

The tolerant recipient: looking great in someone else's genes

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Commentary

Potent new immunosuppressive drugs have saved the lives of thousands of recipients of solid organ transplants (1, 2). However, these drugs need to be taken for the life of the graft, and they are associated with many severe side effects, including nephrotoxicity, susceptibility to opportunistic infections, accelerated atherosclerosis, and malignancy. As a result, the induction of donor-specific tolerance has been one of the primary goals of researchers in the field of transplantation immunology. While donor-specific transplantation tolerance has been achieved many times in rodent models, it has proven much more difficult to effectively translate these achievements into preclinical models using large animals such as swine, dogs, or nonhuman primates, much less to introduce such strategies into the clinic (3). For unknown reasons, large animals and humans are much more resistant to the induction of immunologic tolerance than are rodents and other small mammals. Consequently, it is usually necessary to test novel strategies for efficacy, as well as toxicity, in large-animal models. Unfortunately, in most such instances the approaches tested have not lived up to their initial promise. One exception to this is the use of bone-marrow transplantation to induce mixed hematopoietic chimerism. This strategy capitalizes on the seminal observation by Medawar and coworkers that immature lymphocytes are tolerized by encounter with antigen, rather than activated by it (4). In its [...]

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Potent new immunosuppressive drugs have saved the lives of thousands of recipients of solid organ transplants (1, 2). However, these drugs need to be taken for the life of the graft, and they are associated with many severe side effects, including nephrotoxicity, susceptibility to opportunistic infections, accelerated atherosclerosis, and malignancy. As a result, the induction of donor-specific tolerance has been one of the primary goals of researchers in the field of transplantation immunology.

While donor-specific transplantation tolerance has been achieved many times in rodent models, it has proven much more difficult to effectively translate these achievements into preclinical models using large animals such as swine, dogs, or nonhuman primates, much less to introduce such strategies into the clinic (3). For unknown reasons, large animals and humans are much more resistant to the induction of immunologic tolerance than are rodents and other small mammals. Consequently, it is usually necessary to test novel strategies for efficacy, as well as toxicity, in large-animal models. Unfortunately, in most such instances the approaches tested have not lived up to their initial promise.

One exception to this is the use of bone-marrow transplantation to induce mixed hematopoietic chimerism. This strategy capitalizes on the seminal observation by Medawar and coworkers that immature lymphocytes are tolerized by encounter with antigen, rather than activated by it (4). In its original incarnation, experimental mixed hematopoietic chimerism was created by complete lymphoid/myeloid ablation of the recipient, followed by reconstitution with a mixture of allogeneic donor and self bone marrow (5, 6). This induces donor-specific tolerance as the preparative immune ablation abolishes the response of pre-existing T and B cells, while the pres-

ence of donor antigens (on the donor marrow) during immune reconstitution induces tolerance in newly maturing T and B cells. The use of T cell-depleted bone marrow prevents graft-versus-host disease, which would otherwise occur from the allogeneic lymphocytes reacting to recipient antigens.

This very effective strategy is limited by the high level of toxicity of the preparative regimen, and for many years, most clinicians doubted the practicality of this approach. However, recent innovations, such as the use of high-dose bone marrow, and adjunctive agents such as pharmacologic immunosuppression or antibodies that block T-cell costimulatory pathways, may greatly reduce the accompanying toxicity, and they suggest that it may hold promise for clinical use (7, 8). Indeed, mixed hematopoietic chimerism through bone-marrow transplantation has been used to treat one patient with multiple myeloma and end-stage renal failure (9), although in this situation donor and recipient were MHC-matched and disparate only for minor histocompatibility antigens. Nevertheless, this individual is now 18 months post-renal transplantation and

chimeric state of the recipient) has been shown to correlate with tolerance (11). However, other observations suggest that the mechanisms of tolerance may be more complex. First, in some models, tolerance can persist even after chimerism is lost (12). Second, it may not be necessary to tolerize the recipient to all transplantation antigens prior to graft implantation. For example, while the direct injection of donor cells into the thymus of mice can be used to induce transplantation tolerance (13), it may not be necessary to express all donor antigens in the thymus of the recipient. In fact, intact MHC antigens may not be required at all, as thymic injection of immunogenic peptides derived from MHC class II molecules may be effective at inducing transplantation tolerance (14). How is tolerance induced under these circumstances to antigens not encountered at the time of the tolerizing maneuver? Currently, it is believed that tolerance induced to some antigens expressed by the allograft can be extended to other antigens expressed on the same graft cells. This phenomenon, termed "linked suppression," is exerted by regulatory T cells, acting

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has normal renal function despite having no immunosuppression for over a year — an impressive achievement.

The mechanism of tolerance induction by this approach is believed to involve deletion of donor-reactive T cells during their maturation in the thymus (10). Indeed, in many studies, the presence of donor cells in the thymus (presumably occurring as part of the

through soluble mediators such as IL-10 and TGF- β , and perhaps through contact-dependent mechanisms as well (15).

In this issue of the *JCI*, LeGuern and colleagues make several important observations that consolidate and extend these previous observations (16). Using a well-established model of renal transplantation in partially inbred miniature swine, they show that

infusion of autologous bone-marrow cells (following preparative irradiation) transfected with a single donor-type MHC class II antigen, can be combined with a short (12-day) course of the immunosuppressive drug cyclosporine to induce long-term graft survival, and even true donor-specific tolerance. In doing so, they provide proof of principle of the use of gene delivery into bone marrow cells to induce transplantation tolerance in large animals, and they further demonstrate that it is not necessary to deliver all the donor alloantigens. While previous studies have shown that the short course of cyclosporine used can prevent rejection of MHC class II matched grafts, it does not prevent rejection of class II mismatched grafts, such as those used by LeGuern and colleagues (17). Since miniature-swine tissues, like human tissues, express at least two distinct MHC class II antigens (DR and DQ) that can be the target of rejection, this study (16) shows that delivery of only one of the two antigens on the bone marrow cells is needed to prevent rejection. Presumably, linked suppression operates in these circumstances, although that still needs further investigation. It should also be noted that, although only a limited number of animals were studied, DQ was more effective as a transgene than DR.

How then can these findings be applied to the clinic? First, they suggest another means to reduce the toxicity of bone-marrow transplantation. The engraftment of autologous cells requires less recipient conditioning and is not associated with a risk of graft-versus-

host disease. Second, they suggest that it may not be necessary to tolerize to all antigens. Third, they show that conventional immunosuppressive drugs, such as cyclosporine, may be part of a tolerizing protocol, an important point given recent observations indicating that cyclosporine may interfere with other strategies of tolerance induction (18). One item that requires further investigation is the timing between the bone-marrow transplantation procedure and the transplant. In the study by the LeGuern group (16), the renal transplant was not performed for at least 150 days after the bone-marrow transplant. Unless the two procedures can be done virtually simultaneously, this would limit its usage to living donor transplantation (and perhaps xenotransplantation). Of course, in order to apply this protocol to living donor transplantation other issues would have to be overcome, most prominently the need to have access to recipient cells transfected with donor genes. Nevertheless, if such a strategy were successful in humans, the benefit would likely be so great that the impetus for living donation would be even stronger for patients with end-stage kidney, liver, lung, and pancreatic disease.

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