Editorial

Allergy and Chronic Obstructive Pulmonary Disease

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Allergy, airway hyperreactivity (AHR), and allergic asthma are risk factors of chronic obstructive pulmonary disease (COPD), a heterogeneous disease presenting with various phenotypes. An allergic phenotype of COPD, characterized by more severe respiratory symptoms and higher risk of acute exacerbations, was described recently.[1] Further investigations into the role of allergy in the pathogenesis and/or expressions of COPD may lead to new modalities targeting the allergic component, a potentially treatable feature of a progressive disease like COPD.

Allergy in Chronic Obstructive Pulmonary Disease

Studies have shown that AHR was not only an independent predictor of COPD development in the general population,[2] but also a risk factor for rapid progression of airway obstruction in patients with mild COPD.[3] Atopy determined by increased level of immunoglobulin E (IgE), was inversely associated with forced expiratory volume in 1 s (FEV_1)/forced vital capacity independent of smoking status.[4] In a recent study of two separate cohorts of COPD, Jamieson *et al*.[1] defined an "allergic phenotype" by self-reported doctor diagnosed hay fever or allergic upper respiratory symptoms (in National Health and Nutrition Survey III, $n = 1381$), and a detectable specific IgE to perennial allergens (in the COPD and obstructive pulmonary domestic endotoxin, $n = 77$). The "allergic phenotype" accounted for 25% and 30% of the two COPD cohorts, respectively, and this phenotype was associated with increased respiratory symptoms and risk of COPD exacerbations.

The European Respiratory Society Study on COPD (EUROSCOP) found that 18% of the COPD participants were atopic by measuring specific IgE,[5] and a further study demonstrated that atopy was associated with a higher prevalence of cough and phlegm, but not with FEV_1 decline or lung function.[6] Thereafter, the study of Bafadhel *et al*. demonstrated that atopy, defined as a positive skin prick testing and/or elevated allergen-specific antibodies, was present in 34% of COPD patients ($n = 128$). Sensitization to *Aspergillus fumigatus* (positive skin prick test and/or elevated *A. fumigatus* IgE antibodies) was found to be 13%, which was associated with worse lung function (FEV_1% predicted (pred), 39% vs. 51%, $P = 0.01$).[7] Our recent study[8] showed that even among COPD patients without obvious atopy ($n = 273$), the prevalence of elevated total-IgE (T-IgE) and *Aspergillus* hypersensitivity (elevated *A. fumigatus* IgE antibodies) was 47.3% and 15.0%, respectively. Serum T-IgE level was found to be positively correlated with the time length of dyspnea history, and negatively with FEV_1% pred.[8] Although acute exacerbation of COPD can be precipitated by several factors such as infections, the cause of about one-third of severe exacerbations of COPD still cannot be identified.[9] Since the allergic phenotype of COPD was shown to have an increased risk of exacerbations,[1] whether airway allergy plays a role in the susceptibility to, or is an unidentified trigger for exacerbation is worth further study. Longitudinal studies may also be needed to examine the potential role of allergy in disease expression or progression of COPD.

Mechanism of Allergy/Airway Hyperreactivity in Development and Progression of Chronic Obstructive Pulmonary Disease

Although AHR has been taken as an important feature of COPD, little is known about the factors that modulate AHR

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in COPD. In 1998, Renkema *et al*.[10] explored the effects of AHR and serum level of IgE on the progression of COPD. An interesting finding of this study was that a higher initial serum IgE level was not only independently associated with a lower histamine provocative concentration causing a 20% drop in FEV_1 (PC20), but also with a slower annual decline of PC20, but no significant associations were found between initial blood eosinophils and level or decline of PC20.[10] Recently, a study by Stoll *et al*.[11] found that patients with COPD displayed an overexpression of the high-affinity IgE receptor (FcεRI) on plasmacytoid dendritic cells (pDCs), providing some clues to the role of IgE in the development/progression of COPD. They found that compared with never smokers, current smokers displayed an increased expression of the FcεRI on myeloid and plasmacytoid DCs. In patients with COPD, the expression of the FcεRI on pDCs increased from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage 2 to GOLD Stage 4 and was correlated with parameters of lung function. Patients with severe COPD and patients with allergic asthma displayed a similar FcεRI overexpression on plasmacytoid DCs. In all groups, there was a positive correlation between serum levels of T-IgE and the FcεRI expression on plasmacytoid DCs.[11] These results suggest that IgE may be involved in the pathogenesis/progression of some phenotypes of COPD.

With the increasing use of high-resolution computed tomography in the assessment of COPD, a high prevalence of bronchiectasis was found among COPD patients, especially those with the moderate-severe disease.[12-16] It was demonstrated by several studies that the existence of bronchiectasis was associated with more severe symptoms, higher frequency of exacerbations and mortality in patients with COPD.[13,17-19] Recently, we investigated the factors associated with the coexistence of bronchiectasis and moderate-severe COPD. Interestingly, we found that increased level of serum T-IgE was an independent risk factor for coexistence of bronchiectasis in COPD, and its level was correlated with the extent of bronchiectasis.[12] Most recently, another study by our team showed that comorbid bronchiectasis in COPD (COPD-Bx) may be associated with enhanced airway inflammation, possibly by a T-helper type 2 (Th2)-dominant mechanism.[20] Sputum eosinophils were found increased in COPD patients with chronic rhinosinusitis (CRS) compared to those without CRS, and more notably, higher in COPD-Bx patients with CRS.

Cigarette smoking can result in either panlobular emphysema (PLE) or centrilobular emphysema (CLE), and the latter shows worse remodeling and narrowing of small airways, which can result in the airflow obstruction similar to asthma. Ballarin *et al*.,[21] by analyzing the pathological features of resected lung samples, demonstrated that the counts of mast cells in small airways and alveolar walls were significantly increased in CLE compared with those of PLE and the controls, and the increase of mast cells in airway smooth muscle was related to AHR (PC20) in CLE. These results suggest that cells and molecules from allergic reactions may be involved in the airway diseases leading to CLE.

As some COPD patients present characteristics of asthma (asthma-COPD overlap syndrome as an example), it is possible that asthma-related inflammatory pathways play a role in the development/progression of COPD in a subgroup of patients. Recently, Christenson *et al*.[22] investigated gene expression signatures of Th2 inflammation in patients with COPD. In their study, disease-associated gene expression alterations of airway epithelial cells were evaluated in an asthma cohort (n = 105) and two COPD cohorts (n = 237, 171). The Th2 signature (T2S) score, a gene expression metric induced in Th2-high asthma, which had been shown to be correlated with asthma-related features and response to corticosteroids in COPD in a randomized, placebo-controlled trial (the Groningen and Leiden Universities study of corticosteroids in obstructive lung disease; n = 89), was evaluated in these COPD cohorts.[22] They found that the 200 genes most differentially expressed in asthma versus healthy controls were enriched among genes associated with more severe airflow obstruction in these COPD cohorts, suggesting a significant overlap of gene expression between COPD and asthma. In both COPD cohorts, a higher T2S score was associated with worse lung function, but not asthma history. Higher T2S scores correlated with increased eosinophils in airway walls, percentage of blood eosinophils, bronchodilator reversibility, and improvement in hyperinflation after corticosteroid treatment. The association of the T2S score with increased severity and "asthma-like" features (including a favorable corticosteroid response) in COPD suggests that Th2 inflammation may be important in a COPD subset that cannot be identified by clinical history of asthma.[22]

Treatable Features Associated With Allergy in Chronic Obstructive Pulmonary Disease

Studies on the clinical features related to allergy and its association with treatment may lead to "targeted therapy" for specific subgroups of COPD. Fattahi *et al*.[6] investigated the factors associated with atopy (defined by positive specific IgE) based on the COPD cohort participating in the EUROSCOP. They also monitored the incidence and remission of respiratory symptoms of patients during 3-year follow-up and association of atopy with lung function decline. They found that compared with nonatopic COPD patients, atopic COPD patients were more likely male, younger and had overweight/obesity. Atopy in COPD was associated with an increased incidence and prevalence of respiratory symptoms. Compared to non-atopic COPD patients, those with atopy more often showed remission of symptoms when treated with budesonide.[6] They suggested that evaluation of atopy be recommended in the diagnostic workup and management of COPD.

Blood eosinophil count is gaining attention recently as a maker for response to inhaled corticosteroids (ICS) in COPD. It was

demonstrated that about 37% of COPD patients had blood eosinophil counts persistently ≥2%,[23] which was sensitive for predicting sputum eosinophilia.[24] Several studies[23,25-30] suggested that higher eosinophil levels in COPD were associated with increased corticosteroid responsiveness. Using the data from the withdrawal of inhaled steroids during optimized bronchodilator management trail, Watz *et al*.[31] found that blood eosinophil counts at screening were related to the exacerbation rate after complete ICS withdrawal in patients with severe to very severe COPD and a history of exacerbations. The counts of 4% or greater, or 300 cells/μl or more might identify a deleterious effect of ICS withdrawal. Since benralizumab (BRL), an anti-interleukin-5 receptor α monoclonal antibody, can deplete blood and sputum eosinophils in asthma, Brightling *et al.* conducted a trial of BRL in the treatment of COPD, investigating whether BRL could reduce the rate of acute exacerbations.[32] They enrolled patients aged 40–85 years, with moderate-severe COPD, at least one acute exacerbation, and a sputum eosinophil count of 3.0% or more within the previous year. Totally, 101 patients were randomly assigned to receive placebo (n = 50) or BRL (n = 51), of whom 88 (87%) patients completed the study. They found that BLR did not reduce the annualized rate of acute exacerbations of COPD compared with placebo in the per-protocol population. However, numerical (but no significant) improvement in acute exacerbations of COPD, specific Saint George's Respiratory Questionnaire, Chronic Respiratory Questionnaire self-administered standardized format, and FEV_1 was observed in BRL-treated patients with baseline blood eosinophils of 200 cells/μl or more or 300 cells/μl or more.[32] The results suggest that the effects of BRL in COPD patients with higher blood eosinophils warrant further investigation.

In summary, COPD is a heterogeneous disease, and there are increasingly data showing that allergy plays important roles at least in a subgroup of COPD patients. Further studies are needed to define the "allergic phenotype" of COPD, to reveal the potential mechanisms of allergy in the development/progression of the disease, and to evaluate the benefits of therapies targeting the allergic or Th2 components of COPD.

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