

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

N Colangelo



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

The Role of Aire, microRNAs and Cell-Cell Interactions on Thymic Architecture and Induction of Tolerance Geraldo Aleixo

Passos, Daniella Areas Mendes-da-Cruz, Ernna Hérída Oliveira, 2016-02-03 The focus of this eBook is to bring new insights into central immune tolerance To fulfill that much has been discussed about the master in the regulation of tolerance the autoimmune regulator Aire gene the main thymus cell type that expresses this gene the medullary thymic epithelial cells mTECs It includes one Editorial and 12 other excellent contributions in the format of mini reviews or original research

papers covering one or more of these aspects promiscuous gene expression PGE epigenetics miRNAs association of the Aire gene and miRNAs thymocyte TEC interaction coxsackievirus and type 1 diabetes exosomes in the thymus thymic crosstalk thymic B cells T cell development chemokines and migration of T cells miRNAs and the thymic atrophy cell cell interactions and thymus ontogeny Authors raised hypothesis discuss concepts and show open questions The remaining important issues to resolve questions within the central tolerance research are briefly discussed below The first mini review is authored by Olga Ucar and Kristin Rattay They focused on the posttranscriptional control of PGE by miRNAs as well as epigenetic control involving DNA methylation histone modifications and topology of chromosomes These processes represent additional factors to be explored and that might regulate the expression of Aire independent tissue restricted antigens TRAs which are implicated in the central tolerance Are the Eph ephrins important for thymocyte TEC interaction This issue was reviewed by Javier Garcia Ceca and cols The maturation of thymocytes is depending on their interaction with TECs within the thymus Authors argue the importance of Ephs and ephrins on the intrathymic maturation of both thymic epithelial microenvironment and thymocyte maturation and on the recruitment of lymphoid progenitors into the thymus Another stimulating mini review is authored by H l ne Michaux and cols in which they discuss the hypothesis that infection by coxsackievirus B4 CV B4 could be associated with etiopathogenesis of type 1 diabetes mellitus T1D Authors consider that besides their tropism to the pancreatic beta cells CV B4 could also involve the thymus Once within this organ the virus might somehow perturbs central tolerance to the insulin family triggering thus autoimmune T1D Our group contributed with a mini review focusing on cell cell interactions within the thymus involving TECs and thymocytes and the role of the Aire gene on the induction of central tolerance throughout the modulation of TRA expression in mTECs In addition we discuss the recent evidence that Aire also regulate the expression of miRNAs in these cells On its turn the Aire dependent miRNAs might exert control over TRAs We raise issues that besides the transcriptional control exerted by Aire PGE could also be being controlled through posttranscriptional mechanism involving miRNAs A very pertinent question raised by Gabriel Skogberg and cols is on the role of exosomes on TRA presentation by TECs to thymocytes and its implication in the thymocyte selection Exosomes may be liberated by TECs to the extracellular milieu and transport TRAs as well as MHC molecules establishing intercellular communication to enhance antigen presentation to developing thymocytes Authors discuss how intercellular communication via exosomes within the thymus could have consequences on TRA presentation and finally on central tolerance The thymic crosstalk i e the reciprocal control by the close contact between TECs and thymocytes which influences the differentiation of both types of cells was elegantly reviewed by No lla Lopes and cols Authors discuss the role of dendritic cells DCs subsets in the process of deletion of autoreactive T cells and the generation of natural Tregs and raise questions how hematopoietic cells may control the organization of the thymic medulla Thymus is an organ composed of different cell types including TECs DCs macrophages among other cell types and of course thymocytes Recently researchers have identified an unexpected cell

type formed by B cells which may be originated from intrathymic B lymphopoiesis or immigration from the periphery Tomoyoshi Yamano and cols contributed with a mini review discussing the role of thymic B cells expressing MHC II CD80 and Aire in the crosstalk with CD4 single positive cells Authors raise questions how these cells might play a role as antigen presenting cells in an unpredicted way within the thymus The regulation of T cell development is apparently well resolved however several unsolved questions remain This important aspect is represented in this Research Topic through the mini review by Iris Caramalho and cols Authors show new questions on the beginning of Treg lineage commitment their spatial localization within the human thymus and their molecular components Cell migration within the thymus is crucial for the central tolerance Developing thymocytes migrate throughout the thymus being exposed initially to the cortex and then to the thymic medulla where they respectively undergo positive and negative selection Chemokines represent key regulators for thymocyte migration Zicheng Hu and cols argue the role of chemokines in the thymic cell migration and induction of central tolerance Thymic atrophy during senescence is widely recognized however poorly understood In addition to the atrophy due to senescence thymus involutes in response to a variety of stimuli including microbial infections The mouse model of Trypanosoma cruzi infection corresponds to an adequate mouse model to access this question Leandra Linhares Lacerda and cols show results on the role of miRNAs on regulation of chemotaxis which contribute to a better understanding while incites new issues of thymic involution Cellularity of mTECs is pivotal for cell cell interactions within the thymus which is required for central tolerance Taishin Akiyama and cols argue the role of cytokines on cellularity of mTECs focusing into the molecular basis of cell cell interactions opening perspective on the use of mathematical models for understanding these processes Thymus morphogenesis is a central point with many open questions The mini review authored by Arnon Dias Jurberg and cols addresses the role of the large superfamily of TGF beta bone morphogenetic protein ligands in the thymus morphogenesis and in T cell differentiation This eBook provides an international and updated insight into the latest developments and open questions on the cellular and molecular bases of central tolerance induction

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 J 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 **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 *Paul's Fundamental Immunology* Martin Flajnik,2022-07-19

Selected as a Doody's Core Title for 2022 Defining the field of immunology for 40 years Paul's Fundamental Immunology continues to provide detailed authoritative up to date information that uniquely bridges the gap between basic immunology and the disease process The fully revised 8th edition maintains the excellence established by Dr William E Paul who passed away in 2015 and is now under new editorial leadership of Drs Martin F Flajnik Nevil J Singh and Steven M Holland It's an ideal reference and gold standard text 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 **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 **Tolerogenic**

Antigen-Presenting Cells - Modulating Unwanted Immune Response at Their Core John Isaacs,Catharien

Hilkens,2019-12-27 *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 Therapeutic Immunosuppression A.W.

Thomson,2012-12-06 Therapeutic immunosuppression has very broad applications in clinical medicine ranging from prevention and treatment of organ and bone marrow transplant rejection management of various autoimmune disorders e g rheumatoid arthritis skin disease and asthma Whereas traditionally only a small repertoire of immunosuppressive agents was available for clinical use recent discoveries have significantly increased the number of approved agents resulting in numerous trials to further evaluate their potential In addition products of the biotechnology industry monoclonal antibodies cytokines cytokine antagonists and other products of genetic engineering that target key molecular pathways in disease pathogenesis have either already made or are on the verge of making an important impact on treatment There is also considerable interest in the potential of cell based therapies particularly hematopoietic stem and dendritic cell therapy of allo and autoimmunity Important recent advances in the immunotherapy of allergic diseases are also covered in this book Gene therapy offers considerable promise for suppressing pathogenic processes in either transplantation or autoimmune disorders The possibility of combining these important new advances to maximize benefit to the patient and to minimize possible untoward effects which are also given extensive coverage in this book is one of the most exciting challenges of contemporary medicine This volume is intended both for practising physicians and surgeons and for biomedical scientists at the graduate postdoctoral levels and is designed to provide the theory behind these various approaches to immunosuppression and to provide state of the art reviews of current developments in each area Each chapter is contributed by one or more experts in the field There was a need to bring this information together in a single volume as much of the key recent developments have been dispersed throughout the biomedical literature largely in specialized journals Since as in the past important developments in immunosuppressive therapy in one branch of medicine i e transplantation are likely to benefit another e g dermatology rheumatology gastroenterology cross disciplinary coverage of the mechanistic basis of the various therapeutic strategies in a single volume is likely to convey the potential of advances in therapy in the most coherent manner possible

New Insights into Thymic Functions during Stress, Aging, and in Disease Settings Nicolai Stanislas van Oers,Dong-Ming Su,Ann Chidgey,Jarrod 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

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Advances in Immunology, 1987-11-10 Advances in Immunology

The Physiology of Immunity James A. Marsh, Marion D. Kendall, 1996-07-24 The study of neuroendocrine immune interactions has become a highly visible and fast growing segment of mainstream immunology This book provides an overview of the immune system and in depth coverage of the many different areas that make up neuroendocrine immune research The main emphasis is on the physiology of the processes involved stressing an integrated approach to immunology The text is organized in seven sections beginning with an introduction to the immune system Section II outlines how the central nervous system CNS communicates with central and peripheral lymphoid organs Section III provides information on factors from the immune system that act as messengers to the CNS The metabolic regulation of growth and development is discussed in Section IV Section V examines the interactions occurring between the reproductive and immune systems The effects of other physiologic stressors on immunity are reviewed in Section VI Section VII considers cyclic and periodic influences on the immune system Finally there is a consideration of a new unifying theory for immunology Students researchers clinicians and veterinary scientists can discover new areas of interest in specific diseases and immune interactions in this novel presentation

Mechanisms of Immune Regulation R. D. Granstein, 1994 Immunologists molecular and cell biologists oncologists pharmacologists and those working in the pharmaceutical field will find this book of particular interest

Signaling Mechanisms Regulating T Cell Diversity and Function Jonathan Soboloff, Dietmar J. Kappes, 2017-03-27 T cells play a vital role mediating adaptive immunity a specific acquired resistance to an infectious agent produced by the introduction of an antigen There are a variety of T cell types with different functions They are called T cells because they are derived from the thymus gland This volume discusses how T cells are regulated through the operation of signaling mechanisms Topics covered include positive and negative selection early events in T cell receptor engagement and various T cell subsets

Thymic Stromal Alterations and Genetic Disorders of Immune System Claudio Pignata, Ana E. Sousa, 2015-12-07 The pathogenic mechanisms underlying primary T cell disorders are mainly related to molecular alterations of genes whose expression is intrinsic to hematopoietic cells However since the differentiation process requires a crosstalk among thymocytes and the thymic microenvironment molecular alterations of genes involved in the differentiation and functionality of the stromal component of the thymus may lead to a severe T cell defect or failure of central tolerance as well The first example of severe combined immunodeficiency SCID not related to an intrinsic alteration of the hematopoietic cell but rather of the thymic epithelial component is the Nude SCID phenotype inherited as an autosomal recessive disorder whose hallmarks are the T cell defect and the absence of the thymus The clinical and immunological phenotype is the human equivalent of the murine Nude SCID syndrome which represents the first spontaneous SCID identified in nude mice in 1966 For over 3 decades studies of immune system in these mice enormously contributed to the overall knowledge of cell mediated

immunity in the assumption that the athymia of these mice was solely responsible for the T cell immunological defect This syndrome is due to mutations of the transcription factor FOXP1 belonging to the forkhead box gene family which is mainly expressed in the thymus and skin epithelial cells where it plays a critical role in differentiation and survival An alteration of the thymic structure is also a feature of the DiGeorge syndrome DGS which has been long considered the human counterpart of the nude mice phenotype This syndrome is frequently associated to a deletion of the 22q11 region which contains approximately 30 genes including the TBX1 gene which is responsible for most of the clinical features of DGS in humans and mice In this syndrome common manifestations are cardiac malformations speech delay hypoparathyroidism and immunodeficiency even though the immunological hallmarks of the T cell defect in DiGeorge syndrome are profoundly different from those reported in human Nude SCID The divergence of the phenotype among these 2 entities raised the possibility that the FOXP1 transcription factor represents the real key stromal molecule implicated in directing the hematopoietic stem cell toward a proper T cell fate Thymic stromal component of the primary lymphoid organ is also required to negatively select the autoreactive clones a process driven by the expression of tissue specific antigens TSA by medullary thymic epithelial cells mTECs The expression of genes encoding TSA antigens is mediated by autoimmune regulator AIRE gene encoding a transcription factor expressed in mTECs Molecular alterations of this gene are associated to autoimmune polyendocrinopathy candidiasis ectodermal dystrophy APECED a rare autosomal disorder which may be considered the prototype of an autoimmune disease due to the failure of central tolerance homeostasis All these experiments of nature led to unravel novel pathogenic mechanisms underlying inherited disorders of immune system and of note to clarify the pivotal role of epithelial cells in the maturation and education process of T cell precursors **Avian Cellular**

Immunology JagdevM. Sharma,2018-01-29 Knowledge regarding avian cellular immunity has expanded rapidly within the last few years and new information continues to accumulate It is now a well established fact that cell mediated immunity plays a major role in the defense against neoplastic and non neoplastic diseases in chickens The principle objective of Avian Cellular Immunology is to compile the latest information available on various aspects of avian cellular immunity The book contains chapters written by leading experts in the field and covers topics including cell surface markers T cell immunity natural immune functions the role of macrophages in cellular immune functions cellular immune suppression and tolerance cellular immune systems in avian species other than chickens the role of cellular immunity in neoplastic and non neoplastic viral diseases cell mediated immune mechanisms in bacterial and parasitic infections and autoimmune disorders

Cumulated Index Medicus ,1996

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