

# Immunology of Transplantation

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**I**N THIS article we review some old and recent work on a model of experimental rat kidney transplantation that may explain why early acute rejection seems to be a self-limited process and differs from chronic rejection.

## EXPERIMENTAL MODEL

Most MHC-incompatible, orthotopic renal allografts are promptly rejected in rats if no immunosuppressive therapy is given to the recipient. Nevertheless, in several donor/recipient combinations, long-term survival of MHC-incompatible grafts can be achieved if the immunosuppression is withdrawn 2 weeks after transplantation. We have investigated one such model that consists of AS strain recipients (*RT-1<sup>c</sup>*) transplanted with kidneys from AUG (*RT-1<sup>c</sup>*) or (AS × AUG)<sub>F<sub>1</sub></sub> donors. Long-term survival of these allografts can be obtained by treating the recipient rat for 10 days after transplantation with cyclosporine (CyA) and withdrawing the drug thereafter.<sup>1</sup> During the period of long-term survival, two mechanisms ensure that the graft is not rejected: (a) loss from the graft of highly immunogenic, MHC-incompatible dendritic cells (DC); and (b) the presence of suppressor T cells.<sup>2</sup>

## IMMUNOGENICITY OF A GRAFT AND THE ROLE OF DC

Normal AUG or <sub>F<sub>1</sub></sub> kidneys survive for less than 11 days if transplanted into untreated, normal AS recipients. However, if an (AS × AUG)<sub>F<sub>1</sub></sub> kidney transplanted into an AS recipient is protected from acute rejection by enhancement protocols or 10-day treatment with CyA, and is then retransplanted 1 to 3 months later into another untreated AS recipient, the kidney is not rejected.<sup>3</sup> This is due to the loss of allogeneic DC from the graft.<sup>4</sup>

There is some variation in the extent to which immunogenicity is lost, depending on the donor/recipient combination.<sup>5</sup> If AUG donors are used, long-term survival in the primary AS recipient is observed following the standard 10-day therapy with CyA, but if the kidney is then retransplanted into another AS recipient, slow rejection occurs, with a median survival of the grafts of 22 days. These results led us to postulate that sensitization to MHC-incompatible grafts occurs by two pathways<sup>4</sup>: (a) direct pathway—activation of a recipient's T cells by donor (ie, allogeneic) DC harboured by the graft. In vitro DC are unique in their capacity to trigger the proliferation of T cells in primary mixed lymphocyte cultures<sup>6</sup>; and (b) indirect pathway—this is the route by which all non-DC cells of an allograft trigger a response, and is identical to the route taken by conventional antigen, ie, cell fragments are phagocytosed, processed into small peptide fragments

and presented by the recipient's own antigen-presenting cells. This pathway is of course self-MHC restricted.

Since the hypothesis was first postulated by Lechler and Batchelor in 1982, several examples of self-MHC restricted T cells, specific for peptides derived from allogeneic MHC polymorphisms, have been reported in the literature. It is clear that indirect pathway T cells can be induced but the role of these cells in allograft rejection remains to be clarified.

We have grown rat alloreactive T cells with the properties expected of cells sensitized by the direct pathway. The cells are of AS strain origin and were sensitized in vitro with AUG strain antigen-presenting cell suspensions enriched for dendritic cells. The properties of one cell line, L10, and one putative clone, L12.4, have been studied in vitro and in vivo.<sup>7</sup>

Both L10 and L12.4 are specific for one of the *RT-1<sup>c</sup>* class II polymorphisms. The line has minimal cytotoxicity, and the clone has none, but both proliferate specifically when cocultured with AUG antigen-presenting cells, and secrete IL-2. The specific proliferative response is blocked by monoclonal antibody specific for AUG class II polymorphisms, but not by monoclonal antibody specific for AUG class I. In different experiments, 86% to 95% of the cells in the T-cell line expressed CD4, and >97% in the case of L12.4.

We have tested the effector function of L10 and L12.4 on kidney allograft rejection. Recipients were AS rats irradiated 24 hours earlier to minimize responses from their own immune systems. They were allografted with an AUG kidney, and injected with T cells within 4 hours of completion of the transplant. Rats of a control group received no T cells; other rats received T cells purified from normal, nonsensitized AS males. Rats in the experimental groups were injected with cells of the AS anti-AUG T-cell line, or the presumptive T-cell clone, L12.4. The recipient's own right kidneys were removed 4 or 7 days later. Graft rejection was assessed from recipient survival and serial estimations of blood urea nitrogen (BUN).

In our experiments, two types of AUG kidneys were transplanted, either those derived from normal AUG male donors, or AUG kidneys depleted of native passenger

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leukocytes by the "parking" method. The results of these experiments were as follows:

1. Irradiated AS rats, not given any T cells, accept the kidneys from normal AUG donors for more than 50 days.
2. The rats transplanted with kidneys from normal AUG donors, but which received 55 to 86 million normal AS T cells suffered early acute or subacute graft rejection in three of five recipients; two rats in the group lived beyond 50 days with normal urea levels.
3. All the rats transplanted with normal AUG kidneys and which also received 10 million of the L10 cell line or L12.4 clone rejected their graft acutely.
4. In contrast, none of the rats transplanted with passenger-cell-depleted kidneys and infused with 10 million of the L10 cell line rejected their grafts, and five of seven rats given 7 to 9 million L12.4 cells survived indefinitely.

The results show that the effector function of T cells sensitized by the direct pathway depends upon the number of native dendritic cells present in the target kidney graft. As the native dendritic cell population is replaced by host-derived, and thus nonimmunogenic, dendritic cells, so the alloreactive T cells sensitized by the direct pathway become unable to damage the graft.

One possible explanation for the impotence of direct pathway-sensitized T cells in the dendritic cell-depleted AUG grafts could be a lack of expression of target AUG MHC class II. In confirmation of experience of others, we also observed specific expression of RT1.B products on

tubular epithelial cells of passenger cell-depleted AUG kidney grafts. What happens to the direct pathway-sensitized T cells that accumulate in the kidney allograft? Our most recent data show that AUG renal tubular epithelial cell cultures do not activate the clone L12.4, but render it nonresponsive.

#### CONCLUSIONS

Acute early rejection of an allogeneic kidney graft is mediated by a population of T cells sensitized by the direct pathway; as the graft loses its content of incompatible dendritic passenger cells, the direct pathway-sensitized T cells lose their capacity to cause graft rejection. Instead, these cells appear to be made unresponsive.

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