

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⁺) 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⁺ 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

**Bela Bodey, Stuart E. Siegel, Hans E.
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Role Of Thymus In Tolerance Induction:

Immunological Aspects of Neoplasia — The Role of the Thymus Bela Bodey, Stuart E. Siegel, Hans E.

Kaiser, 2006-04-11 Our work began where the greatest classical morphologists left off their best work was the start of ours As our work progressed the rigidity of basic previous embryological principles was broken down as scientific knowledge advanced At the same time the molecular biological characterization of the cell surface receptor systems progressed enormously with the invention of NUMEROUS monoclonal antibodies Thus thymology became once again very important because the thymus is the first and central organ of the human immunological system Then the question of immuno neuroendocrine regulation arose and has only been partially answered Our book seeks to explore what has not been explored The topic of thymic epithelial cells is a unique one and has never been explored in any previous book as it is explored in this one Only a handful of great thymologists remain in the world today especially after the great loss the medical community suffered with the passing of Dr Good the list includes but is not limited to Dr Ritter and Dr Kendall in England Dr Savino in Brazil Dr Dardenne in France Dr von Gaudecker in Germany a few others in Belgium and Holland and it is our hope that Dr Bodey is among them Nonetheless a book on the thymus has not been written in the last five years and a book such as this one has never been This book is based on a 30 year period of research and includes references from a broad range of sources spanning the globe and all sources even those that were the beginning of thymic research The book thus is uniquely well rounded more so that previous works *Specificity and Function of Clonally Developing T Cells* Bernhard Fleischer, Jörg

Reimann, Hermann Wagner, 2012-12-06 **Thymus Function and Aging: A Focus on Thymic Epithelial Cells** Mariastefania Antica, Valentin Shichkin, Isabella Screpanti, Maria Pia Felli, 2022-09-23 *Thymic Development and Selection of T Lymphocytes* Thomas Boehm, Yousuke Takahama, 2013-11-06 The thymus is an evolutionarily ancient primary lymphoid organ common to all vertebrates in which T cell development takes place Failing thymus function is associated with immunodeficiency and or autoimmunity In this volume leading experts provide a comprehensive overview of recent advances in thymopoiesis research The chapters cover the development of the thymic epithelial microenvironment address the formation of a diverse and self tolerant repertoire of T cell receptors as the basis for cellular immunity discuss the mechanisms by which progenitor cells colonize the thymus and detail the molecular basis for T lineage decisions The reviews illustrate the important role of the multifaceted process of thymopoiesis for adaptive immunity **Thymic Epithelial Cells:**

New Insights into the Essential Driving Force of T-Cell Differentiation Marita Bosticardo, Izumi Ohigashi, Jennifer Elizabeth Cowan, Nuno L. Alves, 2021-09-30 **Mechanisms of Lymphocyte Activation and Immune Regulation III** Sudhir Gupta, William E. Paul, Max D. Cooper, Ellen V. Rothenberg, 2012-12-06 Recent advances in the understanding of the major events that shape the immune recognition system have been remarkable The analysis of immunoglobulin Ig gene organization and Ig repertoire diversification in lower vertebrates has provided new insight into this process in mammals

Similarly the understanding of the early development of lymphocytes and of the acquisition of immunological tolerance has been aided by elegant studies in quail chicken chimeras using the power of the distinctive markers of the constitutive cells of these birds Great strides have been made in understanding the role played by major histocompatibility complex MHC molecules in antigen presentation and in repertoire selection within the thymus The use of transgenic mice expressing specific T cell receptor TCR genes has elucidated the process of both positive and negative selection In parallel there has been considerable progress in our understanding of tolerance based in part on the use of markers for the V β genes of T cell receptors and in part on the analysis of the behavior of long term T cell lines This has led to the realization that both clonal deletion and clonal anergy may play critical roles in the maintenance of unresponsiveness to self antigen Molecular analysis of the requirements for expression of membrane immunoglobulin molecules has revealed the existence of a complex that appears to be of critical importance in mediating signalling through Ig receptors In addition major insights have been obtained into the regulation of expression of genes of immunologic interest

Fundamental Immunology William E. Paul, 2012-12-03 This standard setting textbook has defined the field of immunology since 1984 and is now in its Seventh Edition continuing to deliver the detailed authoritative and timely coverage readers expect This comprehensive up to date text is ideal for graduate students post doctoral fellows basic and clinical immunologists microbiologists and infectious disease physicians and any physician treating diseases in which immunologic mechanisms play a role Now full color throughout the book's fully revised and updated content reflects the latest advances in the field Current insights enhance readers understanding of immune system function The text's unique approach bridges the gap between basic immunology and the disease process Extensive coverage of molecular biology explains the molecular dynamics underlying immune disorders and their treatment Abundant illustrations and tables deliver essential information at a glance Plus a convenient companion website features the fully searchable text and image bank This is the tablet version of Fundamental Immunology which does not include access to the supplemental content mentioned in the text

Thymus Transcriptome and Cell Biology Geraldo A. Passos, Daniella Arêas Mendes-da-Cruz, Wilson Savino, 2025-03-11 This volume focuses on a challenging field in biomedicine the genetic control of central immune tolerance The thymus gland is a lymphoid organ implicated in T cells maturation differentiation and selection Its function is associated with the control of immune homeostasis in the body establishing central immune tolerance and preventing the onset of autoimmune diseases This book focuses on thymus development their cellular components and their respective function and the peculiar gene expression profiling transcriptome found in the medullary thymic epithelial cells mTECs that are implicated in the self representation in the thymus and the Autoimmune regulator Aire gene Chapters also explore the mutations in the Aire gene manifestation of autoimmune diseases and the role of cell cell interactions within the thymus with implications in the negative selection elimination of nascent autoreactive T cells in preventing aggressive autoimmunity This new edition includes two new

chapters devoted to the genome editing of the Aire gene through Crispr Cas9 system and thymic involution All chapters have been updated to reflect the latest research in the field *New Insights into Thymic Functions during Stress, Aging, and in Disease Settings* Nicolai Stanislas van Oers,Dong-Ming Su,Ann Chidgey,Jarrold Dudakov,2020-12-23 This eBook is a collection of articles from a Frontiers Research Topic Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series they are collections of at least ten articles all centered on a particular subject With their unique mix of varied contributions from Original Research to Review Articles Frontiers Research Topics unify the most influential researchers the latest key findings and historical advances in a hot research area Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office frontiersin.org/about/contact

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