cage or by pleural adhesions? Does contraction of the inspiratory rib cage muscles (load sharing) or contraction of abdominal muscles (i.e., respiratory alternans) influence caudal diaphragm dome velocity? Other questions are sure to arise as this new method for evaluating diaphragm function evolves over the next decade. ■

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The ABCs of Granulomatous Lung Diseases: Age-associated B Cells

At the mention of B cells, your likely first thought is the production of antibodies, mostly beneficially directed against microbial threats but also potentially pathogenic, as when allergy is triggered in a susceptible host by excessive antigenic exposure or when inappropriate self-sensitization leads to autoimmunity (1). Immunoexclusion by secretory IgA is essential to prevent bacterial damage to the lower airways (2, 3), and IgG indispensably protects against respiratory viruses (4), a current worldwide concern. However, independently from immunoglobulin production, B cells also play important roles as antigen-presenting cells (5) and as regulatory cells akin to regulatory T cells (6). Hence, defining mechanistically what B cells are doing in specific lung diseases is a crucial investigative area.

Lying beneath the broad umbrella of possible B-cell functions in lung diseases are a lot of things, not all good. In asthma, their roles range from propagating T-helper cell–mediated responses to antigens such as house dust mites to IgE elaboration by specific memory B cells (7). As chronic obstructive pulmonary disease severity mounts, there are progressive increases in the numbers and size of B-cell–rich lung lymphoid follicles (8–10) and in concentrations of autoantibodies in blood and lung samples, especially in the emphysematous phenotype (11). Less is known about B-cell immune

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profiles in granulomatous lung diseases, which include sarcoidosis, chronic beryllium disease (CBD), and hypersensitivity pneumonitis (HP) (12). Hypergammaglobulinemia (including autoantibodies) is well recognized in sarcoidosis, and B cells form prominent infiltrates at the periphery of lung granulomas in CBD (13) and in sarcoidosis, where they contain IgA-producing plasma cells (14). Case report evidence of responses to rituximab exists for extrapulmonary sarcoidosis but not for pulmonary disease (reviewed in [15]). By contrast, data from a murine model implies a MyD88-dependent protective role of B cells in CBD (13). The increasingly evident complexity of B-cell subsets (16) indicates a need for closer examination in granulomatous lung diseases.

An apt choice for this examination is age-associated B cells (ABCs) (17). As that name implies, ABCs increase in frequency with aging, in which they contribute to inflammation (18), but they are also associated in both humans and mice with persistent viral infections including HIV (19, 20) and with autoimmunity (21). ABCs are primarily tissue-resident cells that appear to be antigen experienced. Via high-level expression of costimulatory molecules, they present antigens to and polarize T cells. ABCs have unique gene expression profiles, including the typically T-cell–restricted transcription factor T-bet and CD11c, generally a mononuclear phagocyte receptor. There is consensus that ABCs in humans and rodents have low expression of CD21, the receptor for complement component C3d (and Epstein-Barr virus) that fuels B-cell activation. But like many emerging scientific stories, understanding of ABCs is hampered by disagreement on multiple other points, especially how to define them by surface receptor expression, which is essential to permit isolation for analysis, hence the interest in the FcRLs (Fc receptor–like proteins) as possible means to untangle ABC heterogeneity (17, 21). These CD307 gene family members differ markedly in number, structure, and cell-type distribution between species, suggesting strong ongoing evolutionary pressure (22).

In this issue of the *Journal*, Phalke and colleagues (pp. 1013–1023) (23) from the laboratory of the renowned immunologist Philippa Marrack extend their seminal work on ABCs (21, 24–27). Acknowledging the nomenclature controversies (19, 28, 29) by referring to them as "ABC-like cells," they present several novel, interesting findings. First, they used flow cytometry to characterize peripheral blood and BAL of patients with the granulomatosis lung diseases sarcoidosis, CBD, and HP or with beryllium sensitivity (BeS). They identified two main ABC-like subpopulations, both with high CD11c and low CD21 expression: one T-bet high and another T-bet low to negative. CD11c expression correlated positively with levels of T-bet and of FcRLs 2–5. These are important data for the question of what constitutes a human ABC. Second, they found increased numbers of ABC-like cells in peripheral blood (relative to healthy subjects) in patients with BeS, CBD, HP, and particularly sarcoidosis; an important caveat here was the significantly younger age of their control subjects. In patients with disease, ABC-like cells were further enriched in BAL, relative to their own blood. Interestingly, patients with sarcoidosis on disease-modifying treatments had fewer ABC-like cells than untreated patients. Third, regardless of participant disease status, ABC-like cells expressed less FcRL1 and more FcRL2, 3, 4, and 5 relative to non-ABC–like B cells ("other B cells"). Fourth, besides defining correlations between individual receptors compatible with coregulation, they surprisingly found no significant difference in percentages of BAL ABC-like cells between individuals with BeS versus established CBD (23).

This study demonstrates that B cells, specifically the subset we feel based on these results deserve simply to be called ABCs, may be doing something important in three granulomatous lung diseases believed to result from inhalational exposures. This commonality is intriguing, considering their disparate mechanisms: directly antigenic (HP), caused by HLA-DP allele-specific T-cell responses (BeS, CBD), and still unknown (sarcoidosis). That commonality makes understanding how ABCs are recruited into lung and their interactions once there key research priorities, especially for sarcoidosis. Phalke and colleagues also deserve praise for using difficult-to-acquire human samples to address the diversity of FcRL expression, an issue of fundamental immunological interest and more practical for studies of viable cells than T-bet.

Exactly what ABCs are doing in these diseases remains unclear. Implying causality would exceed the associational, cross-sectional nature of their data and was wisely not claimed. Because circulating ABCs are increased in multiple diseases and in aging, their utility to make any specific diagnosis is limited (30). Nevertheless, combining the equivalent percentages of BAL ABC in BeS and CBD (23) with the protective role of conventional B cells in a transgenic model of CBD (13) suggests an intriguing possibility. ABCs may be recruited by granulomatous inflammation without an essential role in initiating pathology, but once there, responding to local IL-21 (31, 32), their T-bet+ clones in particular (20) might drive T-cell responses. This hypothesis merits testing in experimental models of granulomatous and other lung diseases. B cells justifiably deserve their place in the spotlight in lung pathology. ■

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New Imaging Tools Allow Bronchopulmonary Dysplasia to Enter the Age of Precision Medicine

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, and best estimates suggest it affects roughly 20,000–30,000 infants annually in the United States alone (1, 2). According to the "classical" National Institute of Child Health and Human Development definition (3), about 13,000 infants/yr in the United States are affected by severe BPD requiring positive pressure support at 36 weeks corrected gestational age, with an estimated mortality of 1,000–2,400 deaths annually (4, 5). This is a substantially higher annual incidence than all of childhood cancer with similar or worse survival. Unfortunately, despite decades of preventative efforts, rates of BPD have not improved and indeed seem to be increasing steadily as our abilities to save extremely preterm infants improve. The International Neonatal

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