Rev. Inst. Med. trop. S. Paulo
46(6):343-344, November-December, 2004

BOOK REVIEW*

ANNUAL REVIEW OF IMMUNOLOGY, vol. 22, 2004; edited by William E. PAUL, C. Garrison FATHMAN & Laurie H. GLIMCHER. Palo Alto, Annual Reviews, 2004. 1041 p. ilust. ISBN: 0-8243-3022-6. ISSN: 0732-0582.

Two chapters in this volume deal with **Immunology of Infectious Diseases and Vaccines.** Only 5% to 10% of immunocompetent humans are susceptible to tuberculosis, and over 85% of them develop the disease exclusively in the lungs. Tuberculosis in mice is also exclusively a lung disease that is progressive and lethal, in spite of the generation of Th1- mediated immunity. In a very interesting issue, R.J. NORTH & Y-J. JUNG first argue that mouse tuberculosis and tuberculosis in guinea pig and rabbit are models of tuberculosis in susceptible humans. Second, the authors discuss that inability to resolve infection and prevent disease may not be a consequence of the generation of an inadequate number of Th1 cells but of an intrinsic deficiency in macrophage function that prevents these cells from expressing immunity. The purpose of immunological memory is to protect a host from reinfection, to control persistent infection, and to protect immunologically immature fetuses and neonates by passive transfer of maternal antibody. Based on experimental models, R.M. WELSH *et al.* describe how T and B cell memory is generate in response to virus infections and how these cells respond when the host is infected again by similar or different viruses. They conclude that although armed with highly distinct effector functions, there are many parallels between the T cell and B cell components of the immune response and their conversion into memory. The authors also argue that memory B and T cell responses are long-lived in the absence of antigen, but they are modulated and influenced by other infections and that memory B and T cells can either provide protective immunity or contribute to immunopathology on infection with homologous or heterologous viruses.

The area of **Lymphocyte Development and Differentiation** has been the target for several publications in previous volumes of this scientific series. Efficient recognition of foreign pathogens by T cells requires adhesive interactions between T cells and other cell types, such as endothelial cells and antigen-presenting cells (APCs), and with components of the extracellular matrix. J.T. PRIBILA *et al.* discuss the role of integrins in T cell- mediated immunity, with a focus on how these receptors participate in lymphocyte recirculation and T cell activation, how antigen stimulation regulates integrin activity, and how integrins define functionally unique subsets of T cells and APCs. Although NK cells play important roles in host defense against various infectious agents, they are critical in host defense against viral infections. In a very didactic way, W.M. YOKOYAMA *et al.* provides an overview of the dynamic *in vivo* life of NK cells from their development in the bone marrow to their mature cellular responses in the periphery and their ultimate demise, with emphasis on mouse NK cells and viral infections. Memory is the hallmark of the acquired immune system. In the B cell system protective memory is mediated by plasma cells that secrete antibodies, whereas reactive memory is mediated by memory B cells that proliferate and differentiate to plasma cells in response to secondary antigenic stimulation. Recent studies indicate that memory T lymphocytes contain distinct populations of central memory (T_{CM} cells) and effector memory (T_{EM}) cells characterized by distinct homing capacity and effector function. In a very interesting chapter, F. SALLUSTO *et al.* review the heterogeneity of the current models for memory T cells generation and maintenance in humans and mice. Investigators would like to understand how T cells live and die in the intact animal. Numerous experiments show that the factors affecting T cell viability vary depending on the type and status of the T cell involved. In a very interesting review, P. MARRACK & J. KAPPLER focus on naïve, activated, and memory T cells survival separately, and discuss experiments done *in vitro* and in mice lacking or containing normal populations of lymphocytes. Finally, M. BUSSLINGER focuses on the transcription factors that regulate early B-lymphopoiesis in the bone marrow.

Much information has been obtained on the area of **Phagocytosis and Inflammation**. In a very exciting issue, G. WICK *et al.* put out new autoimmune hypothesis for atherogenesis in the context of many data that speak for an important role of inflammatory-immunologic processes. The authors focus on the concept that cellular and humoral immunity to the phylogenetically highly conserved antigen heat shock protein 60 (HSP60) is the initiating mechanism in the earliest stages of atherosclerosis. The discovery that the Toll and img pathways are required for defense against fungal and bacterial infection in *Drosophila* was pivotal in studies of both mammalian and *Drosophila* immunity. In an interesting chapter, C.A. BRENNAN & K.V. ANDERSON review the *Drosophila* genetics of innate immune recognitions and regulation of immune responses. As the authors anticipate, one of the future researches in the *Drosophila* immunity is likely to define mechanisms that allow *Drosophila* blood cells may carry out a form of self-nonself recognition that is independent of microbial pattern recognition. Trauma and infection may result in excessive collateral damage to normal tissues, and the failure to control activated immune cells may cause diseases as cancer, heart disease, atherosclerosis, and sepsis. M.V. SITKOVSKY *et al*. focus on the search for the physiological mechanisms ("OFF signals") that limit collateral tissue damage by immune cells including extracellular adenosine and immunosuppressive A_{2A} adenosine receptors. Targeting A_{2A} receptors by pharmacologically enhanced levels of endogenously formed adenosine and the combined use of selective A_{2A} agonists with anti-inflammatory and pathogen-destroying drugs in clinical applications are also discussed. Human vascular endothelial cells (EC) basally display Class I and II MHC-peptide complexes on their surface and come in regular contact with circulating T cells. J. CHOI *et al*. propose that EC present microbial antigens to memory T cells as a mechanism of immune surveillance. The authors describe both how EC can activate T cells by presenting antigens and how T cells can modify crucial EC functions, including antigen presentation. Because EC in various vascular beds differ in their properties, an attractive consideration of EC heterogeneity is discussed.

Two chapters are dedicated to **Regulation of the Immune System.** In the 1960s, J. Gowars discovered that lymphocytes recirculate from the blood into lymphoid organs ("homing") and back to the blood. Taking a monoclonal antibody strategy to decipher the molecular basis of this interaction, Gallatin et al. discovered a cell surface antigen on lymphocytes. Finally, the subsequent cloning of this molecule led to the identification of L-selectin (CD 62L). Beyond its general role in lymphocyte homing to secondary lymphoid organs, L-selectine is implicated in inflammatory processes, hematogenous metastasis of carcinoma cells, and implantation of early mammalian embryo. The current knowledge about the ligands engaged by L-selectin during normal and pathological processes is reviewed by S. ROSEN. CD40/CD154 interactions govern both the magnitude and quality of humoral- and cell-mediated immunity. Many effector mechanisms of inflammation are abolished as a result of CD154 blockade, but there is evidence that CD154 blockade may, in some instances, engender long-lived, antigen-specific tolerance. S. A. QUEZADA *et al.* present and discuss the prospects for inducing long-lived antigen-specific tolerance in a model of allograft tolerance through CD154 blockade.

The area of **Cytokines** is examined in three chapters. Mammals generate a diverse array of antimicrobial proteins, represented by defensins or cathelicidins. D. YANG *et al.* discuss defensines and also outline the multiple effects of cathelicidins and eosinophil-derived neurotoxin (EDN) on host immune cells and their roles in innate and adaptive antimicrobial immunity. Chemokines compose a sophisticated communication system used by all cell types, including immune cells. In a very interesting issue, A. ROT & U.H. von ANDRIAN summarize current understanding of the mechanisms that regulate the cellular perception and pathophysiologic meaning of chemokines. As pointed out by the authors, like any other communication system the chemokine network bears several noteworthy attributes of a language, which they call the "Chemokinese". In a very exciting issue, the

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

basic general rules of the "grammar of "Chemokinese" and how it applies to cell communication in the process of inflammation and immune responses are discussed. Finally, S. PESTKA *et al.* provide a comprehensive analyses of Class 2ζ-helical cytokines (IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26), interferons and interferon- like molecules, and related receptors. The authors focus on evolution and crystal structures of these molecules providing insights and perspective into the immunology of these proteins.

Two chapters in this volume deal with **Autoimmunity.** How self-tolerance is achieved has been a key issue in immunology for nearly 50 years since the proposition of the clonal selection theory. Among the mechanisms of immunologic self-tolerance, the contribution of regulatory T cells (T_R cells) or even their existence as a cellular entity has been controversial until recently. T_R cells are heterogeneous in phenotype, function, and the way of generation. Some are naturally occurring; others are induced by specific ways of antigenic stimulation. Genetic defects that primarily affect their development or function can indeed be a primary cause of autoimmune and other inflammatory disorders in humans. In his excellent chapter, S. SAKAGUSHI discuss how naturally arising CD25+CD4+ T_R cells contribute to the maintenance of self-tolerance and negative control of various immune responses and how they can be exploited to prevent and treat autoimmune disease, allergy, cancer, and chronic infection, or establish donor-specific tolerance. The evidence is overwhelming from both the clinical observations and animal models that the classical complement pathway proteins play a protective role against the development of systemic lupus erythematosus (SLE). In an up-to-date chapter, A.P. MANDERSON *et al.* first discuss clinical associations between the complement system and SLE. Second, they review finding from animals with complement deficiency that has confirmed the link between deficiency of classical pathway proteins and predisposition to the development of SLE. Finally, the authors focus on the hypothesis that has been advanced to explain these associations.

The intestine of higher vertebrates has three defined anatomical compartments which contain T lymphocytes. The gut-associated lymphoid tissues (GALT), including Peyer´s patches and mesenteric lymph nodes, contain T cells in organized lymphoid structures. The lamina propria harbors T cells scattered among nonlymphoid cell types. Finally, numerous intraepithelial lymphocytes (IEL) reside as single cells between the intestinal epithelial cells. There is several evidence that the IEL provide qualitatively and quantitatively major contributions to the biology of the mucosal and systemic immune systems. H. CHEROUTRE discusses the biology of IEL, with an emphasis on the subsets that express an ζηTCR, and their key role in the unique intestinal defense mechanisms that have evolved in mammals.

The field of **Immunodeficiency** includes only one excellent chapter by R. BUCKLEY. Human severe combined immunodeficiency (SCID) is a pediatric emergency. Infants with this condition are profoundly lymphopenic and may die of infection before their fist or second birthdays. It is now know that SCID can be caused in humans by mutations in at least nine different genes. Approaches to immune reconstitution have included bone marrow transplantation and gene therapy. Many studies clearly demonstrate that transplantation of T cell-depleted HLA-identical or HLA-haploidentical bone marrow is highly effective in reconstituting T cell immunity in all of the known genetic types of SCID. Because of serious adverse events, retroviral gene therapy trials are currently on hold. In a didactic way, R. BUCKLEY reviews molecular defects in human SCID and discusses current progress in immune reconstitution.

Asthma is a result of airway inflammation and remodeling. Th2 cells are continually active in the airways, even when disease is quiescent. These cells contribute to the inflammatory response and to airway remodeling by producing cytokines. IL-13 is the key effector cytokine in asthma and stimulates airway fibrosis through the action of matrix metalloproteinases on TGF-η and promotes epithelial damage, mucus production, and eosinophilia. IL-4, IL-5, and IL-13 produced by non-TCD4 cells may be essential for the development and perpetuation of asthma. L. COHN *et al.* review some of the mechanisms by which inflammatory and structural cells in the airways communicate to intensify disease and ultimately promote persistence and progression of asthma.

In the area of **Tumor Immunology**, S. WON & O.N. WITTE focus on the impact that imatinib mesylate (a direct inhibitor of ABL, ARG, KIT, and PDGFR tyrosine kinases) has had on the treatment of chronic myelogenous leukemia (CML) as well as other blood neoplasia and solid tumors with etiologies based on activation of tyrosine kinases. The concept that the immune system can recognize and eliminate primary developing tumors in the absence of external therapeutic intervention has existed for nearly 100 years. Most recently, it was demonstrated that the immune system not only can protect the host against tumor development but also, by selecting for tumors of lower immunogenicity, has the capacity to promote tumor growth. These dual effects of the immune system on developing tumors prompted G.P. DUNN *et al.* to refine the cancer immunosurveillance hypothesis into one they termed cancer immunoediting. In a very interesting chapter, the authors define and discuss the three Es of cancer immunoediting: elimination, equilibrium, and escape.

The field of **MHC** is examined in two chapters. Dendritic cells (DCs) are highly efficient antigen-presenting cells (APCs) that collect antigen in body tissues and transport them to draining lymph nodes. DCs are well equipped to distinguish between self- and nonself- antigens by the variable expression of cell-surface receptors such as C-type lectin receptors (CLRs) and Toll-like receptors (TLRs). There is evidence that in the stead state, DCs are not immunologically quiescent but use their antigen-handling capacities to maintain peripheral tolerance. In contrast, efficient antigen-specific immune activation occurs upon encounter of DCs with nonself-pathogens. T.B.H. GEIJTENBEEK *et al.* propose the hypothesis that cross talk between TLRs and CLRs, differentially expressed by subsets of DCs, accounts for the different pathways to peripheral tolerance, such as deletion and suppression, and immune activation. CD1-restricted T cells carry out effector, helper, and adjuvant-like functions and interact with other cell types including macrophages, dendritic cells, NK cells, T cells, and B cells, thereby contributing to both innate and adaptive immune responses. In an up-to-date chapter, M. BRIGL & M.B. BRENNER first summarize the major features of CD1 genes and proteins, the patterns of intracellular trafficking of CD1 molecules, and how they sample different intracellular compartments for self- and foreign lipids. Second, the function of CD1-restricted T cells in antimicrobial response, antitumor immunity, and in regulation of balance between tolerance and autoimmunity is discussed.

Like all other antibodies self-reactive antibodies are produced in developing B cells by V(D)J recombination in the bone marrow. In the past 20 years transgenic experiments in mice have shown that at least three mechanisms regulate auto-reactive antibodies during B cell development: receptor editing, deletion, and anergy. The prevalence of autoantibodies in the initial antibody repertoire, their regulation by receptor editing, and the role of the recombinase proteins (RAG1 and RAG2) in this process are reviewed by M. JANKOVIC *et al.*

In the area of **Lymphocyte Surface Antigens and Activation Mechanisms** current understanding of E3 ubiquitin ligases in both innate and adaptive immunity is summarized by Y-C LIU. Cytokines are crucial to maintaining healthy and play also an important role in the onset and progression of disease. It has become clear that cells have evolved sophisticated mechanisms to prevent excessive responses to cytokines. In a very interesting chapter, W.S. ALEXANDER & D.J. HILTON focus on the suppressors of cytokine signaling (SOCS) family of cytoplasmatic proteins that completes a negative feedback loop to attenuate signal transduction from cytokines that act through the janus kinase / signal transducer and activator of transcription (JAK/STAT) pathway. Recent advances in the understanding of phosphoinositide 3-kinase (PI3K) signaling mechanisms in different immune cells and receptor systems are reviewed by J.A. DEANE & D.A. FRUMAN.

Finally, the prefatory chapter "Genetics, FACS, Immunology, and Redox: a tale of two lives intertwined" written by LEONARD A. HERZENBERG & LEONORE A. HERZENBERG is obligatory to all readers.

This volume of the **Annual Review of Immunology** offers a broad updated information on selected topics for students and researchers focusing recent progress on Basic and Clinical Immunology in a didactic manner of presentation.

Myrthes Toledo Barros, MD, PhD
Disciplina de Imunologia Clínica e Alergia
Hospital das Clínicas da Faculdade de
Medicina da Universidade de São Paulo

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