What Lies beneath: Preformed Autoantibodies and Lung Transplantation

There is increasing evidence that autoimmunity plays an important role in the progression of chronic lung diseases such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis (1–4). The identification of functionally active (and pathogenic) autoantibodies with specificities for defined self-antigens provides unique insights into the complicated immunology of these disorders, and draws attention to a previously underappreciated pathway involved in the regulation of lung inflammation. Although previous studies have largely focused on the autoantibody repertoires and mechanisms in chronic lung diseases, the potential impact of preexistent autoimmunity in the setting of lung transplantation remains largely unexplored.

In this issue of the *Journal*, Patel and colleagues (pp. 678–686) provide some clues to answering this question (5). Their study extends previous observations that showed the presence of increased concentrations of circulating autoantibodies with specificities for extracellular matrix (ECM) in a 6-month smoking model of emphysema. Patel and colleagues used lungs from smoke-exposed mice and non–smoke-exposed controls as donor organs in allogeneic pulmonary transplantations, and found that ischemia/reperfusion injury and antibody/complement deposition were increased in recipients of the smoke-treated allografts. In a subsequent series of unique and clever experiments, the authors further substantiated the impact of preformed autoantibodies by eliminating confounding effects of alloreactivity in a syngeneic lung transplantation model. In these studies, the administration of serum from smoke-exposed mice resulted in increased antibody/complement deposition and lung injury that was clearly independent of allogeneic responses. Moreover, this injury was attenuated when IgG and IgM antibodies were depleted from the smoke-exposed serum. This study adds to prior literature identifying the importance of non-human leukocyte antigen autoantibodies in the pathogenesis of transplant-related lung injury (6, 7). In particular, the current report adds to other evidence that suggests that preformed autoantibodies, which are especially increased in patients with certain chronic lung diseases, contributes to post-transplant allograft dysfunction (8).

Although it is provocative, this observation should be considered in a broader context. First, "conventional" autoantibody syndromes are typified by the presence of multiple concurrent specificities, and there is reason to believe that the same holds true in chronic lung diseases. The present study was limited to assessments of anti-ECM autoantibodies, whereas the impact of immunoglobulins with avidities for other lung-specific and extrathoracic autoantigens could be of significant interest. The possibility that the autoreactivity to ECM observed here was due to smoke-induced modifications that rendered self-proteins immunogeneic (i.e., neoantigens) was not explored in this study, although this process may contribute to pathogenic autoreactivity in humans (2). In addition, in most human disorders the various IgG fractions are generally believed to be more pathogenic than IgM, and fractionation and individual transfers of these immunoglobulins might have been enlightening. Furthermore, the development of antibodies against peptide antigens is dependent on the concurrent presence of T-cell reactivity against those same epitopes (9, 10). However, the present study does not shed light on how cellular autoreactivity against ECM (11) or other autoantigens contributes to lung injuries after transplantation. Finally, the long-term impact of these autoantibodies (and autoreactive T cells) was not assessed in this transplant model. It can be predicted that when such studies are performed, they will add considerable value to our understanding of long-term allograft loss.

Despite these understandable limitations, this paper provides important insights into post-transplant lung injury. It may have considerable value in providing a template for future studies to further delineate the autoimmunity of post-transplantation allograft injuries. These investigations could include adoptive transfers of autoreactive T cells from smoke-exposed, emphysematous animals, with and without immunoglobulin fractions, to parse out the respective effects of these immune response elements. Perhaps most importantly, the model detailed here, or minor variations of this model, might be a valuable vehicle for preclinical studies of potential therapies. These could include tests of complement inhibitors (12), as the authors mention, or refinements of other modalities focused on autoantibody reduction pretransplantation (13). ■

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

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