cysteinyl leukotrienes and their receptors (14, 15), and overexpression of PgD_2 (16). Thus, it is intriguing that the current study, although confirming the presence of a Th2 signature, does demonstrate a hint at other distinctive features of AERD. Although excessive granulocyte–macrophage colony–stimulating factor and MCP-1 may support a more robust Th2 process, the dearth of tissue plasminogen activator is quite intriguing, suggesting a role for the procoagulation pathway and fibrin deposition that perhaps drives some of the aggressive remodeling that defines this disorder. Activation of the coagulation pathway might also be consistent with recent studies demonstrating a role for platelet-associated inflammation in AERD (17), which is another area of research largely unexplored in these diseases and inviting further research. ■

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"B" for Bad, Beneficial, or Both? Lung Lymphoid Neogenesis in Chronic Obstructive Pulmonary Disease

Lymphoid neogenesis, the formation of tertiary lymphoid structures (1), within distal lung parenchyma indisputably characterizes advanced chronic obstructive pulmonary disease (COPD) (2, 3). Many such lung lymphoid follicles (LLFs) contain germinal centers, indicating immunoglobulin class-switching. Some LLFs in advanced COPD produce auto-antibodies that could fuel lung destruction (4, 5). These findings make lung B cells highly suspicious, especially when congregating in LLF.

However, proximity does not prove culpability. It is challenging to know conclusively when LLF are detrimental and when they are responding appropriately to threatening microbial

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signals. The stakes on this question are substantial. COPD is on track to become the world's leading killer within this century. Therapies proven to arrest its progression in individual patients are lacking. B cells could be eliminated therapeutically in COPD using rituximab, if proven to be prudent. Are LLF B cells in advanced COPD bad, or beneficial? Or might they have begun good but become subverted by the processes they sought to control?

In this issue of the *Journal*, new clues come from two groups (6, 7) with long-term interest in this question. Polverino and colleagues (pp. 695–705) primarily used human lung tissue resected for clinical indications supplemented by *in vitro* experiments (6), whereas Seys and colleagues (pp. 706–718) also employed their established murine cigarette smoke-exposure model (7). Both studies convincingly associate LLF accumulation in COPD with dysregulation of B-cell activating factor (BAFF), and the latter found that blocking BAFF partially reduced lung pathology in mice (7).

BAFF is a 285-amino acid glycoprotein essential for the survival of conventional B cells beyond the first (T1) post–bone marrow stage. Known formally as tumor necrosis factor ligand superfamily member 13B (TNFSF-13B) (plus multiple aliases reflecting discovery by several groups), BAFF exists as a transmembrane protein (CD257) and as active cleaved and secreted soluble molecules. Its predominant sources are monocytes, macrophages, conventional and follicular dendritic cells, and some T cells. Human B cells do not normally produce BAFF, but can during Epstein Barr virus infection or after *in vitro* stimulation via their B-cell antigen receptor plus CD40 (8). BAFF deficiencies are associated with immunoglobulin deficiency, whereas excesses are found in autoimmune diseases including systemic lupus. BAFF binds to three receptors, including most specifically and avidly to BAFFR.

These interesting papers contain both congruent and complementary findings. Each elegantly demonstrated BAFF expression within human LLF. Seys and colleagues found increased lung concentrations of both BAFF messenger RNA and protein in Global Initiative for Obstructive Lung Disease (GOLD) stage II COPD, relative to never-smokers, but importantly, neither differed significantly from smokers without obstruction (7). Focusing on LLF and examining a wider COPD severity range, Polverino and colleagues demonstrated that BAFF expression by LLF B cells correlated directly with LLF size and COPD spirometric severity, and inversely with apoptotic B-cell detection (6). They further showed that cigarette smoke extract induced concentration-dependent effects on murine B cells *in vitro*: low levels induced BAFF, whereas high levels caused apoptosis that could be blocked by exogenous BAFF, unexpectedly in a nuclear factor-κB-dependent manner (6). Closing the loop mechanistically, Seys and colleagues tested BAFF blockade in their murine model, using a decoy receptor (BAFFR-Fc) both prophylactically and therapeutically. BAFFR-Fc administration reduced LLF extent and lung inflammation and reduced emphysema, but only when used prophylactically, and then only as assessed by destructive index, but not by mean linear intercept.

Both studies meticulously employed cutting-edge techniques and a robust number of human subjects (146 [6] and 70 [7], respectively). Limitations are minor (e.g., immunolocalization was complicated by the likelihood that not all BAFF was cell-associated), leading to the prudent characterization of staining, as "in the vicinity of" B cells, $CD4^+$ (but not $CD8^+$) T cells, and fibroblastic reticular cells (7). The latter are one of three stromal cell types essential for lymphoid neogenesis (9), a point adding to mechanistic understanding of BAFF in COPD.

So, do these novel discoveries constitute another "smoking gun" (10) establishing adaptive immunity as central to COPD progression? Before reaching that verdict, we urge caution, based on the timing of LLF expansion, confirmed by both studies to be primarily late during COPD progression, and the dominant role in immune system development of interactions with microbes, especially bacteria.

In multiple longitudinal studies, FEV_1 declined more greatly in spirometrically mild COPD than in advanced disease. Yet lung B-cell (and T-cell) abundance is low in GOLD stage I COPD (2), unlike the expansion of lung mononuclear phagocytes that begins soon after initiating smoking (11). This disparity between histology and spirometry suggests that, despite the intriguing effects of BAFF blockade in mice (7), whatever processes drive the initial transition from preserved to impaired lung function in some human smokers (Figure 1, *transition 1*), they are unlikely to be caused by lung B cells, as neither they nor LLF are common at that stage.

Similarly, although the lung microbiome community structure of smokers without airflow obstruction does not differ from that of never-smokers (12), what data exist (13) indicate it changes progressively in the fraction of smokers who progress to COPD (Figure 1, *transition 2*). No publications have yet directly related reduced lung microbiome diversity to LLF extent. Nevertheless, reasonable doubt should exist that early lung lymphoid neogenesis develops independent from lung microbiome alteration, which neither study claims. Conversely, autonomous BAFF elaboration could plausibly contribute to dysregulated inflammation or even frank autoimmunity in advanced COPD, especially combined with the known defective function of both T-regulatory and T-helper cells (14, 15).

Hence, important new insights have been gained from these papers (6, 7), but even more must be learned before novel therapies, including the several BAFF-inhibitory drugs under evaluation in multiple myeloma, can be contemplated for use in COPD. The markedly abnormal lung microbiome of some patients with advanced COPD likely drives symptoms and contributes to exacerbation severity, and thereby mortality. Specific IgA may be important for these patients, and is certainly essential to maintain homeostasis with our gut microbiome. Moreover, B cells also inhibit inflammation via IL-10 or IL-35 (16), which merit greater study in COPD. Before testing BAFF elimination, it will be crucial to identify and validate biomarkers that define in exactly which COPD phenotypes lung B cells are misbehaving versus beneficial. Intervening earlier in COPD progression will require determining whether lung dysbiosis, perhaps in association with specific COPD endotypes, causes the initial transition to airflow obstruction (Figure 1, *transition 1*) or is simply a biomarker for the processes that do. Both goals can be accomplished most expediently by longitudinally analyzing the interplay of pulmonary immunity, lung microbiome, and clinical outcomes in cohorts

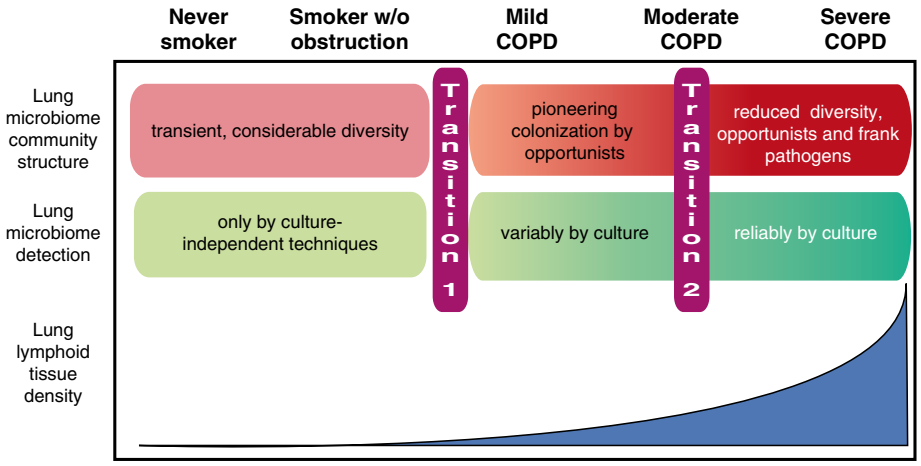

Figure 1. Relationship between lung microbiome community structure and intrapulmonary lymphoid tissue abundance in cigarette smoking–induced chronic obstructive pulmonary disease (COPD). In never-smokers and smokers without airflow obstruction, lung bacterial communities are diverse and shaped by repeated elimination of bacteria derived from the upper airway. Lung bacteria are detectable only by sequencing, and some may be nonviable. In mild to moderate COPD, although sequencing indicates that microbe numbers are not necessarily greater, they become variably detectable by culture (indicating viability). Whether this change (*transition 1*) causes obstruction or is a marker of shared underlying causes is undefined. A further change occurs in moderate to severe COPD (*transition 2*), with reduced diversity and predominance of opportunistic and even pathogenic species. The relationship of this transition to spirometric severity differs between COPD phenotypes, and whether it drives progression outside exacerbations is unproven. Importantly, expansion of lung lymphoid follicles occurs relatively late during pathogenesis and parallels altered microbial community structure.

of patients with COPD of distinct phenotypes and a range of severities. ■

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Low-Flow Extracorporeal Carbon Dioxide Removal
Moving Closer to Reality

In patients with acute respiratory failure, invasive mechanical ventilation may be applied to ensure adequate gas exchange while unloading the respiratory muscles. However, the consequences of invasive mechanical ventilation may include ventilator-associated pneumonia and ventilator-induced lung injury (VILI), and in patients with obstructive lung disease, dynamic hyperinflation and worsening of intrinsic positive end-expiratory pressures may result (1).

Lung-protective ventilation strategies, as originally defined by the ARDSNet ARMA trial, using low tidal volumes and limited airway pressures, aim at minimizing stress and strain in patients with the acute respiratory distress syndrome (ARDS) (2). More recent findings suggest that at least in some patients with ARDS, the conventional strategy may not be protective enough to prevent tidal hyperinflation (3), and that plateau airway pressures lower than 30 cm H_2O may be required to further reduce VILI (4). As a logical consequence, the concept of ultraprotective ventilation has been introduced (5). However, such an approach, as well as any attempt to limit delta pressure, further reduces alveolar ventilation, thus increasing Pa_{CO_2} and ultimately lowering pH values. In the 1970s, the idea arose to separately regulate ventilation and oxygenation by combining invasive mechanical ventilation with an extracorporeal support device aimed mainly at CO_2 removal (6). The amount of CO_2 removed by the extracorporeal circuit directly corresponds with the extent to which alveolar ventilation can be reduced.

The invasiveness of extracorporeal lung support is closely related to the amount of blood that has to be pumped through an artificial lung. As CO_2 removal is highly dependent on the partial pressure gradient between the dissolved CO_2 in the blood phase and the CO_2 in the gas phase of an oxygenator, the use of low-flow extracorporeal lung support techniques has been suggested for CO_2 removal to compensate for the reduced alveolar ventilation in patients with hypercapnic respiratory failure or to apply ultraprotective ventilator settings in patients with ARDS.

The rationale for high-flow extracorporeal membrane oxygenation is to rescue patients from acute life-threatening hypoxemia, which might justify the higher risks associated with the use of large cannulas and high blood flow rates. The rate of complications reported using pumpless arteriovenous systems or pump-driven mid- to high-flow venovenous extracorporeal assist devices ranges between 10 and 25% and might even be higher (7). The theoretical rationale behind the use of low-flow extracorporeal support is to use smaller cannulae and lower extracorporeal blood flow rates, removing CO_2 directly from the blood to modulate the degree of VILI or dynamic hyperinflation, to avoid endotracheal intubation during noninvasive ventilation, or to allow early extubation and weaning from invasive mechanical ventilation (7–12). Enhancing the efficiency of CO_2 removal is the key to minimizing blood flow requirements, and therefore cannula size. With current technology, lower blood flows limit the amount of CO_2 removal, and therefore lessen the potential benefits.

In this issue of the *Journal*, Zanella and colleagues (pp. 719–726) report on the successful use of an electrodialysis chamber integrated into an extracorporeal circulation system to significantly increase the amount of dissolved CO_2 in the blood before it passes through a conventional oxygenator, so-called respiratory electrodialysis (13). With this set up, the authors were able to demonstrate that, while using the same blood flow, nearly double the amount of CO_2 per minute could be removed from the blood of healthy pigs when compared with a conventional extracorporeal CO_2 removal device.

Zanella and colleagues developed the very clever concept of increasing the CO_2 partial pressure in the blood phase by increasing the amount of dissolved CO_2 through acidification. Their first approach consisted of blood acidification with hydrochloric acid or lactic acid, referred to as "acid load CO_2 removal, or $ALCO_2R$" (14). $ALCO_2R$ increased membrane lung CO_2 removal to 50% of the total carbon dioxide production at a blood flow rate of 250 ml/minute by converting bicarbonate ions into dissolved CO_2 via acidification with metabolizable acids for blood entering a membrane lung, which provided the proof of principle. The current, more sophisticated approach uses an electrodialysis chamber for blood acidification without adding any external acid valences. With this approach, the authors nearly doubled the CO_2 removal rate for a given blood flow, thus opening the window for more efficient CO_2 removal, without the need to infuse exogenous acid. A similar technique immobilizes carbonic anhydrase on the surface of the membrane to improve CO_2 removal efficiency by enzymatically releasing CO_2 from serum bicarbonate (15). Reports on this technique, although very interesting, suggest it may currently be less effective than respiratory electrodialysis, and technical hurdles remain.

Zanella and colleagues provide evidence that their set-up is mostly free of serious adverse effects. Certainly, further studies are needed to better define the potential effects of the rapid pH and electrolyte shifts within the device, which are required for the technique, on the functionality of erythrocytes and other corpuscular blood components. The authors point out that a 40% increase in serum creatinine levels was noted in the pigs. This is clearly something that requires clarification in further studies of this technique. It must also be noted that the experiments were