Update in Chronic Obstructive Pulmonary Disease 2017

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Chronic obstructive pulmonary disease (COPD) remains an area of considerable interest among healthcare providers, clinical investigators, and lung biologists, not in small part because of its profound impact on health care, both at present and forthcoming (1). According to the Global Burden of Disease Study, more than 250 million people suffer from COPD worldwide, and about 3 million people died from it in 2016 (2, 3), which places COPD in the top four in causes of death (4). In this Update, we summarize the progress made in 2017 in understanding the pathogenesis and clinical aspects of COPD and discuss how this knowledge can lead to novel therapies.

Origins and Natural History of COPD

In 2017, the iconic article by Fletcher and Peto, in which they pioneered the concept of the natural history of COPD as a gradual accelerated decline in FEV₁ due to smoking, celebrated its 40th anniversary with an excellent tribute by Vestbo and Lange (5). In this tribute, the authors discussed recent progress in understanding the developmental trajectories of COPD, beyond the simplistic perception of excessive FEV₁ decline as an obligatory or exclusive pathway to COPD. For example, the inability to attain maximal lung function in early adulthood, a starting point for physiological, age-related decline in FEV₁, may lead to COPD in susceptible individuals without excessive FEV₁ decline after that point.

In support of this concept, Bui and colleagues (6) analyzed data from the Tasmanian Longitudinal Health Study, in which 1,389 children born in 1961 were evaluated spirometrically at age 7 years and then at age 45 years. They found that lower FEV₁/FVC ratio at age 7 years is associated with an increased risk of COPD and asthma–COPD overlap syndrome, but not asthma alone. Among subjects with COPD, a higher proportion of never-smokers than ever-smokers had lower FEV₁/FVC at age 7 years. This observation implies that early-life factors may interfere with lung maturation during childhood and contribute to COPD development independent from smoking.

Different insights were provided in the U.K. study by Allinson and colleagues (7), who analyzed data for 5,362 individuals born in March 1946 whose lung function was assessed between ages 43 and 60 to 64 years. In this study, individuals with adverse early-life exposures, such as infant respiratory infection and home overcrowding, developed lower FEV₁ and FVC values by age 43 years, but only if they had also become smokers. This suggests the possibility that smoking may lead to COPD by preventing the restoration of lung maturation after negative early-life exposures.

Genetic Determinants

Genetic susceptibility is one of the determinants of lung function and risk for COPD. The International COPD Genetics

Consortium study (8) analyzed 63,192 individuals to identify candidate loci, which were then tested using the U.K. BiLEVE (Biobank Lung Exome Variant Evaluation) cohort. In addition to capturing previously known COPD risk genes, this study identified several genetic variants associated with disease and/or lung function involving *DSP* (desmoplakin), coding for a desmosome component, and *SFTPD* (surfactant protein D). A parallel study included 48,943 subjects from the U.K. BiLEVE cohort (9) and identified genes associated with FEV₁ and FVC, including *CHRM3* (cholinergic receptor muscarinic 3) and genes related to the phosphoinositide 3-kinase pathway.

Boueiz and colleagues (10) evaluated association of genetic variations with computed tomography (CT) data in 11,532 subjects and found that specific loci near known COPD risk genes *HHIP* (hedgehog-interacting protein) and *CHRNA5* (cholinergic receptor nicotinic α 5 subunit) have the strongest association with emphysema; they identified new associations, including those related to transforming growth factor- β , NF- κ B (nuclear factor- κ B), and endothelial cell signaling. By relating their identified SNP data to the Encyclopedia of DNA Elements (ENCODE) and Roadmap Epigenomics project databases, they found that COPD-associated loci are frequently detected within annotated enhancer regions that regulate gene expression in fetal lung, fibroblasts, and lymphoid cells.

Because of psychosocial and biological factors, COPD is known to affect men and

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women differently. Amaral and colleagues (11) evaluated the relationship between sex, smoking patterns, and lung function in the U.K. Biobank cohort and found that when adjusted to the same dose of smoking, women are at a greater risk for airflow obstruction than men, suggesting that females may respond differently to smoking. In their search for sex-specific genetic traits that underlie the differential susceptibility of women to COPD development, Hardin and colleagues (12) identified a SNP in *CELSR1* (cadherin EGF LAG seven-pass G-type receptor 1), a cadherin-related gene implicated in lung development, as being associated with COPD in females but not males. *CELSR1* expression was higher in female versus male fetal lung during the lung development period when airway morphogenesis occurs. SNPs in the *CELSR1* gene were not associated with COPD in never-smokers, suggesting that they may influence response to smoking.

Pre-COPD/Early COPD

Although COPD is defined using a post-bronchodilator FEV₁/FVC ratio less than 0.70 on spirometry, this cutoff is arbitrary, and there is accumulating evidence pointing toward the existence of a prediagnostic stage (“pre-COPD” or “early COPD”) that is characterized by COPD-like symptoms and manifestations of airway remodeling and emphysema typical for COPD (13). Numerous imaging-based methodologies have been established to estimate the presence and extent of structural abnormalities in the lung in smokers not meeting criteria for obstruction on spirometry and to monitor the progression of these abnormalities over time. One of these metrics, the ratio of expiratory to inspiratory mean lung density has been developed by Bodduluri and colleagues (14) as an alternative measure of gas trapping that adjusts for emphysema and has stronger associations with small airways disease than existing measures of gas trapping. By measuring the expiratory to inspiratory mean lung density ratio in more than 8,000 participants of the COPDGene study, they found that in more than 26% of smokers without COPD, lung regions considered normal on CT scan using standard thresholds show signs of gas trapping, and this was independently

associated with FEV₁ and progressively increased from mild to severe COPD (14). These changes may eventually progress into spirometrically detectable airflow obstruction and provide an explanation for the respiratory symptoms in “healthy” smokers.

Another marker of early COPD development could be the overproduction of mucus, indicative of chronic bronchitis known to precede COPD in a considerable subset of smokers (15). By analyzing 917 samples from subjects who participated in SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study), Kesimer and colleagues (16) found increased concentrations of airway mucins in the sputum of smokers without COPD compared with never-smokers. In subjects with COPD, mucin concentration correlated with disease severity and a history of exacerbations.

Undiagnosed COPD and Diagnostic Instability

Although some symptomatic smokers do not meet spirometric criteria for COPD, many patients remain undiagnosed despite having airflow obstruction. Çolak and colleagues (17) analyzed data from 95,288 individuals from the Copenhagen General Population Study and found that of the subjects who met criteria for COPD, 78% were undiagnosed, and 71% of these undiagnosed patients with COPD were symptomatic and had elevated risks for exacerbations, death, and other adverse outcomes (17).

Despite the fact that research efforts to extend the use of spirometry to diverse populations (18) and to stratify disease cohorts (19) have been fruitful, in many ways spirometry remains problematic even as a basic assessment tool. By analyzing two large COPD cohorts, the Lung Health Study and the CanCOLD (Canadian Cohort of Obstructive Lung Disease) study, Aaron and colleagues (20) found that 20% of patients with mild to moderate COPD had their FEV₁/FVC cross into the nondiagnostic range of greater than 0.70 over a 5-year follow-up period. This phenomenon, termed “diagnostic instability,” was especially true among patients whose initial FEV₁/FVC was close to 0.70. “Diagnostic reversal” was also observed in this analysis, where up to 10% of patients had their FEV₁/FVC improve

and stabilize above the 0.70 threshold. Encouragingly, sustained smoking cessation resulted in an odds ratio of 2.92 for having diagnostic reversal compared with ongoing smokers (20), highlighting the importance of smoking cessation in changing the natural history of COPD, especially in patients with mild disease.

Structural Changes in the Lung

Although FEV₁ decline is influenced by both airway remodeling and reduced lung elastic recoil due to emphysema, recent evidence suggests that it is the former—the derangement of small airways—that ultimately results in airflow limitation in COPD (21). Characteristic features of such derangement are the disappearance of small airways and the remodeling of the remaining bronchioles, which may precede emphysema (21). To provide novel insights into the relationship between airway remodeling and emphysema, Tanabe and colleagues (22) used micro-CT technology that enables visualization of small airways to evaluate preterminal bronchioles in patients with centrilobular and panlobular emphysema (CLE and PLE, respectively) compared with normal lungs. This study showed that, although the alveolar region is considered the primary site of emphysema, preterminal bronchioles undergo structural changes in CLE and PLE lungs: they become shorter and lose their circular luminal shape. Compared with normal and PLE lungs, marked changes in the wall of preterminal bronchioles were observed in CLE, which correlated with fewer alveolar attachments, further supporting the concept that the pathogenesis of emphysema in COPD might begin with the derangement of small airways (21, 22).

Once established, emphysema may propagate itself by spreading to surrounding normal tissue. Changes in transpulmonary pressure due to breathing or coughing may cause over time sequential destruction of alveolar walls surrounding emphysematous areas, where the mechanical stability of extracellular matrix is compromised because of ongoing disease (23, 24). To evaluate this possibility, Bhatt and colleagues (23) analyzed volumetric CT scans obtained from 714 subjects enrolled in the COPDGene study. By quantifying regional parenchymal volume change with

respiration in the emphysematous and surrounding “normal” areas of the lung, the authors found that in individuals with emphysema, normal-appearing lung regions on CT have altered regional expansion, and these areas of mechanically affected lung (MAL) have a spatial relationship with emphysematous areas. The number of MAL areas could independently predict lung function change over time, suggesting that MAL regions could represent areas of “lung at risk” for emphysema progression (23).

Biologic Mechanisms

The destructive character of pathologic changes in COPD suggests that failure of physiologic regenerative mechanisms to maintain tissue integrity may represent the unifying principle of disease pathogenesis. Reduced regenerative capacity of airway epithelial progenitors could contribute to the loss of airways observed in COPD, whereas the pathogenesis of airway remodeling may involve pathologic reprogramming of these progenitor cells by aberrantly activated signaling pathways. Zuo and colleagues (25) identified a novel mechanism of interconnected pathogenesis of all major airway epithelial lesions in COPD, which involves a step-wise activation of the epidermal growth factor (EGF) receptor in airway basal progenitors. As a triggering event, smoking-induced EGF shifts basal progenitors toward squamous differentiation accompanied by production of another EGF receptor ligand, amphiregulin, which promotes basal cell and mucous cell hyperplasia. By comparing the transcriptomes of proximal and distal airway epithelium, Yang and colleagues (26) identified region-specific signatures and found that the distal airway epithelium in COPD undergoes smoking-dependent transition toward a proximal airway-like pattern. This repatterning was mediated by EGF signaling in small airway basal progenitors and occurred independently from classic histologic lesions (26), implying that it may represent an early event during disease development (27).

Altered epithelial differentiation may contribute to decreased airway host defense potential. By analyzing 1,104 small airways from donors with and without COPD, Polosukhin and colleagues (28) observed a

deficiency of secretory IgA (sIgA) on the surface of small airways from subjects with COPD, which was associated with mucous and squamous metaplasia. sIgA is delivered to the apical surface via the polymeric immunoglobulin receptor, whose expression is dependent on epithelial differentiation. COPD airways with low sIgA levels showed higher levels of bacterial DNA, thicker walls, and increased number of neutrophils and macrophages (28), linking altered airway epithelial differentiation, host defense, tissue remodeling, and inflammation. As further evidence supporting this link, Kedzierski and colleagues found that airway epithelial cells from subjects with COPD fail to upregulate SOCS (suppressor of cytokine signaling)-5 in response to influenza virus infection, resulting in increased EGF receptor signaling that facilitates viral pathogenesis (29) and also mediates airway epithelial remodeling (25).

Altered maintenance of the alveolar epithelium by region-specific progenitors, type 2 alveolar cells, may contribute to pathogenesis of emphysema. Baarsma and colleagues (30) found that alveolar epithelial repair mediated by canonical Wnt (wingless-type MMTV integration site family) signaling in type 2 cells can be inhibited in COPD because of upregulation of a noncanonical signaling mediated by Wnt5A induced in lung fibroblasts undergoing smoking-associated senescence. As another mechanism for decreased canonical Wnt signaling relevant to the pathogenesis of emphysema, Skronska-Wasek and colleagues (31) showed reduced expression of Wnt receptor Frizzled-4 in the lungs of subjects with COPD that correlated with smoking history and severity of airflow obstruction. Inflammation may also play a role in mediating destructive changes in the lung parenchyma. Increased numbers of macrophages and T cells, accompanied by upregulation of a molecular signature of T-helper cell type 1-related inflammation, have been found in the small airway and alveolar tissue in association with emphysema (32).

Exacerbations

COPD is not only a disease of steady decline in lung function but also one that is punctuated by difficult-to-predict

exacerbations with significant clinical consequences. Han and colleagues (33) analyzed the pattern of exacerbations among patients with 3 years of complete follow-up data in the SPIROMICS cohort. Although increased exacerbation rate correlated strongly with a history of exacerbations, the overall pattern was highly heterogeneous, with only 2% of patients having two or more exacerbations in each of the 3 years that would warrant classification as “frequent exacerbator.” There are clearly subgroups of patients with COPD who are at higher risk for having exacerbations, but “frequent exacerbator” appears to be a heterogeneous phenotype that is stable neither in a population nor across time. By the same token, Dransfield and colleagues (34) examined the follow-up data on 2,000 patients from the COPD Gene study and observed that the excessive decrease in FEV₁ after a severe exacerbation was the greatest in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 COPD, an extra 87 ml/yr. Although the mean rate of exacerbations was higher in patients with GOLD 4 than GOLD 1 COPD, more than 20% of patients with GOLD 1 COPD experienced at least one exacerbation during the follow-up, with 8% experiencing a severe exacerbation. With the addition of a *post hoc* analysis of another large clinical trial showing the efficacy of the combination of inhaled corticosteroid and long-acting β -agonist in reducing the rate of moderate and severe exacerbations (35), it is more obvious than ever that preventing exacerbations should be a goal for every provider caring for patients with COPD (36).

Multimorbidity

COPD is increasingly being recognized as a multimorbid, systemic disease. For example, COPD and congestive heart failure are both diseases with an increased ventilatory drive, and Rocha and colleagues (37) showed that patients with COPD–congestive heart failure overlap syndrome, particularly those with resting hypoxemia, have worse ventilatory efficiency and more dynamic hyperinflation, likely resulting in more severe dyspnea and worse exertional tolerance. The proposed mechanisms of left ventricular dysfunction associated with COPD include mechanical effects from hyperinflation as well as pulmonary

microvascular damage induced by smoking, an endothelial injury phenotype recently reported also in the kidneys of patients who smoke (38). These findings suggest that medications traditionally used in cardiovascular disease may have a role in the management of COPD, altering pathways not classically believed to be pertinent in COPD pathogenesis.

Treatment

Smoking Cessation

Many patients continue to smoke after being diagnosed with COPD, even though smoking cessation is the only etiology-oriented treatment approach that has been shown to prevent disease progression. This was again demonstrated in a recent U.K. study, in which Josephs and colleagues (39) analyzed the data of 16,479 patients with COPD having different smoking histories and found that compared with active smokers, ex-smokers had reduced risk of death, hospitalization, and emergency department attendance, regardless of age or lung function.

Pharmacologic Therapy

Whether patients with mild COPD warrant pharmacologic therapy is currently unknown. To address this question, Zhou and colleagues (40) conducted a clinical trial in which 841 patients with mild to moderate COPD were randomized to tiotropium versus placebo. They showed a 157-ml between-group difference in prebronchodilator FEV₁ at 24 months, as well as slower decline in FEV₁ and longer time to first exacerbation in the tiotropium group. Although the high inhaler compliance rates seen in this study cannot be expected among minimally symptomatic patients outside of a trial setting, this study raises interesting questions about the treatment of mild COPD.

Regarding the management of moderate to severe COPD, the FULFILL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) trial (41) demonstrated that triple therapy result in improved FEV₁ and respiratory symptoms, as well as a reduction in the rate of moderate/severe exacerbations, compared with inhaled corticosteroid/long-acting β -agonist. In the TRINITY (Single Inhaler Extrafine Triple Therapy versus Long-Acting Muscarinic

Antagonist Therapy for Chronic Obstructive Pulmonary Disease) trial, 2,691 patients with severe COPD were randomized to a single-inhaler triple therapy, triple therapy in separate inhalers, or long-acting muscarinic agonist alone (42). Fixed-combination therapy was superior to tiotropium monotherapy in reducing the yearly rate of moderate to severe exacerbations by about 20%, the first long-term study to show this effect when comparing triple therapy to long-acting muscarinic agonist alone. Fixed-combination single-inhaler triple therapy was neither inferior nor superior to open-combination triple therapy in this study, but future trials should consider reexamining whether a single-inhaler triple therapy would be superior to multiinhaler therapy in real-world patients.

Novel Therapies

One approach to treating COPD could be the use of therapies that target pathways important for COPD pathogenesis that have already been found to be effective for other diseases. An example of this is using monoclonal antibodies against IL-5, a cytokine that activates various aspects of eosinophil biology, in patients whose disease is driven by eosinophilic inflammation, as is known for asthma and probably is relevant for some patients with COPD (43). Clinical trials already frequently analyze outcomes for interactions with eosinophils *post hoc* (44), with earlier observations suggesting that increased blood eosinophils correlate with favorable response to glucocorticoid therapy; more recently, in the SPIROMICS study, Hastie and colleagues (45) found that high concentrations of sputum eosinophils define a subset of subjects with COPD with more severe airflow obstruction and more frequent exacerbations. To address whether targeting IL-5 will provide therapeutic benefit in COPD, Pavord and colleagues (46) randomized patients with moderate to severe COPD with elevated blood eosinophil counts to receive the monoclonal antibody mepolizumab against standard care. Although the results of this study were somewhat disappointing, it appears that anti-IL-5 therapy is effective in a subset of patients with COPD, and further studies are needed to elaborate on this.

Nonpharmacological Approaches

Treatment modalities outside of pharmacologic therapy continue to be

explored for patients with severe COPD, especially in means of lung volume reduction (LVR). Kemp and colleagues (47) conducted the first multicenter randomized controlled trial using endobronchial valves for LVR in patients with COPD on optimal medical management without collateral ventilation in the target lobe. At 3 months and 6 months after the procedure, patients in the endobronchial valves group had improved FEV₁, 6-minute-walk distance, and respiratory symptoms. However, adverse events continue to be a concern, as almost 30% of patients who received an endobronchial valve developed a pneumothorax. It will be of interest to see if risk stratification scores currently applied in assessment for surgical LVR (48) can also improve patient selection for endoscopic LVR procedures.

In the management of hospitalized patients with COPD exacerbations, a recent multicenter clinical trial evaluated the role of helium-oxygen mixture (Heliox) in the prevention of endotracheal intubation in patients with hypercapnic COPD exacerbations requiring noninvasive ventilation (NIV) (49). Because of the low overall rate of the primary outcome, the study was stopped prematurely after 445 patients, at which point there was no significant difference between the groups. Another study showed that with stringent patient selection, aggressive NIV titration, and adherence monitoring, discharging patients with severe COPD with home NIV may prevent further exacerbations or readmissions to the hospital in this group of high-risk patients (50).

Pulmonary Rehabilitation

Nolan and colleagues (51) sought to improve on the approach to pulmonary rehabilitation by using pedometer-directed step targets to improve patients' exercise tolerance but found no difference between the study and control groups in the amount of time expending at least 3 metabolic equivalents after 8 weeks of intervention. Although there is likely a role for the integration of new technology in improving the physical activity level of patients with COPD (52), this study shows that this is not accomplished by providing numerical goals alone (53).

Future Perspectives

Despite the magnitude of the problem and significant progress in understanding the

pathophysiology and clinical aspects of COPD, specific mechanisms underlying COPD development and heterogeneity remain poorly understood, and no therapy so far has been shown to prevent long-term decline in lung function (54). Although standard COPD therapies target common pathways mediating symptoms in many patients, distinct mechanisms may underlie unique “natural histories” and clinical

phenotypes in individual patients or groups of patients. Future therapies would ultimately require a transition from classic, population-based thinking about disease toward precision medicine approaches on the basis of the knowledge of specific pathophysiological patterns and disease-driving mechanisms in each patient. This could be achieved through a broader use of patient-derived organotypic models of

COPD, such as airway and lung organoids (55–57), in which disease mechanisms can be identified, reconstructed, and targeted in a tissue- and patient-specific fashion. ■

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