Airway Mucins in Chronic Obstructive Pulmonary Disease

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Chronic bronchitis, also known as chronic mucus hypersecretion, is common in cigarette smokers and is a key component of chronic obstructive pulmonary disease (COPD). After the publication of the seminal study by Fletcher and Peto in the 1970s, chronic bronchitis was recognized as being associated with cigarette smoking and conferring a predisposition to lower respiratory infections, but was reported as not influencing the progressive airway obstruction that is characteristic of COPD. However, a number of later studies showed that chronic bronchitis was indeed not a benign feature of COPD and was clearly linked to disease progression, hospital admission, and mortality.

Recent data suggest that chronic bronchitis may particularly develop in smokers during middle age and runs a dynamic course, and the longer a patient with COPD has chronic bronchitis, the faster airway disease progresses. Patients with chronic bronchitis are more prone to exacerbations of their COPD than those without chronic bronchitis, and thus sputum production is more common in the frequent-exacerbation phenotype. This is not surprising, because chronic bronchitis is associated with airway bacterial infection and increased airway inflammation.

Chronic bronchitis is classically diagnosed from the patient’s history and defined as 3 consecutive months of cough and sputum production over a period of 2 years. However, symptoms of chronic bronchitis may be variable over time, decreasing with smoking reduction or cessation and increasing with COPD exacerbations. Because chronic bronchitis is an important risk factor for the development and progression of COPD, early diagnosis in these patients is important. It would advance the art if there were a validated biomarker for chronic bronchitis, because diagnosis based on patient report may not be accurate.

In this issue of the Journal, Kesimer and colleagues describe the relationship between airway mucins and features of chronic bronchitis. Mucus that is formed in the airways is a protective barrier and consists of globular proteins, macromolecular mucins (especially MUC5AC and MUC5B), and water. Airway mucins are thought to be important in airway mucus transport, but when mucin levels rise above a threshold, the “two-gel hypothesis,” detailed in the report by Kesimer et al., predicts that mucus accumulation occurs, leading to sputum production, increased airway inflammation, infection, and airflow obstruction, which are features consistent with progressive COPD.

In a large, well-phenotyped cohort of the Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS), Kesimer and colleagues test the hypothesis that airway mucin concentrations are associated with sputum production in COPD and are also a marker of disease severity. The results show that airway mucin levels are higher in current or former smokers with sputum production than in persons without sputum production or those who have never smoked. Airway mucins are also related to the severity of COPD and increase with worsening disease. Patients with COPD who had two or more exacerbations in the previous year had higher airway mucin levels than those with no exacerbations. This was expected, because exac-
Exacerbation frequency is associated with chronic bronchitis. However, only 36 patients in this study had two or more exacerbations in the previous year, and thus larger studies are needed to test the relationship between exacerbation frequency and airway mucin levels. SPIROMICS participants with chronic bronchitis who were symptomatic had higher airway mucin levels than those who were asymptomatic, even when spirometric values were normal; this is an interesting finding, because symptoms are important drivers of disease progression and exacerbation.

Computed tomographic (CT) scans were performed in the SPIROMICS cohort, and airway mucin levels were higher in participants who had a diagnosis of chronic bronchitis with or without emphysema on CT than in those without chronic bronchitis.

Other respiratory conditions, such as asthma, are also associated with increased mucus hypersecretion, and approximately 15% of the current or former smokers in the SPIROMICS cohort reported current asthma. These participants had higher airway mucin levels than controls who had never smoked, and the influence of asthma on mucin levels was maintained after adjustment for smoking. A diagnosis of childhood asthma also was associated with higher mucin levels, but there was no relationship between airway mucin levels and asthma biomarkers. The data confirmed the predominance of MUC5B in COPD as concentrations increased with greater severity of disease, but also showed that MUC5AC concentrations rise disproportionately with smoking, especially in mild-to-moderate disease.

Finally, the authors tested whether airway mucins could be used as a biomarker of chronic bronchitis, but the receiver-operating-characteristic analysis was suboptimal in the SPIROMICS cohort. However, results in a small independent cohort were more favorable. The variability that was observed may be due to the definitions of chronic bronchitis currently being used or, more likely, the use of highly codified methods for gathering sputum specimens in the independent cohort. Chronic bronchitis is also variable over time, and efforts must now be made to improve and validate a new definition of the disorder.

This important study shows that airway mucins are related to smoking, respiratory symptoms, and disease severity and exacerbations in COPD and further consolidates the central role of chronic bronchitis in COPD. Airway mucins are a key target for the development of new interventions in COPD. Further study is needed to understand the mechanisms of how mucins contribute to the development of airway inflammation and the progression of airflow obstruction. Airway mucins also show promise as a biomarker of chronic bronchitis, but first more work is needed to refine the definition and detection of the disorder. However, we now know that chronic bronchitis occurs in middle age in smokers, before airflow obstruction is even detected. Thus, the exciting prospect is that airway mucins may eventually predict who will have disabling symptoms from COPD.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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