Published in final edited form as:
Transplantation. 2009 May 15; 87(9 Suppl): S67–S69. doi:10.1097/TP.0b013e3181a2a6b8.

Mechanisms of transplantation tolerance in animals and humans[1]

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Abstract

Donor-specific immune tolerance would avoid the toxicities of chronic immunosuppressive therapies while preventing graft rejection. Hematopoietic cell transplantation has shown preliminary success for intentional tolerance induction in pilot clinical trials. The mechanisms of tolerance in these trials and the animal studies leading up to them are discussed.

Keywords

tolerance; thymus; chimerism; T-cells

Immune tolerance would avoid the need for chronic immunosuppressive therapy, with all of its toxicities, that is currently required to prevent graft rejection. Tolerance would also prevent chronic rejection, the major cause of late graft loss. The established mechanisms of transplantation tolerance include clonal deletion, anergy and suppression. Mixed hematopoietic chimerism provides a powerful means of achieving transplantation tolerance and, under different conditions, may involve some or all of the above mechanisms of tolerance.

Mixed allogeneic chimerism can be induced in mice receiving non-myeloablative conditioning that does not eliminate host hematopoiesis. Successful engraftment of allogeneic hematopoietic stem cells is associated with life-long co-existence of donor-and host-derived hematopoietic progeny in all lineages. In order to achieve allogeneic hematopoietic stem cell engraftment, both intrathymic and peripheral T cell-mediated alloreactivity must be overcome (1). This can be achieved in mice, for example, using the combination of T cell-depleting mAbs and thymic irradiation (2). More minimal conditioning has involved a single treatment with costimulatory blockade, involving anti-CD154 plus CTLA4Ig (3,4) or anti-CD154 alone, with (5) or without (6) CD8 T cell depletion. In all of these models, engrafted allogeneic hematopoietic stem cells provide a life-long source of progenitor cells that seed the thymus, giving rise to antigen-presenting cells (APC) which mediate clonal deletion of any newly-developing donor-reactive T cells (7,8). Host APC also populate the thymus, so intrathymic deletion of cells recognizing both the donor and the host occurs (7).

[1]This work was supported by NIH grants RO1 HL49915, PO1 HL18646, RO1 CA079989, PO1 CA111519, the Multiple Myeloma Research Foundation, and Immune Tolerance Network Protocols NKDO1 and NKDO3.

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In the regimens involving costimulatory blockade, peripheral mechanisms, including anergy and deletion (9–11), promote tolerance of the pre-existing donor-reactive T cell repertoire. While the ultimate fate of pre-existing peripheral donor-reactive CD4 and CD8 T cells is deletion in both cases (9,10), the mechanisms leading to this deletion differ for the CD4 and CD8 subsets. In the case of CD4 cells, specific deletion of donor-reactive cells is preceded by anergy, then proceeds over a period of 4–5 weeks. No role for regulatory cells can be detected (9) and anti-CD154 is required only for CD40 blockade, demonstrating no other critical function (12). CTLA4 plays an important role that is intrinsic to the CD4 cell being tolerized and does not reflect a role for a regulatory cell population (13). Peripheral donor-reactive CD8 cells are also deleted by the combination of allogeneic bone marrow transplantation (BMT) and anti-CD154, but this deletion occurs more quickly, over a period of 1–2 weeks. Importantly, this CD8 tolerance is dependent on the presence of a CD4 cell population that does not have characteristics of “natural” Treg and is only required for the first 10–14 days until the CD8 cells are deleted (10). The tolerization of CD8 cells is dependent on PD-1/PD-L1 interactions, while that of CD4 cells is independent of this interaction. Moreover, tolerance of CD8 cells uniquely depends on interactions involving recipient class II major histocompatibility complex (MHC), recipient dendritic cells and recipient B cells, none of which can be shown to be involved in CD4 cell tolerance (14). The requirements of donor APCs to achieve recipient CD4 and CD8 T cell tolerance may also differ: tolerance of CD8 cells alone depends on expression of MHC class II by the donor, and donor cells are particularly effective at inducing deletion and tolerance of recipient CD8 cells (15).

Mixed chimerism also has a role in the treatment of hematologic malignancies. Graft-versus-host disease (GVHD) is currently the major toxicity of hematopoietic cell transplantation. However, GVHD is also associated with beneficial graft-versus-leukemia/lymphoma (GVL) activity (16). In mice, non-myeloablative conditioning that includes in vivo T-cell depletion of the recipient, when followed by bone marrow transplantation that is T-depleted in vivo, leads to mixed chimerism without GVHD. Donor lymphocyte infusions (DLI) given later mediate GVH responses that convert mixed to full donor chimerism, and that mediate GVL effects, but without GVHD (17–20), which is a disease of epithelial tissues (skin, intestines, liver). Inflammation in the GVHD target tissues plays a critical role in determining whether or not activated GVH-reactive T cells remain in the lymphohematopoietic system (where they mediate GVL) or traffic to the GVHD target tissues (21). This concept was translated into clinical protocols using anti-T-cell antibody as well as thymic irradiation for recipient and donor marrow T-cell depletion, and, most recently, using ex vivo donor CD34+ cell selection from G-CSF mobilized peripheral blood. Clinical data have confirmed the feasibility of this approach in patients (22–26).

In view of our clinical and laboratory results, we performed pilot studies of combined human leukocyte antigen (HLA)-identical related donor kidney and bone marrow transplantation in patients with renal failure due to multiple myeloma. Paradoxically, although some of the patients had only transient chimerism, renal allograft tolerance was achieved (27). Even more surprisingly, some patients accepting their kidneys without immunosuppresison demonstrated sensitized anti-donor T cell responses in association with marrow rejection. Cytotoxic activity against donor renal tubular cells has not been detected, suggesting a form of “split tolerance” (28). We have recently extended combined non-myeloablative BMT and kidney transplantation to the haploidentical setting in patients who have renal failure but do not have a malignancy, using a protocol that led to transient mixed chimerism without GVHD in early studies in patients with hematologic malignancies (25). Four of 5 patients have accepted their renal allografts for periods of several years without immunosuppressive therapy (29), providing proof of principle that this approach can be used to induce tolerance across HLA barriers in humans. All of the tolerant patients developed donor-specific unresponsiveness in in vitro cell-mediated lympholysis assays and mixed lymphocyte reactions, indicating that the tolerant state

was systemic. While still under active investigation, the mechanisms of tolerance in this group of patients show some contrasting features compared to those in patients receiving HLA-identical combined kidney and bone marrow transplants (29,30). In both trials, it is unlikely that central deletion could be the major mechanism maintaining long-term tolerance as it is in some of the animal models involving durable mixed chimerism, as chimerism was only transient in many of these patients. Further studies to elucidate the tolerance mechanisms in these patients should help to promote the wider applicability of this approach.

Acknowledgements

I thank Ms. Kelly Walsh for expert assistance with the manuscript.

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