Foxp3$^+$ T lymphocytes: immune regulators within the lung allograft

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Antibody-mediated rejection (AMR) has emerged as an important cause of lung graft failure. In the current issue of the *JCI*, a study by Li et al. identifies a critical role of Foxp3$^+$ T cells residing within lung allografts in the regulation of AMR. This study not only provides new insights into the nature of lung allografts as a primary site where T and B cell priming and immune regulation can occur, but also introduces the mouse orthotopic lung transplant as a model for studying the immunobiology of AMR. Because AMR can be so difficult to effectively treat in lung transplant recipients, the development of an animal model is a major advance in understanding the immunopathogenesis of AMR.

The lung allograft functions as a secondary lymphoid organ

While the prevailing view in solid organ transplant and other areas of immunology is that adaptive immune responses are initiated and regulated in secondary lymphoid organs, such as lymph nodes and spleen, the lung has its own secondary lymphoid tissue in the form of bronchus-associated lymphoid tissue (BALT). Antibody-mediated rejection (AMR) has become an increasingly recognized contributor to acute and chronic lung allograft dysfunction in lung transplant recipients, leading to a recent consensus definition from the International Society for Heart and Lung Transplantation (ISHLT) (1). In the current study by Li et al., the authors demonstrate that lung allograft–resident Foxp3$^+$ cells are the master regulators of allogeneic humoral responses and reside in BALT structures, which limits humoral immune responses (ref. 2 and Figure 1). The authors show that when allografts from tolerant mice are transplanted into a second recipient, depleting these allograft regulatory T cells consistently results in AMR. Therefore, the regulation of allogeneic humoral responses continues to occur within the lung allograft itself. This finding parallels that of a previous report by the same group demonstrating that, very shortly after transplantation, priming of alloreactive T cells occurs within the lung allograft as well (3). Understanding these unique aspects of immune activation and regulation of alloimmune responses in lung transplantation is critically important in order to better adapt current immunosuppressive strategies that are broadly applied across multiple organs to an allograft that is truly, itself, a secondary lymphoid organ.

Pulmonary AMR is characterized pathologically by acute lung injury

As AMR in lung transplant has only recently been fully recognized as an important cause of lung allograft dysfunction, the description and definition of underlying pathology are also recent and evolving. Here, the authors describe lung allograft pathology in mouse recipients with antibodies directed against alloantigen known to be the cause of allograft injury. These lung allografts are characterized by pathology completely consistent with acute lung injury (ALI) and diffuse alveolar damage/alveolar edema with hyaline membrane formation, along with complement deposition and airway epithelial injury. Interestingly, ALI pathology has been shown to be a common manifestation of AMR in lung allograft recipients, making this AMR mouse model important in a pathologic correlate context (4). Indeed, as similar pathology can be seen with multiple other potential lung allograft insults (ischemia-reperfusion, infection, aspiration, viral infection, etc.), it is often difficult in the clinical realm to determine the cause of ALI when it occurs in the lung allograft. However, Foxp3$^+$ regulatory CD4$^+$ T cells may be essential for the resolution of ALI regardless of the cause of ALI. In a previous study by D'Alessio et al., Foxp3$^+$ CD4$^+$ T cells were shown to mediate resolution of ALI in mice treated with intratracheal LPS (5). The study in this current issue highlights the importance of considering AMR in patients that demonstrate ALI pathology without other identifiable causes and shows that preserving the presence of Foxp3$^+$ regulatory CD4$^+$ T cells may be important in the prevention and resolution of ALI from any cause in lung transplantation.

Retransplantation of Foxp3$^+$-depleted lung allografts: model of pulmonary AMR

One of the many challenges in uncovering cellular and molecular mechanisms contributing to allograft dysfunction in lung transplantation has been the lack of animal models that adequately mimic the human scenario. For example, achieving a reproducible animal model to study obliterative bronchiolitis, a manifestation of chronic allograft rejection in lung transplant recipients, remains challenging, though some progress has recently been made (6). Here, Li et al. have used an elegant retransplantation experimental method and have demonstrated that selective depletion of

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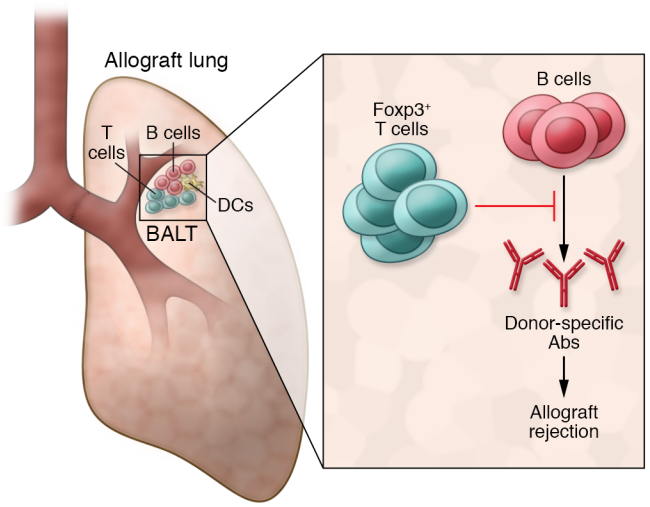

Figure 1. Foxp3⁺ T lymphocytes in BALT regulate B and T cell alloimmune responses in the lung allograft. Lung allografts are primary sites where T and B cell priming and immune regulation can occur. Foxp3⁺ T cells residing within lung allografts regulate AMR. Preserving the presence of Foxp3⁺ regulatory CD4⁺ T cells may be important in the prevention and resolution of ALI from any cause in lung transplantation.

graft-resident Foxp3⁺ CD4⁺ T cells results in pulmonary AMR. Moreover, this retransplantation AMR model is the first model in which endogenous donor-specific antibody (DSA) is *generated by the lung recipient*, making it highly useful for the study of DSA immune responses. Both the pathology, characterized by ALI, and the mechanism of injury, demonstrated by the generation of allogeneic humoral B cell responses in concert with T cells, replicate the clinical scenario of AMR in human lung recipients. While the experiments required to generate this mouse model of pulmonary AMR are labor intensive and require significant expertise to conduct, the model itself enables mechanistic studies that will facilitate further understanding of how better to prevent AMR in lung transplantation as well as how to treat it once it occurs. Importantly, the authors show that two ligand-receptor pathways known to be important for the generation of antibody, the CD40 ligand/CD40 and CXCR5/CXCL13 pathways, are critical for the generation of DSA and pulmonary AMR pathology. For these reasons, the study by Li et al. represents an exciting step forward in the field and is a platform for the development of potential novel therapies for pulmonary AMR that may have a substantial translational impact in lung transplant recipients.

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