

# Role of the Thymus in Transplantation Tolerance in Miniature Swine. I. Requirement of the Thymus for Rapid and Stable Induction of Tolerance to Class I-mismatched Renal Allografts

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## Summary

The almost uniform failure in transplant patients of tolerance-inducing regimens that have been found to be effective in rodents, has made it necessary to examine large animal models before testing of new approaches clinically. Miniature swine have been shown to share many relevant immunologic parameters with humans, and because of their reproducible genetics, have proved extremely useful in providing such a large animal model. We have previously shown that indefinite systemic tolerance to renal allografts in miniature swine is induced in 100% of cases across a two-haplotype class I plus minor histocompatibility antigen disparity by a 12-d course of Cyclosporine A (CyA), in contrast to irreversible rejection observed uniformly without CyA treatment. In the present study, we have examined the role of the thymus during the induction of tolerance by performing a complete thymectomy 21 d before renal transplantation. This analysis demonstrated a striking difference between thymectomized and nonthymectomized animals. Thymectomized swine developed acute cellular rejection characterized by a T cell (CD25<sup>+</sup>) infiltrate, tubulitis, endothelialitis and glomerulitis, and anti-donor CTL reactivity in vitro. Nonthymectomized and sham thymectomized animals had a mild T cell infiltrate with few CD25<sup>+</sup> cells and no anti-donor CTL response in vitro. These results indicate that the thymus is required for rapid and stable induction of tolerance.

Many methods by which transplantation tolerance can be induced in rodents have failed when applied to large animals or to patients (1–4), making testing in large animals a necessary step before applying new techniques clinically. Miniature swine provide the only large animal model in which one can reproducibly study the effects of selective matching within the MHC on parameters of transplantation (5–7). We have therefore used MHC inbred and recombinant lines of miniature swine extensively for preclinical studies of transplantation tolerance (8–12). Previous studies from this laboratory have demonstrated that tolerance to renal allografts in miniature swine occurs spontaneously in about one-third of animals selectively matched for class II antigens and mismatched for a single class I MHC locus plus minor antigens (8, 13). The induction of spontaneous long-term tolerance was associated with a transient antidonor class I humoral response which has been shown to be almost entirely of the IgM class. Rejection animals developed antidonor class I IgG and promptly rejected their allografts. The failure to switch from IgM to

IgG in spontaneous acceptors, suggested that the pathway to tolerance involved a deficiency of T cell help. Studies in miniature swine mismatched for two class I haplotypes were consistent with this hypothesis. Such animals reject renal allografts in 100% of cases without immunosuppression, but when T cell help was limited by the administration of a 12-d course of Cyclosporine A (CyA), 100% of animals developed long-term tolerance (9). Subsequent studies demonstrated that transplants of second renal allografts, MHC-matched to the original donors, were accepted without further immunosuppression if grafted at the time of the transplant nephrectomy (14). These results indicate that long-term graft acceptance is associated with the induction of systemic tolerance.

The role of the thymus has been shown to be critical for systemic central tolerance to self antigens in which poten-

\*Abbreviations used in this paper: CD, cluster of differentiation; CML, cell-mediated lysis; CyA, Cyclosporine A; GIC, graft-infiltrating cell; PAS, periodic acid-Schiff; POD, postoperative day; PSL, percent specific lysis; SLA, swine lymphocyte antigen.

# Role Of Thymus In Tolerance Induction

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