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B Cells Caught in the Act: Class Switching to IgA in Lung Lymphoid Follicles in Chronic Obstructive Pulmonary Disease

Searching unceasingly throughout the body, antibodies pursue their targets like relentless wraiths. Antibodies of the IgG subclasses can initiate target lysis either directly by activating the classical complement cascade or by alerting cellular effectors such as natural killer cells via activating Fcγ receptors to inflict the lethal hit by antibody-dependent cellular cytotoxicity (1). The Fc portions of IgG and IgM induce myeloid cell phagocytosis, and the Fc fragment of IgE launches mast cell degranulation. Distributing throughout total body water, antibodies ensure that the immune system is constantly and everywhere vigilant.

Antibody class switching relates directly to chronic obstructive pulmonary disease (COPD) pathogenesis. Ever since Cosio and Guerassimov proposed an autoimmune etiology of COPD (2), and lung lymphoid follicles (LLFs) (3) and elastin-specific antibodies (4) were demonstrated in advanced emphysema, the question of how autoantibodies might contribute to COPD progression has engendered intense investigation (5). Indeed, unbiased analyses of gene expression strongly link lung B cells to emphysema (6, 7).

However, humoral immunity includes a gentler component, secretory immunoglobulin A (sIgA), which is crucial to maintain mucosal barriers against bacteria transgression (8) and, when focally absent, is also intimately involved in COPD pathology (9). sIgA possesses two superpowers: it promotes immune exclusion by chaining respiratory microbes to mucus, and it neutralizes proinflammatory factors such as LPS, typically without inducing inflammation. sIgA activates neither the classical complement cascade nor phagocytes, with the exception of eosinophils (reviewed in Reference 10), via its several receptors (11). sIgA's importance is illustrated by the resources expended on its production: ∼3 g daily, mostly excreted into the gut to maintain symbiosis with commensal bacteria (12).

Previous key observations about IgA in lung host defense and pathology were made by the group at the Université Catholique de Louvain (13–15). It is only fitting that Ladjemi and colleagues (pp. 592–602) contribute another in this issue of the *Journal* (16). Using lung tissues removed for clinical indications (subjects with COPD, $n = 37$; control subjects, $n = 34$) plus murine models of chronic *Pseudomonas aeruginosa* and of smoking, they assessed Ig class expression by B cells in LLFs in COPD and during chronic lung infection. The study has several technical strengths, including rigorous

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quantification of immunohistochemical staining results using color deconvolution and a melting-curve analysis of the PCR reactions that independently confirmed IgA production.

There are multiple novel and interesting results. The first is that IgA^+ B cell numbers were increased in LLFs in distal lung parenchyma in subjects with COPD relative to smokers without COPD, and correlated with spirometrically defined severity (16). That was not true in proximal airways, which do not depend on sIgA transcytosis, extending previous studies (3, 9). IgG^+ B cells were not similarly increased, a crucial finding that is considered further below. Interestingly, LLF IgA^+ B cells were also increased in their murine models by infection, but not by cigarette smoke exposure. The survival of human peripheral blood B cells *in vitro* was unexpectedly prolonged by cigarette smoke extract, but not by LPS—a finding that merits mechanistic investigation in future studies.

The central results provide clues to the control mechanisms within LLFs of Ig class switching, the quintessential example of T-cell help. In lymph node germinal centers, Ig class switching depends largely on a specialized $CD4^+$ T-cell subset, T follicular helper (Tfh) cells. This independent lineage is identified by expression of the transcription factor B cell lymphoma 6, which the authors examined. LPS can also induce human IgM^+ memory B cells to switch directly to IgA secretion, an intriguing possibility given the observation by Ladjemi and colleagues that most LLF B cells (70–80%) were IgM^+. Nevertheless, another key finding is the expression of IL-21 within LLFs in COPD by T cells, including IL-17–secreting T (T17), but not Tfh, cells. These results support a seminal murine study that showed that LLF development depends on T_{17} cells and $CD11b^{high}$ conventional dendritic cells, unlike the formation of lymph nodes, which requires lymphoid inducers (17). Along with the relative paucity of follicular dendritic cells in LLFs, these findings provide novel insights into the rules governing LLF formation in COPD.

IL-21 is a four-α-helical bundle cytokine that signals via the common receptor γ chain, as do IL-2, -4, -7, -9, and -15 (18). IL-21 promotes B-cell maturation outside the bone marrow. It drives division of naive human B cells, accelerates Ig affinity maturation and differentiation into plasma cells, and, with CD40L, increases IL-10 secretion by class-switched memory B cells (19). Without appropriate costimulation, however, B cells exposed to IL-21 undergo apoptosis, a check on bystander activation. Similarly, in the absence of granulocyte-macrophage colony-stimulating factor, IL-21 induces apoptosis of conventional dendritic cells, as another means to maintain self-tolerance (20). IL-21 has opposite effects on two types of T regulatory cells (T_{Reg}), favoring expansion of T effectors over $Foxp3^+$ T_{Reg} (21) while supporting the differentiation of $Foxp3^-$ IL-10–producing Tr1 cells (22). Thus, IL-21's actions are complex, and although it has been reported to be overproduced in several autoimmune diseases (18), its ultimate role in COPD pathogenesis requires further study.

Because LLFs are not unique to COPD, as the authors point out, this study has broader importance. LLFs also occur in cystic fibrosis and bronchiectasis, which are clearly linked with chronic bacterial overgrowth, but also in idiopathic pulmonary fibrosis, pulmonary hypertension, and lung cancer, which are generally not considered to be. Hence, understanding LLFs could help explain how adaptive immunity is involved in a wide range of lung diseases. In other organs, lymphoid neogenesis (the more general term for such ectopic lymphoid tissue) is implicated as an antigen-driven process associated with autoimmunity (23). Whether the same is true during the entire decades-long evolution of heterogeneous conditions such as COPD remains an unsettled question.

Regarding the source of the antigens that drive IgA production in COPD, Ladjemi and colleagues suggest both pathogens and altered self. This prudently impartial hedge acknowledges the current limits of our understanding. Still, IgA's chiefly noninflammatory properties suggest that regardless of the stimulus, the B cells that make it in LLFs in COPD are unlikely to contribute to tissue destruction. IgA is not entirely devoid of pathological potential, as shown by IgA nephropathy, the most common glomerular disease outside of sub-Saharan Africa (24), and its involvement in several uncommon forms of bullous skin disease (25). At least in the kidney, IgA appears to be capable of activating complement via the lectin pathway. However, with these exceptions, IgA antibodies are not implicated in autoimmunity. Hence, it is significant that Ladjemi and colleagues found so few IgG-secreting B cells in COPD. A final implication of this study is that the answer to the question of whether LLF B cells in COPD are bad or beneficial (26) is that many appear to be trying to help. Such a wealth of insights from catching B cells in the act. ■

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"There Is Nothing New Except What Has Been Forgotten"*: The Story of Mechanical Ventilation during Extracorporeal Support

Forty years ago, Kolobow and colleagues described a variant of "apneic oxygenation," where the lung is inflated at constant pressure with 100% oxygen and carbon dioxide is removed by an extracorporeal circuit (1). These pioneers in investigating extracorporeal support were prescient in recognizing that it was unclear whether using positive end-expiratory pressure (PEEP) 5 cm H_2O to keep the lungs inflated above the FRC represents the "optimal requirement or whether pressure is desirable or even necessary for optimal performance." They went on to suggest that this "alternative to breathing" may affect the practice of mechanical ventilation, especially in difficult cases. Eventually, extracorporeal support may obviate the need for mechanical ventilation altogether, providing a true lung rest in conditions in which the use of a ventilator is "not desired or is contraindicated, or where it must be terminated" (2). However, recent reports have provided mixed results (3, 4). Until this issue is resolved, mechanical ventilation will play an important role in patients on extracorporeal support (5). Thus, finding the optimal interface between mechanical ventilation and extracorporeal support remains important, with most efforts to date focused on reducing the intensity of mechanical ventilation through changes in one (or more) ventilatory parameters (Table 1) (6).

In this issue of the *Journal*, Araos and colleagues (pp. 603–612) examine the old concept of near-apneic ventilation (7) and its effects on lung injury and fibroproliferation in an experimental model of severe acute respiratory distress syndrome (ARDS) supported with venovenous extracorporeal membrane oxygenation (ECMO) for 24 hours (8). Lung injury was induced in pigs ($n = 18$) by repeated saline lavage followed by 2 hours of injurious mechanical ventilation. The animals were then randomized into three groups: nonprotective (PEEP, 5 cm H_2O; V_T, 10 ml/kg; respiratory rate [RR], 20 breaths/min), conventional protective (PEEP, 10 cm H_2O; V_T, 6 ml/kg; RR, 20 breaths/min), and near-apneic (PEEP, 10 cm H_2O; driving pressure, 10 cm H_2O; RR, 5 breaths/min). Sham animals ($n = 6$) received neither lung injury nor ECMO. Among the lung-injured pigs, minute ventilation, driving pressure, and mechanical power were lowest in the near-apneic group. The effect of the ventilatory strategy on the degree of lung injury and early fibroproliferative response among the groups was variable. Although the histological appearance of injury was lowest in the near-apneic group, there was no difference in

*Quote from Marie Antoinette (1755–1793)

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