Commentary: T cells regulate lung transplant rejection in mice and men

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Left to right: Jason M. Gauthier, MD, Wenjun Li, MD, and Daniel Kreisel, MD, PhD

Central Message

Lung transplant acceptance appears to be facilitated by regulatory T cells in both humans and mice, suggesting a novel means of preventing chronic rejection.

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Since the advent of lung transplantation, chronic lung allograft dysfunction (CLAD) has been the number one cause of long-term mortality.¹ A subset of T cells, known as regulatory T cells (Tregs), have been shown to suppress inflammatory responses after organ transplantation. Much of what is known about the role of Tregs in suppressing alloimmune responses has come from experimental studies of kidney, heart, pancreatic islet, liver, and bone marrow transplantation. On the basis of these findings, 2 phase I clinical trials in which adoptively transferred Tregs were administered after kidney transplantation have been completed.^{2,3} Such clinical progress has yet to be made for lung transplantation, however, because the role of Tregs in this setting is just beginning to emerge.

In 2017, Abrams and colleagues⁴ performed a series of canine lung transplants mismatched for minor histocompatibility antigens without immunosuppression and infused recipient-derived, in vitro major histocompatibility antigen-primed Tregs cells that were selected on the basis of their expression of CD25, a putative surface marker of Tregs, shortly after graft reperfusion. They found that allograft survival correlated with the in vitro suppressive capacity of the infused Tregs. Shortly thereafter, Warnecke's group at Hannover Medical School,⁵ one of the most distinguished lung transplant centers in the world, reported that an increased frequency of peripheral Tregs shortly after lung transplantation in human patients is associated with protection from CLAD. To study these findings, this group recently established an elegant model of transplant atherosclerosis in humanized mice, whereby peripheral leukocytes from a human lung recipient are transferred into an immunodeficient mouse that receives a segment of a pericardiophrenic artery from the human lung donor. With this model, the Hannover researchers have shown that transfer of recipient-derived leukocyte preparations rich in Tregs abrogates atherosclerosis of the human donor arterial segments.⁶

In this issue of the *Journal*, Siemieni and colleagues⁷ from the Hannover lung transplant group extend these findings to show that leukocyte preparations taken from patients who ultimately develop CLAD results in more severe atherosclerosis of the transplanted arterial segment in the humanized mice. Perhaps more importantly, they have found that adoptive transfer of Treg-enriched leukocyte preparations is able to abrogate this process. In our own laboratory, we have observed that lymphoid follicles rich in Tregs are abundant in both human and mouse lung transplant grafts that are accepted long term.⁸ When we selectively deplete lung-resident Tregs from tolerant murine pulmonary allografts, they develop antibody-mediated rejection, associated with small airway destruction reminiscent of CLAD in human recipients.⁹ These observations have suggested that the immune tolerance conveyed by Tregs occurs locally within allografts, which is distinctly different from other solid-organ transplants, in which immune regulation occurs in peripheral lymphoid tissues. Our findings reinforce those of Siemieni and colleagues⁷ to suggest that deleterious alloimmune responses after lung transplantation are suppressed by Tregs and set the stage for tolerance. Novel strategies that enrich Tregs after human lung transplantation are called for, and we hope these recent findings will lead to clinical trials in the near future.

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