7. Sze MA, Dimitriu PA, Suzuki M, McDonough JE, Campbell JD, Brothers JF, *et al*. Host response to the lung microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 192:438–445.

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

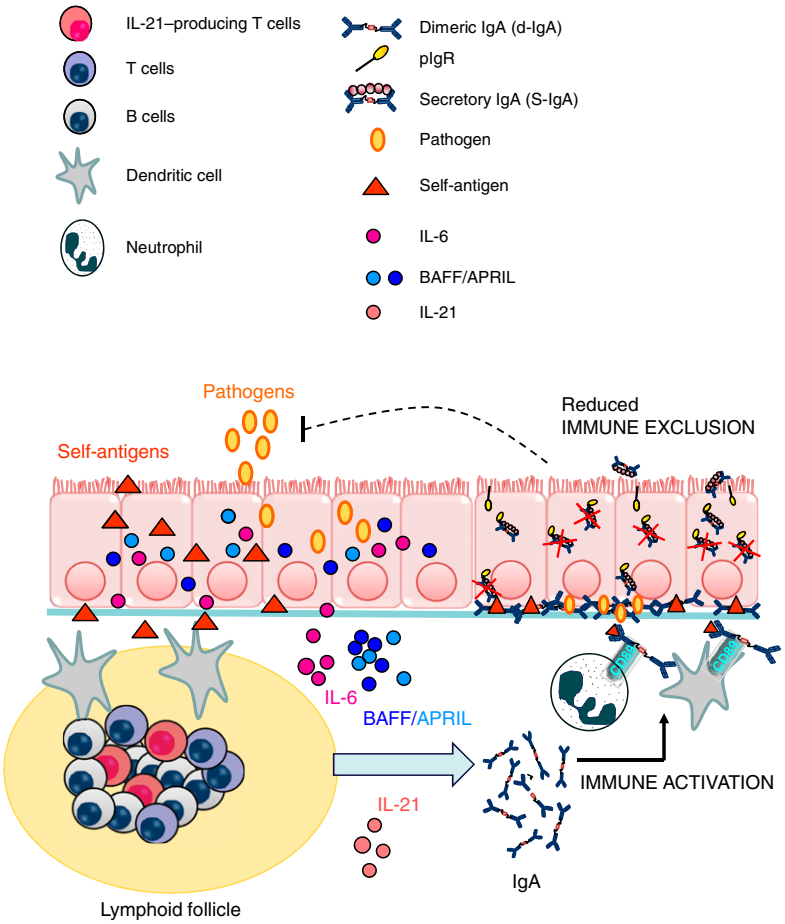

Figure 1. Microbial and (modified) self-antigens may trigger the generation of peribronchial lymphoid follicles where adaptive production of IgA antibodies takes place, probably upon activation by BAFF (B cell–activating factor), APRIL (a proliferation-inducing ligand), IL-6, and IL-21. After downregulation 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).

Originally Published in Press as DOI: 10.1164/rccm.201812-2249LE on January 11, 2019

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 pIgR (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 pIgR 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 $pIgR^{-/-}$ mice that develop age-related emphysema through an innate neutrophilic response to airway microbiota (16). Thus, it is possible that upregulation of IgA occurs in severe COPD as an attempt to counteract abnormal host–microbial interactions and/or ongoing inflammation (17), and failure to do so due to altered transport at the apical surface of the airway epithelium could contribute to the disease (summarized in Figure 1).

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

1. Ladjemi MZ, Martin C, Lecocq M, Detry B, Aboubakar Nana F, Moulin C, *et al*. Increased IgA expression in lung lymphoid follicles in severe COPD. *Am J Respir Crit Care Med* [online ahead of print] 19 Oct 2018; DOI: 10.1164/rccm.201802-0352OC.
2. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, *et al*. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:2645–2653.
3. Burgel PR, Paillasseur JL, Janssens W, Piquet J, Ter Riet G, Garcia-Aymerich J, *et al*.; Initiatives BPCO, EABPCO, Leuven and 3CIA Study Groups. A simple algorithm for the identification of clinical COPD phenotypes. *Eur Respir J* 2017;50:1701034.
4. Gohy ST, Ladjemi MZ, Pilette C. Lung lymphoid neogenesis in cystic fibrosis: a model of adaptive responses to bacteria? *Eur Respir J* 2017;49:1700380.
5. Martin C, Thévenot G, Danel S, Chapron J, Tazi A, Macey J, *et al*. *Pseudomonas aeruginosa* induces vascular endothelial growth factor synthesis in airway epithelium *in vitro* and *in vivo*. *Eur Respir J* 2011; 38:939–946.
6. Baraldo S, Turato G, Lunardi F, Bazzan E, Schiavon M, Ferrarotti I, *et al*. Immune activation in α1-antitrypsin-deficiency emphysema: beyond the protease-antiprotease paradigm. *Am J Respir Crit Care Med* 2015; 191:402–409.
7. Polverino F, Seys LJ, Bracke KR, Owen CA. B cells in chronic obstructive pulmonary disease: moving to center stage. *Am J Physiol Lung Cell Mol Physiol* 2016;311:L687–L695.
8. Bonniaud P, Fabre A, Frossard N, Guignabert C, Inman M, Kuebler WM, *et al*. Optimising experimental research in respiratory diseases: an ERS statement. *Eur Respir J* 2018;51:pii: 1702133.
9. Ladjemi MZ, Lecocq M, Weynand B, Bowen H, Gould HJ, Van Snick J, *et al*. Increased IgA production by B-cells in COPD via lung epithelial interleukin-6 and TACI pathways. *Eur Respir J* 2015;45:980–993.
10. Pilette C, Godding V, Kiss R, Delos M, Verbeken E, Decaestecker C, *et al*. Reduced epithelial expression of secretory component in small airways correlates with airflow obstruction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163:185–194.
11. Polosukhin VV, Cates JM, Lawson WE, Zaynagetdinov R, Milstone AP, Massion PP, *et al*. Bronchial secretory immunoglobulin a deficiency correlates with airway inflammation and progression of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 184:317–327.
12. Gohy ST, Detry BR, Lecocq M, Bouzin C, Weynand BA, Amatngalim GD, *et al*. Polymeric immunoglobulin receptor down-regulation in chronic obstructive pulmonary disease: persistence in the cultured epithelium and role of transforming growth factor-β. *Am J Respir Crit Care Med* 2014;190:509–521.
13. Ladjemi MZ, Gras D, Dupasquier S, Detry B, Lecocq M, Garulli C, *et al*. Bronchial epithelial IgA secretion is impaired in asthma: role of IL-4/IL-13. *Am J Respir Crit Care Med* 2018;197:1396–1409.
14. Carlier FM, Sibille Y, Pilette C. The epithelial barrier and immunoglobulin A system in allergy. *Clin Exp Allergy* 2016;46:1372–1388.
15. Pilette C, Detry B, Guisset A, Gabriels J, Sibille Y. Induction of interleukin-10 expression through Fcalpha receptor in human monocytes and monocyte-derived dendritic cells: role of p38 MAPKinase. *Immunol Cell Biol* 2010;88:486–493.
16. Richmond BW, Du RH, Han W, Benjamin JT, van der Meer R, Gleaves L, *et al*. Bacterial-derived neutrophilic inflammation drives lung remodeling in a mouse model of chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2018;58:736–744.
17. Gohy ST, Hupin C, Pilette C, Ladjemi MZ. Chronic inflammatory airway diseases: the central role of the epithelium revisited. *Clin Exp Allergy* 2016;46:529–542.