Immune Evasion by Chimeric Trachea

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The types of allogeneic organs and tissues that can be transplanted have expanded considerably in the past three decades. In addition to organs such as liver, heart, lungs, and pancreas, the list of allografts now includes islets of Langerhans and composite tissues such as hands and face. In this issue of the Journal, Delaere and colleagues report the successful transplantation of a tracheal cartilaginous allograft in which the mucosa was first replaced and revascularization established in a heterotopic location in the recipient; the graft was then implanted orthotopically and accepted without immunosuppressive therapy.1

Allografts typically require nonspecific immunosuppressive therapy to prevent rejection. Complications of such treatment include opportunistic infections, cancer, metabolic imbalances, and end-organ damage. Therefore, a major goal of research in transplantation has been to achieve immunologic tolerance, whereby the recipient’s immune system regards donor antigen as “self.” Long-term immunosuppressive therapy would thus not be required to prevent rejection. Although tolerance has been observed serendipitously in a small fraction of transplant recipients who have stopped taking their immunosuppressive medications, grafts are rejected in the vast majority of such patients. Recently, several groups have reported the use of hematopoietic cell transplantation to induce renal allograft tolerance, with early reports of success in both HLA-identical2,3 and HLA-mismatched4 donor–recipient pairs. In the study by Kawai et al., robust T-cell responses to the donor that were present before transplantation disappeared completely, whereas responses to unrelated alloantigens recovered, denoting a systemic state of tolerance.4

Several mechanisms, including deletion and anergy of donor-reactive T cells as well as active suppression, have been implicated in experimental models of tolerance.5 States of “immune ignorance” — due to either a failure of immune sensitization (the afferent arm of the immune response) or a resistance to immune-effector mechanisms (the efferent arm) — have also been reported to protect grafts from rejection.6,7 Both explanations may contribute to the “immune privilege” that has been reported to protect grafts in certain anatomical locations from immune attack.8

Delaere et al. report successful functioning of the tracheal allograft for more than a year without immunosuppressive therapy.1 This achievement represents a new approach to tracheal reconstruction in patients with large tracheal defects that cannot otherwise be surgically repaired. However, the available data suggest that the immunogenic components of the allograft were rejected, so that the only allogeneic components of the functioning graft were the all-important cartilaginous tracheal rings. This outcome reflects the immune privilege enjoyed by chondrocytes, the living cells that produce and maintain cartilage. Although isolated chondrocytes are highly immunogenic,9 chondrocytes in cartilage reside in lacunae surrounded by the collagenous extracellular matrix they produce. They are nourished by diffusion from capillaries.
outside the cartilage. The dense collagenous matrix may prevent antigen from passing into the recipient lymphoid tissues, where sensitization to allografts normally occurs, and may prevent lymphocytes and antibodies from gaining access to the chondrocytes.

In the case described by Delaere et al., recipient sensitization to donor alloantigens occurred, since the donor skin and noncartilaginous components of the tracheal graft were rejected. Assuming that the donor chondrocytes remain viable and are not eventually replaced by recipient chondrocytes, these results suggest that chondrocytes are resistant to attack by immune effectors, providing an example of immune ignorance due to physical isolation.

Although the immune privilege of chondrocytes in situ has previously been recognized and exploited to allow the transplantation of allogeneic articular-cartilage grafts, Delaere et al. have used a unique approach to generate a tracheal allograft in which immunogenic components were replaced by autologous cells. The approach was driven by the technical difficulty in achieving vascularization of a transplanted trachea, which does not have an identifiable vessel for anastomosis with a pedicle graft. These researchers wrapped the tracheal allograft in the subcutaneous fascia of the recipient’s forearm, allowing neovascularization from recipient vessels to take place over a period of 9 months before implantation into the orthotopic site.

During the initial period of heterotopic implantation, rejection was prevented with an immunosuppressive triple-drug regimen similar to that used to prevent the rejection of organ allografts. The membranous posterior wall of the donor trachea underwent avascular necrosis before neovascularization had occurred and was replaced by recipient buccal mucosa sutured to recipient fascia that was wrapped around the posterior tracheal wall. Donor respiratory epithelium persisted while the patient was receiving immunosuppressive therapy, but after withdrawal of this therapy, all donor cells disappeared and the recipient’s buccal mucosa grew over the cartilaginous trachea. By the time of orthotopic implantation, all mucosal tissue and blood vessels in the graft had been derived from the recipient. Although the authors did not directly demonstrate the persistence of donor chondrocytes, presumably the only allogeneic tissue in the orthotopically placed tracheal graft was the cartilage itself: The graft continued to function 1 year after orthotopic implantation, without immunosuppressive therapy.

To gauge the level of immunosuppression, the investigators transplanted a skin graft from the donor behind the recipient’s ear. Immunosuppressive therapy was tapered over a period of 6 weeks and discontinued shortly before the tracheal graft was explanted from the forearm and implanted in the orthotopic site. The withdrawal of immunosuppressive therapy was associated with rejection of the donor skin graft, demonstrating a vigorous immune response to donor alloantigens. The wisdom of using highly immunogenic skin grafts as “indicator” grafts might be questioned, since rejection of less immunogenic grafts has been triggered by the transplantation of highly immunogenic skin grafts. If, as is assumed, the donor chondrocytes did indeed persist in the tracheal graft in this case, the fact that rejection of the skin graft failed to trigger rejection of the donor cartilage is further evidence of the degree to which chondrocytes may be protected from the immune response. Though not evaluated in this study, donor skin-graft rejection would be expected to lead not only to T-cell sensitization but also to an alloantibody response to the donor.

This elegant approach to reconstructing an otherwise irreparable tracheal defect takes advantage of the immune privilege of the cartilaginous component while exploiting the regenerative capacity of the recipient’s mucosal tissue. The success of this approach, if sustained, could provide hope for patients whose tracheal defects cannot otherwise be surgically corrected.

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