Chronic Obstructive Pulmonary Disease: Do Regional Differences in Tissue Inflammation Matter?

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Chronic obstructive pulmonary disease (COPD) is a worldwide health problem, and is associated with frequent hospital admissions, a decrease in quality of life and premature death [1]. Tobacco smoking as the major cause of COPD is supported by studies that showed a two- to threefold increase in the rate of decline in lung function in smokers compared with nonsmokers [1, 2]. Cigarette smoking elicits airway and lung tissue inflammation in all of those who smoke, but clinically significant COPD occurs in only a minority of smokers [3, 4]. In this minority who develop COPD, the inflammatory process is amplified and persists long after the individual has stopped smoking [5–7]. This amplified inflammatory response is thought to cause the tissue remodeling that results in the lesions that have been associated with chronic bronchitis, small airway obstruction and emphysematous tissue destruction [6, 8] and led to the concept that an abnormal inflammatory response to cigarette smoke leads to the development of COPD in susceptible individuals. To complicate issues further, the clinical and pathological spectrum of COPD is broad, with the majority of patients demonstrating a combination of both emphysema and airway disease to varying degrees. The fact that these two significantly different pathological processes develop following the same environmental expo-

sure suggests that regional differences in the immune inflammatory response may play an important role in determining the locations of airway and parenchymal destruction in COPD.

Persistent exposure to tobacco smoke is associated with infiltration by immune inflammatory cells and remodeling of the tissue to produce enlargement of bronchial mucus glands, thickening of the walls and narrowing of the lumen of the smaller conducting airways, as well as emphysematous destruction of the alveolar surface. This inflammatory/immune remodeling process involves a complex interplay between lung epithelial cells, endothelial cells and fibroblasts with the infiltrating neutrophils, macrophages and subpopulations of both CD8+ and CD4+ T cells [6, 8, 9]. Activation and damage of tissues by cigarette smoke cause the release of various inflammatory mediators, cytokines and chemokines that promote the activation of endothelial cells, resulting in the upregulation of adhesion molecules such as intercellular adhesion molecule-1 and E-selectin, thus increasing the accumulation of leukocytes in lung tissues. These leukocytes serve as an additional source of chemoattractant cytokines, promoting additional leukocyte traffic into the lung tissues which are thought to play a pivotal role in the development and progression of COPD.

In this issue of *Respiration*, Isajevs et al. [10] address the issue of regional differences in lung inflammation in COPD and, as expected, found that smokers have both large and small airways inflammation, irrespective of whether they have COPD or not. They also showed significantly more macrophages in larger airways compared to the smaller conducting airways and more neutrophils and CD8+ T lymphocytes in smaller conducting airways compared to the larger airways in COPD subjects. These differences in leukocyte infiltration were present in spite of similar levels of inflammation in larger and smaller airways using NF κ B p65- and HDAC-2-positive cells as biomarkers of tissue inflammation. These markers represent pivotal steps in inflammatory pathways responsible for producing the cytokines and chemokines that recruit leukocytes into tissues. In summary, this study showed significant regional differences in inflammatory cell infiltration that could cause regional differences in tissue pathology in COPD.

A large body of work supports a role for neutrophils in the pathogenesis of emphysema. Neutrophils contain high levels of proteolytic enzymes such as serine proteinases, neutrophil elastase, proteinase-3 and cathepsin G and at least 2 matrix metalloproteinases (MMP8 and MMP9). These enzymes are capable of causing extracellular matrix destruction as well as contributing to mucus hypersecretion in both large and small airways in COPD. Bronchial lavage studies showed that neutrophils come predominantly from larger airways, although the total burden in both large and small airways is higher in smokers and COPD subjects than in nonsmokers [11]. In a study using bronchial biopsies, Lams et al. [12] showed neutrophils in subepithelial regions of all airways of subjects with COPD, while a study using resected lungs showed a relationship between small airway neutrophil infiltration and smoking history but not the severity of obstruction [13]. The role of neutrophils in emphysematous destruction of lungs is more controversial. Studies by Cosio and Guerassimov [14] and Finkelstein et al. [15] using resected lung tissue showed that smoking increases tissue neutrophils, but that there was an inverse relationship between lung tissue neutrophils and emphysematous lung destruction, suggesting that it is unlikely that neutrophils play a role in lung parenchymal damage. In contrast, a study by Retamales et al. [5] showed a significant elevation of neutrophils in severe emphysema (lung tissue from lung reduction surgery) that was related to the severity of emphysema. The study of Isajevs et al. [10] was performed in current smokers with predominantly mild (Global Initiative for Chronic

Obstructive Lung Disease stages I and II) COPD and is therefore not directly comparable with studies performed in subjects with more severe disease. In addition, several studies clearly showed an increase in airspace neutrophils in particular in larger airways that reflect more acute events such as exacerbation or infection [16, 17]. The 'exacerbation status' of study subjects was not well defined in most of the above studies, and this could be a confounding variable that could explain differences between studies.

Macrophages are relatively long-lived cells, especially in smokers, possibly due to reduced macrophage apoptosis, and are crucial in the innate immune response and antimicrobial defense, as well as contributing to the adaptive immune response. Induced sputum contains higher levels of macrophages in smokers and COPD subjects compared to nonsmokers [16, 17], and bronchoalveolar lavage sampling of proximal versus distal bronchi shows an increase in macrophages towards the peripheral airways in current smokers [18]. Macrophages are mostly found in the epithelium (with CD8+ lymphocytes mostly located in the subepithelium) in smokers and COPD subjects. The relatively larger increase in numbers of macrophages in larger versus smaller airways shown by Isajevs et al. [10] is interesting and suggests that macrophages also contribute to large airways inflammation in smokers and in COPD subjects. This finding supports an earlier study by Seatta et al. [19]. Alternatively, it may represent current smoking status in all 'normal' smokers and COPD subjects in the study of Isajevs et al. [10].

The increase in airway lymphocytes, predominantly CD8+ T lymphocytes (and a decrease in CD4+/CD8+ ratio), in smokers and COPD subjects has now been well established in several studies over the last 20 years. These cells are mostly found in the subepithelium and are relatively more abundant in smaller airways, suggesting a crucial role in small airways obstruction and remodeling [19, 20]. The study by Isajevs et al. [10] confirmed these findings, but whether this increased number of lymphocytes and changes in CD4+/CD8+ ratios reflect increased recruitment or prolonged retention of these cells in the lungs of COPD subjects is still a subject of active investigation [21].

Study of the pathogenesis of COPD is a complex and evolving area where much remains to be learned about both the precise function of each individual cell and the interactions between these cells at various sites within the lung. Regional differences in the accumulation and function of these cells may provide insight into both the known regional differences in pathology and persistence

of the inflammatory process long after the primary stimulus (smoking) has stopped. They may also provide insight into why small airways thicken in such close proximity to emphysematous destruction of the alveolar tissue and why emphysematous destruction seems to

predominate in some clinical phenotypes of COPD and airways obstruction in others. If so, this new information could lead to more targeted management and treatment of lung inflammation in different phenotypes of COPD.

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