Interleukin-10 transfection and the donor lung—A still-evolving story

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Central Message

Upregulation of IL-10 expression in the donor lung is of proven early advantage. In a murine model, it now also reduces rejection and fibrosis, but benefits for our patients remain distant.

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Pulmonary transplantation is a struggle. The donor lung is vulnerable to a range of insults—aspiration, transfusion, ventilation, as well as the sequelae of brainstem death. This last insult brings inflammatory upregulation and profound effects on early graft performance and a well-characterized link to late attrition.¹

The impact on our day-to-day clinical practice is depressingly clear. With concerns over damaged organs, we use little more than 20% of potential donor lungs, and patients die on our waiting lists. Chronic graft failure, now all characterized together as chronic lung allograft dysfunction, remains the single most frustrating feature of our specialty. Median survival for the whole population of lung transplant recipients is stuck at around 5 or 6 years; it has changed little over the past 2 decades.²

There are some potential ways out of this predicament; interleukin-10 (IL-10) is a pleiotropic anti-inflammatory cytokine and might just have a key role. Raised expression is beneficial in the early, acutely injured transplant lung. In addition, stable lung transplant recipients appear to have greater levels than those developing as chronic lung allograft dysfunction.³

There is a long story of attempts to increase IL-10 expression in the lung, using a viral vector carrying the relevant IL-10 gene, going back as far as 2001.⁴ The Toronto group, leaders in this field, have shown early benefit in rat and pig lung transplant models. Their seminal *Science* paper showing the same advantage in human lungs using adenoviral transfection and ex vivo lung perfusion dates back to 2007.⁵

This latest paper⁶ concentrates on longer-term effects and uses a lentiviral, not adenoviral, vector. The authors demonstrate that giving the viral carrier into the airway, both to the donor lung at the time of transplant and later, to the lung in the recipient, leads to persistent expression and has demonstrable benefits. There was lower acute rejection at 28 days (although not at 7 days) and probably less fibrosis at the later stage. By extrapolating from some complex

lymphocyte pathways, it seems that there was less late immune activity—equivalent, the authors claim, to less chronic rejection.

This work is an important step, but just a step, to the end result of clinical application. It raises as many questions as it answers. The model, a minor-mismatched mouse transplant, although integral to the gradual development of the approach, is still a long way from clinical lung transplantation. Vector delivery is via the airway, feasible with the tiny dimensions of the mouse lung, but perhaps difficult to reproduce on a human scale. What has happened to the ex vivo lung perfusion delivery, so appealing in exposing only the donor lung, not the whole host, to any downsides of viral transfection?

This is a beautifully performed, elegant set of experiments, with some real and well-argued insights into the mechanisms at the level of the effector immune cells. But, most frustratingly, the authors, for all their background of leading clinical advances, give us no feel for where it is all going. We look toward the next step.

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