

BOOK REVIEW*

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In this volume, two important chapters focus on the area of **HIV-1 vaccines**. The antibody response to HIV-1 *in vivo* is directed against several viral proteins. Because of its surface-exposed location, the glycoprotein gp120 which is anchored to the viral surface by gp41, a transmembrane unit, seemed a natural first choice as a subunit vaccine candidate. However, immunization with recombinant gp120 does not elicit neutralizing antibodies against multiple HIV-1 isolates, and failed to demonstrate efficacy in recent clinical trials. Based on crystallographic studies of gp120 molecules from HIV-1 and SIV and on studies of antibody structures, a number of strategies are being pursued to induce broadly neutralizing anti-gp120 antibodies. In a very informative chapter, two current strategies are discussed by R. PANTOPHLET and D. R. BURTON. Anti-HIV-1 T cell responses are evaded by continuous mutation of the virus. Vaccine strategies that concentrate on stimulating T cell immunity will at best generate reactive and persisting T cell responses that can suppress virus without preventing infection, limiting or preventing the damage the virus cause. Thus, despite increasingly intense efforts, development of a vaccine is still a long way off. This difficult problem and new approaches to protection of macaques against SIV are reviewed by A.J. Mc MICHAEL in a very interesting issue.

Much information has been obtained on the area of **Lymphocyte Development and Differentiation**. NK cells coordinate tumor immunosurveillance and the immune response against pathogens. Although NK precursors and immature NK cells have been identified in mice and humans, the precise sites where NK cell maturation take place are not yet fully defined. However, clear evidence for functional NK cell subsets exists in humans and the presence of NK cells in the thymus and immature NK cells in the liver suggests specific functions for NK cells in the tissues. In an excellent issue, J.P. Di SANTO focuses on murine NK cells, although parallels to human NK cell biology are also made. The developmental branching points between several lymphoid and myeloid lineages are still controversial, and little is known about how their diversification is induced. In a very interesting chapter, C.V. LAIOSA *et al.* first focus on transcription factors and other parameters, such as cytokine receptor signaling. Next, an overview of several current models of hematopoietic lineage trees to identify developmental branching points between the lymphoid and myeloid cell compartments is discussed.

The field of **Lymphocyte Surface Antigens and Activation Mechanisms** is examined in two chapters. Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) (also known as CD152) is a major negative regulator of T cell responses which interacts with the B7-1 (CD80) / B7-2 (CD86) ligands on the surface of an antigen-presenting

cell. W. A. TEFT *et al.* first review the molecular genetics and the evolutionary biology of CTLA-4 and next focus on the physiological implications of its structural features. Signal transduction down the Ras/MAPK pathway, including that critical to T cell activation, proliferation, and differentiation, has been generally considered to occur at the plasma membrane. In addition to plasma membrane, Ras and/or MAPK signaling has now been observed on endosomes, the endoplasmic reticulum, the Golgi apparatus, and mitochondria. In an up-to-date review, A. MOR and M.R. PHILIPS focus on current evidence for Ras/MAPK pathway as an example of compartmentalized signaling.

Evidence has recently been obtained that two very different recombinatorial systems for lymphocyte antigen receptor diversification appeared at the beginning of vertebrate evolution approximately 500 million years ago. Jawed vertebrates (gnathostomes) generate a diverse repertoire of B and T cell antigen receptors through the rearrangement of immunoglobulin V, D, and J gene fragments, whereas jawless fish (agnathans) assemble diverse lymphocyte antigen receptor genes through the genomic rearrangement of leucine-rich repeat (LRR) - encoding molecules. In a very interesting chapter, Z. PANCER and M. D. COOPER first consider the emergence of lymphocytes as a novel circulatory cell type in vertebrates and then discuss phylogenetic aspects of the superfamily of LRR - containing proteins and their role in immunity. Next, the authors conclude their issue with an evolutionary scenario that may explain the sudden appearance of a lymphocyte-based recombinatorial system of anticipatory immunity in the vertebrates.

Despite all efforts, the structural basis for MHC restriction and its implications for positive and negative selection remain elusive. M. G. RUDOLPH *et al.* discuss the recent advances in our understanding of TCR/peptide-MHC recognition and signaling via associated coreceptors.

For B cells, V(D)J recombination leads to the production of immunoglobulin (Ig) proteins composed of heavy and light chains. V(D)J is tightly controlled at the Ig heavy chain locus (IgH) at several different levels and although much has been learned in the last years, many questions regarding the regulation of IgH locus rearrangements remain to be elucidated. D. JUNG *et al.* review advances in understanding regulation of V(D)J recombination at the IgH locus and discuss important areas for future investigation.

Three chapters are dedicated to **Cytokines**. TGF- β s are regulatory molecules with pleiotropic effects on cell proliferation, differentiation,

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

migration, and survival that affect multiple biological processes, including development, carcinogenesis, fibrosis, wound healing, and immune responses. In the last years, generation and analysis of TGF- β 1^{-/-} mice established a central role for TGF- β 1 in inhibiting inflammation and autoimmune diseases and has fostered growing interest in this cytokine in the immune system. In a didactic chapter, M.O. LI *et al.* discuss the multifaceted roles of TGF- β in the immune system with an emphasis on its regulation of peripheral leukocyte functions. Recent discoveries have refined and expanded our understanding of how Th2 differentiation is initiated and reinforced by signals from antigen-presenting cells and cytokine-driven feedback loops. In a very up-to-date chapter, K.M. ANSEL *et al.* focus on recent advances in our understanding of the transcriptional and epigenetic basis of Th2 differentiation. In addition, background to put these recent discoveries into a historical perspective is also provided by the authors. The cytokines IL-2, IL-15, and IL-7 are critical for regulating lymphoid homeostasis. Although these cytokines stimulate similar responses from lymphocytes *in vitro*, they play markedly divergent roles in lymphoid biology *in vivo*. The production of these cytokines, the expression of their receptor chains, the context in which the cytokines are delivered, and their diverse functions in lymphoid homeostasis are discussed by A. MA *et al.*

The area of **Tolerance** is reviewed in a very up-to-date chapter. Recent elucidation of the role of central tolerance in preventing organ-specific autoimmunity has changed current concepts of self/nonself discrimination. Of recurrent interest is the extent to which central mechanisms contribute to T cell tolerance toward the abundance of tissue-restricted self-antigens (TRAs). Thus, in apparent contravention of the rules established for cell type-specific regulation of gene, medullary thymic epithelial cells (mTECs) express a wide mass of tissue-restricted antigens (TRAs). Self-antigens expressed by mTECs represent virtually all parenchymal organs, thereby mirroring the peripheral self. In a very exciting chapter, B. KYEWSKI and L. KLEIN first summarize current knowledge on regulation of TRA expression in mTECs, next review mechanisms of tolerance induction, and finally discuss pathogenesis of autoimmune diseases and other biological process such as fertility, pregnancy, and tumor defense.

The field of **Regulation of the Immune Response** has been the target for several publications in previous volumes in this scientific series. In 2006, this important area is covered in four chapters. Osteoimmunology comprises studies of interplay between the immune system and bone metabolism. Bone provides a microenvironment that is critical for the development of the hematopoietic stem cells (HSCs) from which all cells of the mammalian immune system derive. Investigators now recognize that important niches also exist in the bone marrow for long-lived memory T and B lymphocytes. Simultaneously, various factors produced during immune responses are capable of affecting regulation of bone. In a very interesting and informative issue, M.C. WALSH *et al.* first review bone development and remodeling and then focus on several key areas of crosstalk between the bone and immune system. Additionally, the authors provide a current review of the role of TNF-related activation-induced cytokine (TRANCE) that is essential for osteoclast development in the osteoimmune system. Tolerance to self-antigens is generated through two fundamental mechanisms: (a) elimination of self-reactive cells in the thymus during selection and (b) generation of a variety of peripheral regulatory cells

to control self-reactive cells that escape the thymus. Tolerance is maintained in the periphery through a variety of mechanisms, including a population of regulatory T cells (Tregs) that actively suppress the function of autoreactive T cells. Tregs are identified by their expression of CD4, the IL-2 R α chain (CD25), and the forkhead family transcription factor Foxp3 (CD4⁺ CD25⁺ Tregs). Recent work has shown that Foxp3 is critically important for the development and function of Tregs and that lack of this transcription factor leads to development of fatal autoimmune lymphoproliferative disease. In an excellent review, S.F. ZIEGLER focuses on Foxp3 expression and function and highlights differences between humans and mice regarding Foxp3 regulation. The central phenomenon at issue in immunology is resistance to infection: the fact that we do not passively succumb to microbes when inoculated with them. Genetic analysis demonstrates that preponderance of resistance to infection is inherited rather than acquired, despite the typically environmental status of microbes themselves. The positional cloning of a spontaneous mutation that cause lipopolysaccharide resistance and susceptibility to Gram-negative infection led directly to the understanding that Toll-like receptors (TLRs) are essential sensors of microbial infection. Genetic analysis of host resistance involving TLR signaling is discussed by B. BEUTLER *et al.* In recent years, there has been a renewed interest in the better understanding the contributions of other cell types to the proliferation, effector function, and memory cell behavior of the CD8⁺T cell subset. In addition, there has been increasing attention to the role of CD4⁺T cells in CD8⁺T cell responses, driven in part by a desire to understand better the basis for immune dysfunction in individuals with defects in their CD4⁺ T cell population. F. CASTELLINO and R.N. GERMAIN first review the evidence that CD4⁺T cells have a key impact on CD8⁺T memory cells formation and function, and describe the ongoing controversy about whether such help is antigen specific. Next, they consider the signals involved in producing acute effectors versus long-lived memory CD8⁺ T cells, and the mechanisms underlying the cell-cell associations involved in delivery of such signals. Finally, the authors propose a model based on these new findings that may serve as a general paradigm for cellular interactions that occur in an inflamed lymph node during the initiation of immune responses.

In 2006, two excellent chapters are dedicated to **Phagocytosis and inflammation**. In the last years, numerous lines of evidence have showed that eosinophils are pleiotropic multifunctional leukocytes involved in initiation and propagation of diverse inflammatory responses, as well as modulators of adaptive immunity by directly activating T cells. In an informative chapter, M.E. ROTHENBERG and S.P. HOGAN first summarize the biology of eosinophils and examine new views on the role of these inflammatory cells in homeostatic function, including developmental biology and innate and adaptive immunity. Furthermore, the molecular steps involved in eosinophil development and trafficking are described, with emphasis on the role of the transcription factor GATA-1, the cytokine IL-5, and the chemokine eotaxin. Finally, the role of eosinophils in disease processes, including infections, asthma, and gastrointestinal disorders, and new anti-eosinophil therapeutics are discussed. B. BLOM and H. SPITS focus on current knowledge of human lymphocyte development and the phenotypes and functions of the rare intermediate populations that together form the pathways of development into T, B and NK cells and dendritic cells.

The area of **Autoimmunity** has been the target for several publications in previous volumes of this scientific series. Genetic abnormalities of lymphocyte cell death programs have provided insights into mechanisms of receptor biology and principles of immune homeostasis and tolerance. A failure of regulatory mechanisms can cause lymphocyte depletion and immunodeficiency as well as an excess of lymphocytes and possibly cancer, autoimmune diseases and allergic reactions. It is clear that deficiencies in the death receptor Fas/APO-1 CD95, Fas ligand (Fas-L or CD95L), caspase-8, and caspase-10 primarily affect the immune system. In a very informative chapter, N. BIDÈRE *et al.* highlight the details of the molecular pathogenesis of two major diseases of programmed cell death associated with inherited human mutations: the autoimmune lymphoproliferative syndrome (ALPS) and the caspase-eight deficiency state (CEDS). As pointed out by the authors, whereas ALDS patients show that the consequences of defective apoptosis are lymphoproliferative disease autoimmunity and lymphoma, CEDS cause lymphocytosis due to impaired apoptosis together with immunodeficiency due to defective antigen receptor signaling. The use of protein microarrays in immunology has largely been limited to the profiling of two main classes of proteins: secreted factors and autoantibodies. At present, the main analytes that can be systemically studied in autoimmunity include autoantibodies, cytokines and chemokines, components of signaling pathways, and cell-surface receptors. I. BALBONI *et al.* review applications of proteomics technologies to the study of autoimmune diseases and speculate on their potential impact in the study of autoimmunity. B lineage depletion and the inhibition of B cell activation and survival are beneficial in multiple autoimmune diseases and provide a basis to further explore the role of B cell subsets and their function in health and disease. F. MARTIN and A.C. CHAN examine the emerging immunologic concepts from a number of clinical trials that uses B cell-target therapies.

One chapter deals with **Mucosal Immunity** in a very exciting issue. The anatomy of the mucosal tissues orchestrates immunity: distinct inductive sites (lymph nodes, Peyer's patches, bronchus-associated lymphoid tissue - BALT) and effector sites (lamina propria of the intestine, epithelium, airways) work in concert to provide effective local immunity. In each site, distinct anatomical structures play key roles in mounting and executing both protective and deleterious mucosal T cell responses. Thus, unregulated T cell inflammation can induce pathology as asthma, and inflammatory bowel disease. In their very interesting and informative chapter "Intestinal and pulmonary mucosal

T cells: local heroes fight to maintain the status quo", L. LEFRANÇOIS and L. PUDDINGTON discuss how T cell activation and effector function are generated in the mucosae.

Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment. In the case of human melanoma, patients usually mount a spontaneous T cell response against their tumor. However, therapeutic vaccination of metastatic melanoma patients with tumor antigens is followed by tumor regressions only in a small minority of the patients, probably because of a local immunosuppressive process occurring at the tumor sites. It is possible that in patients who do not respond to the vaccine, the antivaccine T cells succeed in reversing this immunosuppression and trigger a broad activation of other antitumor T cells. In a very interesting issue, T. BOON *et al.* review observations made on melanoma patients regarding antitumoral T cell responses that occur either spontaneously or following vaccination with tumor antigens.

Finally, in the prefatory chapter "The Tortuous Journey of a Biochemist to Immunoland and What He Found There", J.L. STROMINGER summarizes his wonderful scientific journey. In 1951, he initiated his studies of how penicillin kills bacteria. Twenty years later, STROMINGER switched fields and spent part of his professional life studying human HLA proteins. Finally, more recently, he focused on NK cells and their roles in peripheral blood and in the pregnant uterine deciduas.

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 postgraduates and researchers who wish bring themselves up to date on Basic Immunology.

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