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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 last 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, feet and faces. Delaere et al now report the successful transplantation of a tracheal cartilaginous allograft that is first remucosalized and revascularized by the recipient in a heterotopic location, then implanted orthotopically and accepted without immunosuppressive therapy (1).

Allografts typically require non-specific immunosuppressive therapy to prevent rejection. Complications of such treatment include opportunistic infections, malignancies, metabolic imbalances and end organ damage. A major goal of research in transplantation, therefore, has been the achievement of immunological tolerance, wherein the recipient's immune system regards donor antigen as "self", so that chronic immunosuppressive therapy is not required to prevent rejection. While tolerance has been observed serendipitously in a small fraction of transplant recipients who have stopped their immunosuppressive medications, the vast majority of such patients reject their grafts. Recently, several groups have reported the use of hematopoietic cell transplantation to induce renal allograft tolerance, with early reports of success in both HLA-identical (2;3) and HLA-mismatched (4) donor-recipient pairs. In the latter study, robust T cell responses to the donor that were present prior to transplant disappeared completely, while third party alloresponses 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 immunological "ignorance", due either to a failure of immune sensitization (the "afferent" arm of the immune response) or a resistance to immune effector mechanisms (the "efferent" arm), has 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).

In the case report of Delaere et al, function of a tracheal allograft for over a year without immunosuppressive therapy is documented (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 immunologic privilege enjoyed by chondrocytes, the living cells that produce and maintain cartilage. While 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 this case report, recipient sensitization to donor alloantigens occurred, since the donor skin and non-cartilagenous components of the tracheal graft were rejected. Although not directly demonstrated, if the donor chondrocytes remain viable and are not eventually replaced by the recipient, these results illustrate the resistance of chondrocytes to attack by immune effectors, providing an example of immune ignorance due to physical isolation.

While the immune privileged state of chondrocytes *in situ* has been previously recognized (10) and exploited to allow the transplantation of allogeneic articular cartilage grafts (11), Delaere et al (1) have used a unique approach to generate a tracheal allograft in which immunogenic components had been 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. Delaere et al (1) wrapped a tracheal allograft in the subcutaneous fascia of the recipient forearm, allowing neovascularization from recipient vessels to occur over a period of 5 and one half months before implantation into the orthotopic site. During the initial period of heterotopic implantation, rejection was prevented with triple immunosuppression similar to that used to prevent organ allograft rejection. 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 wrapping the posterior tracheal wall. Donor respiratory epithelium persisted while the patient was on immunosuppressive therapy, but all donor cells disappeared and recipient-derived buccal mucosa overgrew the cartilaginous trachea after immunosuppression was discontinued. All mucosal tissue and blood vessels were recipient-derived by the time of orthotopic implantation. While the authors do not directly demonstrate the persistence of donor chondrocytes, the only allogeneic tissue in the orthotopically-placed tracheal graft is presumably the cartilage itself. The graft continues to function one 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. Immunosuppression was tapered over a period of 6 weeks and discontinued shortly prior to tracheal graft explantation from the forearm and implantation in the orthotopic site. Withdrawal of immunosuppression 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 may be questioned, as there are examples in the literature in which rejection of less immunogenic

grafts is triggered by transplantation of highly immunogenic skin grafts (12). If, as is assumed, donor chondrocytes indeed persisted in the tracheal graft, the failure of skin graft rejection to trigger rejection of donor cartilage in this case report 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 trachea takes advantage of the immune privilege of the cartilaginous component while exploiting the regenerative capacity of recipient mucosal tissue. The success of this approach, if sustained, could provide hope for those patients with tracheal defects that cannot otherwise be surgically corrected.

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