstrated similar clinical success on Day 30 between treatment arms, although on Day 10 doxycycline did demonstrate superiority in clinical cure, symptom scores, microbiological outcome, and need for use of open label antibiotics (39). Doxycycline-treated subjects with CRP equal to or exceeding 50 mg/L also had better response on Days 10 and 30 compared with placebo-treated subjects. The role of CRP and other biomarkers such as procalcitonin in guiding antibiotic therapy during acute exacerbations of COPD is worthy of further investigation (40).

THERAPIES

Ultimately it is the hope that insights into disease pathogenesis will lead to new therapies, particularly new classes of therapies.

In 2010 the European Medicines Agency approved the phosphodiesterase-4 inhibitor roflumilast for the treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations. Approval of roflumilast by the U.S. Food and Drug Administration followed. This is the first new class of therapeutic that has been approved for the treatment of COPD in many years. We also continue to learn more about existing therapies and arguably are getting smarter about how to make drug development more efficient. For instance, it had been hypothesized that epidermal growth factor receptor (EGFR) activation mediates airway epithelial mucin overproduction in COPD. A 4-week interventional trial of 48 patients with COPD was able to demonstrate inhibition of EGFR internalization in epithelial cells isolated from subjects treated with an inhaled epidermal growth factor antagonist (41). Mucin stores and mucin gene expression, however, were not significantly decreased, and a significant number of dose-related adverse events were also seen. Although the therapeutic agent tested is not promising, the study is noteworthy in that it demonstrates how both safety and efficacy of a potential novel therapeutic agent can be studied efficiently using relatively small sample sizes.

We also continue to learn more about existing therapies. Although prior studies suggest theophylline restores steroid sensitivity, the mechanism for this has not been completely understood. New evidence indicates that phosphoinositide 3-kinase (PI3K) inhibition may be part of that mechanism and supports further investigation of more selective molecules targeted at PI3K in well-defined patient subgroups (42, 43). Of all the existing therapies we have for COPD, few are known to influence survival. In select patients, however, oxygen is one of those therapies. Unfortunately, a comparison of four commercially available oxygen-conserving devices found significant differences in their ability to maintain a patient's saturation during exercise, suggesting oxygen prescriptions should be based on testing with the device that is actually supplied to the patient (44). One of the few other therapies demonstrated to improve survival in COPD is lung volume reduction surgery (LVRS). It is believed that these benefits result from improvement in respiratory mechanics, but LVRS also results in a decrease in inflammatory mediators including CRP, tumor necrosis factor-α, IL-6, and IL-8 and an increase in α_1-antitrypsin and body mass index (45). Elimination of inflammatory tissue may contribute to these findings; alternatively, surgically induced anatomic changes could result in a reduction in systemic inflammation, which is a novel concept in COPD.

This year we were also challenged to rethink the use of therapeutic classes of bronchodilators in obstructive lung disease. The once-daily long-acting β-agonist indacaterol was compared with the once-daily long-acting muscarinic antagonist tiotropium in COPD (46). Indacaterol was demonstrated to be at least as effective as tiotropium in improving trough FEV_1, dyspnea, and quality of life with similar trends for exacerbations. Conversely, in asthma, the addition of tiotropium versus the long-acting β-agonist salmeterol to an inhaled corticosteroid demonstrated tiotropium to be noninferior to salmeterol with respect to symptoms and superior to salmeterol with respect to prebronchodilator FEV_1 improvement (47).

Pulmonary rehabilitation is an important nonpharmacological therapeutic in COPD. The interaction among respiratory, cardiovascular, and musculoskeletal systems plays a role in exercise limitation in COPD (48). In a study of resistance training during hospital admissions for COPD, increased quadriceps force was seen at discharge and at 1 month follow-up; 6-minute walk distance improvements at discharge as compared with controls were also seen (49). Importantly, this study

demonstrates resistance training can be performed safely and improves postdischarge outcomes (50). Another nonpharmacological intervention in COPD that has been slow in coming is a comprehensive disease management program. However, results from a large, randomized 1-year trial of such a program at five Veterans Affairs medical centers demonstrated a reduction in hospitalizations and emergency room visits (51). More data will be needed to understand the specifics of how and in whom such programs should be further developed and targeted.

CONCLUSIONS

While 2010 may not have produced a "cure" for COPD and certain controversies will always exist (52), at a minimum we are learning to apply more novel, efficient, and comprehensive approaches to our study of the disease that will hopefully speed our understanding. To quote the physician and poet, Oliver Wendell Holmes, Sr., "The great thing in the world is not so much where we stand, as in what direction we are moving." Research in COPD is certainly moving forward simultaneously on multiple fronts, but more than ever we will need to learn how to coordinate that research and integrate information from multiple sources to define COPD phenotypes that will be meaningful for the purposes of research, prognostication, and treatment (36).

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