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

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**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).
need for repeated sampling of the distal lung. In parallel, one should further dissect the cellular and molecular mechanisms that promote, beyond IL-21 and lymphokines, the formation of lung LFs in this disease, using animal models that could better integrate small-airway disease, such as ferrets (8).

Another key question concerns the role of IgA in the COPD lung. Other investigators and we have shown that although its production is upregulated not only in LFs (1) but also more globally in COPD lung tissue (9), its plgR (polymeric immunoglobulin receptor)-mediated transport across the airway epithelium is impaired in patients with severe COPD (10–12) as well as in patients with asthma (13). The loss of plgR in COPD distal airways was correlated with disease severity (12), the presence of opportunistic pathogens and actors in adaptive immunity (11), and increased transforming growth factor β signaling (12). The protective role of IgA at mucosal surfaces (reviewed in Reference 14) involves immune exclusion of pathogens and immunoregulation such as induction of IL-10 (15), and fails in (reviewed in Reference 14) involves immune exclusion of pathogens and immunoregulation such as induction of IL-10 (15), and fails in patients with COPD (10–12)–1700380.

Overall, we agree with Dr. Polverino’s suggestion that we need further studies to elucidate the events that trigger LF formation, which could be the same as those that elicit the switch to IgA, whose role in chronic lung disease needs to be better understood.

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

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References