Rev. Inst. Med. trop. S. Paulo
45(6):343-344, November-December, 2003

BOOK REVIEW*

ANNUAL REVIEW OF IMMUNOLOGY, vol. 21, 2003; edited by William E. PAUL, C. Garrison FATHMAN & Laurie H. GLIMCHER. Palo Alto, Annual Reviews Inc., 2003. 955 p. ilust. ISBN: 0-8243-3021-8. ISSN 0732-0582.

The volume 21 of the **Annual Review of Immunology** offers a broad updated information on selected topics in Basic Immunology for students and researchers.

In 2003, the important area of **Immunology of Infectious Diseases and Vaccines** is covered in three chapters. CD8 T cells respond to viral infections but also participate in defense against bacterial and protozoan infections. Some viruses, such as influenza virus, cause acute infections and are eliminated. In contrast, herpes viruses cause latent infections and remain with the host for life. CD8 T cells play distinct roles in these two circumstances. Bacterial and protozoan pathogens also cause acute and chronic infections, with similar challenges for CD8 T cell-mediated immune defense. In the first chapter in this volume of Annual Review of Immunology, P. WONG & E.G. PAMER summarize recent knowledge of CD8T cell immunity to pathogens, as learned from the major mouse models of infectious disease. Viral, bacterial, and protozoan pathogens that have been used in mouse models to characterize CD8T cell responses are reviewed. Finally, new concepts of CD8T cell-mediated anti-microbial immunity that have emerged from these studies are discussed. Viruses and other invading pathogens have exerted unrelenting selection pressure upon the mammalian host, necessitating the development of a complex and adaptable immune system. Large DNA viruses such as herpesviruses and poxviruses provide some of the most extensive inventories of gene products that serve to defend these viruses against the assault executed by the host immune response. In an excellent review, B.T. SEET *et al*. highlight the many strategies that poxviruses utilize to modulate key components of the innate and acquired immune responses. Immunological memory is the basis for protective vaccines. Successful vaccines have been those that can imitate the generation of neutralizing or opsonizing antibodies responses that seem to be the only limiting factor against acutely cytopathic agents. In contrast, cell-mediated immunity against infections that persist in the host is much more difficult to imitate. In a didactic and informative review, R.M. ZINKERNAGEL summarizes the general parameters of cell- and antibody-mediated immune protection and the basic mechanisms responsible for what we call immunological memory. In his excellent chapter, the author considers some important questions: Have artificial vaccines been "foreseen" by nature? What is the physiological equivalent of our vaccines? What is missing in our knowledge not only about immunity but also about vaccines?

Much information can be obtained on the field of **Lymphocyte Surface Antigens and Activation Mechanisms.** As pointed out by M.L. HERMISTON *et al.*, CD45 was first reviewed by Matt Thomas in 1989 and again by Trowbridge & Thomas in 1994. Our knowledge concerning CD45 has grown significantly during the past eight years. In a very up-to-date chapter, the authors review progress made in keys areas of CD45 biology: structure, regulation of gene expression and alternative splicing, CD45 function in immune cells, and regulation of phosphatase activity. Significant associations that have been reported for autoimmunity, immunodeficiency, malignancy, and perturbations of CD45 function were also discussed. The IgA receptor family comprises a number of five surface receptors including the polymeric Ig receptor involved in epithelial transport of IgA/IgM, the myeloid specific IgA receptor (FcαRI or CD89), the Fcα/μR, and at least two alternative IgA receptors. These receptors for IgA play a significant role *in vivo* in maintaining the integrity of immune responses in systemic and mucosal compartments. In an interesting chapter, R.C. MONTEIRO & J.G.J. van de WINKEL summarize the current knowledge of 5 types of IgA receptors, focusing on CD89. Recent studies supporting a role for IgA antibodies and FcαRI-directed molecules as therapeutics for human diseases are also discussed. Over the past several years, significant advances have been made in elucidating the molecular details of the biochemical cascades triggered by ligand-engagement of immune cell signaling receptors. A key organizing element for signaling receptors appears to be cholesterol- and sphingolipid- rich plasma membrane microdomains termed lipid rafts. M. DYKSTRA *et al*. review evidence that lipid rafts play a role in the regulation of immune cell activation. Over the last years, considerable progress has been made in characterizing and understanding the mechanisms underlying antigen recognition by T cells. P.A. van der MERWE & S.J. DAVIS review recent progress in this area such as: interaction between T cells antigen receptor (TCR) and processed antigen presented on MHC molecules; CD8 and CD4 co-receptor molecules; CD28 and CTLA-4 molecules and their ligands B7-1 and B7-2 expressed on antigen-presenting cells; and, interactions between CD2 and its related ligands.

The area of **Lymphocyte Development and Differentiation** has been the target for several reviews in previous volumes of this scientific series. Homeostasis and normal functioning of the immune system require regulation of the survival of leukocytes. The death of superfluous, defective, damaged, or dangerous cells occurs by apoptosis that can be induced by death receptor ligation or via Bcl-2-inhibitable pathways. In a very interesting chapter, V.S. MARSDEN & A. STRASSER first focus on the role of the Bcl-2 protein family in the control of lymphoid and myeloid cell survival; next, the authors discuss as defects in apoptosis can contribute to autoimmunity, leukemogenesis, and infection. T cells arise from hematopoietic stem cells and their development occurs in the thymus and requires signals from nonhematopoietic stromal cells including various types of thymic epithelial cells and mesenchymal fibroblasts. Positive and negative selection of T cells occurs predominantly in the thymus, were lymphocyte precursors first assemble a surface receptor. The current state of the field regarding the natural ligands and molecular factors required for positive and negative selection is summarized by T.K. STARR *et al.* in a very interesting chapter. The authors also focus on recent data on central tolerance, where it appears that both dominant (T regulatory cell generation) and recessive (clonal delection) mechanisms operate in the thymus. The recognition of the polarized T helper cell subsets Th1 and Th2 has led to an understanding of the role of these cells in coordinate a variety of immune responses, both in responses to pathogens and in autoimmune and allergic disease. The immune system has evolved a magnitude of signal transduction pathways involved in the development of a Th1 or Th2 response. Excellent reviews on Th2 development and the signal transduction pathways and transcription factors involved in Th2 differentiation were subjects in previous volumes of Annual Review of Immunology series. In this volume, S.J. SZABO *et al.* focus on the signaling pathways and transcription factors implicated in Th1 induction, differentiation, and commitment *in vitro* and *in vivo*. Considerable attention is given to the newly identified Th1-inducing cytokines/cytokine receptors IL-23, IL-27, TCCR/WSX-1, and the novel Th1-specific transcription factors T-bet and H1x. Recent advances in understanding the biological nature of hematopoietic stem cells and progenitor cells that have broadened the potential application of these cells in the treatment of diseases such as breast cancer, leukemias, and congenital immunodeficiencies are focused by M. KONDO *et al.* B Cell chronic lymphocytic leukemia (B-CLL) is defined as a proliferation of B lymphocytes that express CD19 or CD20, CD5, CD23, and low levels of IgE and CD79b and CD22 on their surface membranes. In an extensive review, N. CHIORAZZI & M. FERRARINI discuss the cellular origin of B-CLL cells, several aspects of the B cell antigen receptor (BCR) of the leukemia cells, and how the BCR influences the evolution of the leukemic cells from a normal B cell to a clinically manifested B -CLL clone. Finally, K.L.

*This book is available at the Library of the Instituto de Medicina Tropical de São Paulo

CALAME *et al*. review recent work that provides new insights into the transcriptional regulatory mechanisms that are involved in commitment to terminal B-cell differentiation and expression of the plasma cell phenotype.

Two chapters deal with **TOLERANCE** in a very exciting manner. In his chapter, R.H. SCHWARTZ first introduces a new concept for T cell anergy, that is defined by the author as a tolerance mechanism in which the lymphocyte is intrinsically functionally inactivated following an antigen encounter, but remains alive for an extended period of time in the hyporresponsive state. Then, the author focuses on the basic types of T cell anergy that fall into two broad categories. One, clonal anergy, is principally a growth arrest state, whereas the other, adaptive tolerance or *in vivo* anergy, represents a more generalized inhibition of proliferation and effector functions. As pointed out by R.M. STEINMAN *et al.*, the subject of their interesting review, the role of dendritic cells (DCs) in T cell tolerance, may be surprising. The authors discuss, in a very didactic way, several challenging questions related to DCs as tolerogenic cells, such as: how is possible to use low doses of intact antigens to induce tolerance *in vivo*? when DCs are maturing in response to an infection, how do they avoid the risk of inducing autoimmunity to self-antigens and chronic reactivity to environmental proteins? can antigen-specific tolerance be induced in clinical settings, such as transplantation, allergy, and autoimmunity? how are the many known mechanisms for T cell tolerance engaged and controlled in the intact animal and patients? Finally, examples in which antigen presentation via DCs lead to the control of specific tolerance mechanisms in *vivo* are also reviewed.

The important area of **REGULATION OF THE IMMUNE RESPONSE** is covered in three chapters. A novel lymphocyte lineage, Vα14 natural killer T (NKT) cells, is now well established as distinct from conventional αβT cells. In a very up-to-date review, M. TANIGUCHI *et al*. summarize characteristic features of Vα14 natural killer T cells and discuss the remarkable functional diversity of these kind of T cells in various immune responses such as host defense by mediating anti-nonself innate immune reaction, homeostatic regulation of anti-self responses, and anti-tumor immunity. Innate immune defense is less sophisticated than adaptive defense. It includes the epithelial surfaces with mechanical barriers and digestive enzymes, but when microbes penetrate the body, defensive systems capable of distinguishing pathogens from self-structures are required. The Toll-like receptors (TLRs) are primordial structures that recognize the pathogen-associated molecular patterns and are found in insects as well as mammals. In drosophila antimicrobial responses rely on two signaling pathways: the Toll pathway and the IMD (immune deficiency) pathway. In mammals there are at least 10 members of the TLR family that recognize specific patterns of microbial components and regulates the activation of both innate and adaptive immunity. In a very interesting review, K. TAKEDA *et al.* focus on recent progress regarding the functions of TLRs and their signaling pathways. Collectins (mannan-binding-lectin–MBL, and surfactants proteins A and D) and ficolins (L-ficolin, M-ficolin, and H-ficolin), present in plasma and on mucosal surfaces, are humoral molecules which also recognize pathogen-associated molecular patterns. Upon recognition of the infectious agent, the human collectins as well as ficolins, initiate the lectin pathway of complement activation through attached serine proteases. By other hand, surfactant proteins A and D act through other effector mechanisms: direct opsonization, neutralization, and agglutination. In an excellent chapter, structure, function, clinical implications, and phylogeny of human collectins and ficolins, as well as their role in innate immune defense, are reviewed by V. HOLMSKOV *et al.*

Two important chapters focus on **CYTOKINES.** The control of cell survive is believed to involve regulation of the anti-apoptotic machinery. A factor called BAFF was recently discovered that is clearly a survival factor for most B cells. APRIL is a second molecule related to BAFF and shares some of the BAFF receptor yet appears to play a different biological role. F. MACKAY *et al.* focus on recent progress on the survival aspect of BAFF and its receptor interactions as it applies to B cell biology and to other TNF family members. IL-13 was originally described as a T cell-derived cytokine that inhibits inflammatory cytokine production. IL-13 was also thought to be functionally redundant with IL-4. Over last years, knockout animals were instrumental in demonstrating non-redundant roles for IL-13. In this context, T.A. WINN highlights important effector functions mediated by IL-13 and summarizes diverse array of biological activities including: regulation of intracellular parasitism; gastrointestinal parasite expulsion; inflammatory diseases of the lung; cancer; tissue remodeling and fibrosis; finally, regulation and suppression of IL-13 mediated effector function are discussed.

The hallmark of HIV-1 infection is the progressive depletion of $CD4^+$ T cells. Yet the extent and nature of this depletion, and the mechanisms by which it arises, remain highly controversial. In the absence of antiretroviral treatment, HIV-1 replication is extensive throughout the course of infection, while deterioration of conventional measures of immunity is slow, including the characteristic loss of $CD4^+$ T cells that is thought to play a key role in the development of immunodeficiency. D.C. DOUEK *et al.* examines HIV-1 infection from the perspective of lymphocyte dynamics, linking recent empirical and conceptual advances in HIV-1 biology with new insights into T cell dynamics to provide an immunological view of the pathogenesis of this infection. In a very interesting opinion, the authors suggest that profound memory $CD4^+$ T cells destruction occurring during the acute phase may have a crucial impact on the subsequent course of the infection.

Given the number of neoantigens expressed by tumors, a central question in cancer immunology is whether recognition of tumor antigens by the immune system leads to activation (surveillance) or tolerance. As discussed by D. PARDOLL in his excellent review. Does the immune system see tumors as foreign or self? these apparently disparate views can in fact be reconciled into a unified hypothesis in which tumors must develop specific mechanisms to locally inhibit the activation of innate and adaptive immunity to progress successfully through invasive and metastatic stages.

The MHC-encoded proteins are highly polymorphic proteins that constitute the major barrier for allogenic transplantation and are associated to hundred of diseases. The MHC was first discovered in mouse and much of our knowledge about it comes from this mammalian animal model. Available data that can help us to understand the fundamentals of the MHC are summarized by A. KUMÁNOVICS *et al*. In a very interesting review, the authors use the human and mouse sequences as a guide for comparative analyses of organization and origin of this crucial part of the immune system.

The reaction of IgE with its receptors is central to the phenomenon of allergy. An allergic reaction is initiated when an antigen crosslinks immunoglobulin E (IgE) antibodies bound to their high-affinity Fc receptor (FcεRI) on tissue mast cells or blood basophils. H. J. GOULD *et al*. first review recent compelling evidence that the microenvironment in allergic disease favors class switching to IgE in preference to IgG in mucosal tissues; then, they discuss how the high affinity of IgE to mast cell-surface receptors can now be interpreted in terms of the recently determined crystal structures of IgE- FcεRI and IgG-FcγR complexes.

Finally, in his prefatory chapter **The Meandering 45-Year Odyssey of a Clinical Immunologist,** Thomas A. WALDMANN focuses on the cytokines IL-2 and IL-15, which have competitive functions in adaptive immune responses, and on new forms of therapy directed at IL-2 and IL-15 receptors against certain neoplasic diseases and autoimmune disorders and in prevention of allograft rejection.

The tradition of the series **Annual Review of Immunology** is to present the state of the art in different fields of Immunology. Like other volumes, this book is mostly target to posgraduates and researchers who wish bring themselves up to date on Basic Immunology.

Myrthes Toledo Barros, PHD, M.D.
Disciplina de Imunologia Clínica e Alergia
Hospital das Clínicas da Faculdade de
Medicina da Universidade de São Paulo

ANNUAL REVIEWS – science@annualreviews.org
4139 El Camino Way - P.O. Box 10139
Palo Alto, California 94303-0139 - U.S.A.
www.annualreviews.org