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Deconvoluting Chronic Obstructive Pulmonary Disease: Are B Cells the Frontrunners?

To the Editor:

In the era of precision medicine, the observable differences between patients with chronic obstructive pulmonary disease (COPD) are calling into question the current way of classifying subjects with COPD based solely on a measure of their lung function. Computed tomography has been instrumental in identifying COPD subphenotypes, such as airway disease (bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which varies from patient to patient (1). Emphysema is characterized by a molecular signature indicating predominant B-cell activation and lymphoid follicle (LF) formation, which is absent in bronchiolitis regardless of airflow limitation (2).

The exciting work by Ladjemi and colleagues provides a novel insight into the humoral immune pathobiology (or "endotype") in COPD (3). The study shows IgA production occurring in distal airway LFs from patients with severe COPD. This finding raises questions about the role of the distal airways in the pathogenesis and progression of COPD. Disease and loss of terminal and transitional bronchioles are present in the lungs of smokers when no emphysematous destruction is present, indicating that small airway disease may be an early pathological feature of COPD (4). The anatomic sets of distal airways associated with B cell–predominant immune responses and the timing of these responses in the pathogenesis of COPD are still unclear.

Furthermore, Ladjemi and colleagues showed that IL-21, which is crucial for the maturation of B cells into plasma cells capable of producing high-affinity antibodies against foreign antigens (5), was significantly overexpressed in the LFs at all stages of COPD. This finding is in line with previous studies showing the presence of oligoclonal or monoclonal LF B cells in the COPD lung and suggests an immune reaction that is triggered by precise antigens (6). However, because microbial diversity declines as COPD progresses (7), it will be essential to investigate the nature of the antigens that trigger B cell–driven immune responses in the severe stages of COPD, and how precisely the lung microbiome contributes to those responses.

To date, these questions remain unanswered, in large part owing to the difficulty—apart from rare cases—of obtaining repeated samplings of lung specimens from one subject longitudinally, which would allow us to track the pathobiology of COPD over time. Indeed, unlike the airway subphenotype, the emphysematous subphenotype is associated with a B cell–predominant endotype, but the temporal sequence and the extent of the overlap of these two pathologic manifestations, if any, is unknown. Thus, further studies are very much needed to clarify the nature and exact sequence of events leading from a B cell–predominant immune response to LF formation during the onset and progression of distinct COPD subphenotypes. Filling this knowledge gap will be crucial for early COPD diagnosis and intervention on the basis of the immunologic endotype involved. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Polverino

From the Authors:

We thank Dr. Polverino for her letter and interest in our recently published study on IgA production in lymphoid follicles (LFs) from patients with chronic obstructive pulmonary disease (COPD) (1), as well as for her inspiring and stimulating thoughts. Our data show that IgA production occurs in LFs that are present around bronchioles from patients with severe COPD, highlighting the key contribution of the small airways to COPD pathophysiology (2, 3), as well as the relevance of B-cell activation in emphysema, as discussed by Dr. Polverino.

A central question regarding lymphoid neogenesis in COPD lungs relates to the antigenic trigger of this process. There are several possibilities, ranging from adaptive immunity to microbial antigens, as observed in cystic fibrosis (4, 5), to autoreactivity to (modified) self-antigens, as described in emphysema (6, 7). A longitudinal study could indeed be informative about the clinical and pathological events that precede the development of LFs in the COPD lung; however, such a study would be challenging given the

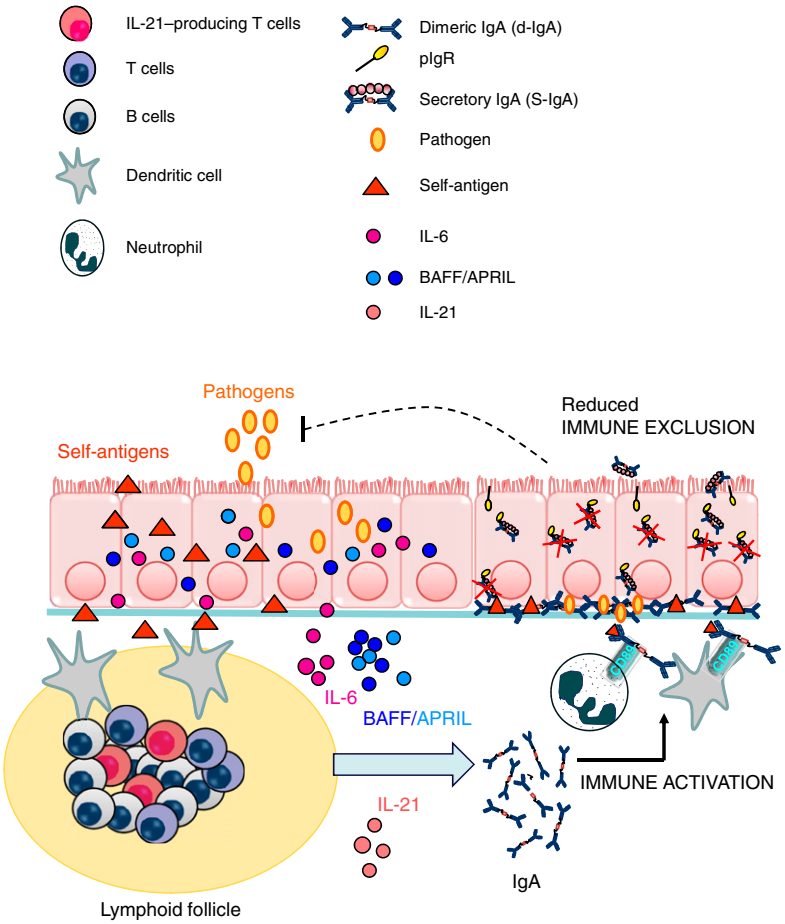

Figure 1. Microbial and (modified) self-antigens may trigger the generation of peribronchial lymphoid follicles where adaptive production of IgA antibodies takes place, probably upon activation by BAFF (B cell–activating factor), APRIL (a proliferation-inducing ligand), IL-6, and IL-21. After downregulation of the transport receptor pIgR (polymeric immunoglobulin receptor) in chronic obstructive pulmonary disease airway epithelium, immune exclusion mediated by secretory IgA is impaired, whereas subepithelial accumulation of (dimeric) IgA could trigger immune activation of myeloid cells and neutrophils expressing Fc RI (CD89).

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