Rev. Inst. Med. trop. S. Paulo
45(1):57-58, January-February, 2003

BOOK REVIEW*

ANNUAL REVIEW OF IMMUNOLOGY, vol. 20, 2002; edited by William E. Paul, C. Garrison Fathman & Laurie H. Glimcher. Palo Alto, Annual Reviews Inc., 2002. 956p. ilust. ISBN: 0-8243-3020-8.

The area of **Infectious Diseases and Vaccines** has been the target for several publications in previous volumes in this scientific series. Over the last decade, HIV has been extensively studied, and a variety of vaccine constructs and strategies have been explored. Lack of adequate $CD4^+$ T cell help in HIV-1 infected individuals may be one of the main determinants of the functional impairment of CTL and the eventual failure of immune control of viremia and clinical disease progression. In a very didactic article, N.L. LETVIN *et al.* discuss current understanding of the roles of cellular and humoral immunity in the containment of HIV-1 replication and describe nonhuman primate models used for assessing HIV-1 vaccine strategies. Although rarely pathogenic, mildly virulent mycobacteria, including BCG and most environmental mycobacteria (EM), may cause a variety of clinical diseases. *M. tuberculosis*, *M. leprae*, and *M. ulcerans* are more virulent, causing tuberculosis, leprosy, and Buruli ulcer, respectively. Exposure to most mycobacteria probably results only rarely in infection. It is clear that only a minority of the individuals infected go on to develop clinical disease. Thus, vulnerability to mycobacteria is the exception rather than the rule in humans, and rare patients with Mendelian disorders have been found to be vulnerable to BCG, a few EM, and *M. tuberculosis*. In an excellent chapter, J. L. CASANOVA & L. ABEL review current genetic knowledge concerning the inheritance of predisposition to mycobacterial diseases in humans during natural conditions of infection.

Five chapters are dedicated to **Lymphocyte and NK Receptors.** There is growing evidence that T cells that can respond to self-antigens are present in the peripheral immune repertoire of all humans and some experimental animals. T cells reactive with myelin antigens and other self-antigens can readily be expanded and cloned from the peripheral blood of healthy individuals. Animals immunized with myelin develop an autoimmune demyelinating disease of CNS called experimental autoimmune encephalomyelitis (EAE) that serves as a model of the human multiple sclerosis (MS). V.K. KUCHROO *et al*. propose a model of EAE and discuss how thymic expression of tissue myelin antigens, and how reactivity with self-and-cross-reactive antigens in the peripheral immune compartment might shape, tune, and regulate the autoreactive T cell repertoire. Natural killer (NK) cells participate in early, innate defense mechanisms through cytotoxic activity against pathogen-infected cells and secretion of cytokines and chemokines that modulate subsequent steps in the adaptative immune response. NK cells can be activated by dangerous cells in several ways, but many mechanisms remain poorly understood. Best identified of the events that activate NK cells is reduced cell-surface expression of MHC class I molecules. NK cells detect down regulation of MHC class I molecules by means of specific membrane receptors, which under most circumstances prevent NK cells from responding to healthy cells expressing the normal complement of autologous MHC class I molecules. One main category of these inhibitory receptors - the killer-cell-immunoglobulin-like receptor (KIR) family - has been defined in humans. C. VILCHES and P. PARHAM discuss how KIR genes have evolved in primates to generate a diverse family of receptor with unique structures that enable them to recognize MHC-class I molecules with locus and allele-specificity, and to modulate innate and adaptative immune responses to specific challenges. K. NATARAJAN *et al.* summarize, in a very didactic way, the structures of the murine and human NK cell receptors that have recently been determined, with emphasis on how they bind different region of their MHC-I ligands, and how this allows the discrimination of tumor or virus-infected cells from normal cells of the host. Immune cells are activated as a result of productive interactions between ligands and various receptors known as immunoreceptors. Signal transduction refers to the process by which extracellular events are transmitted via a receptor or multiple receptors to the interior of the cell. The change in the receptor induced by binding results in kinase activation, phosphorilation of proteins, and cellular activation. Critical kinase substrates include effector enzymes and adapter or linker molecules, which are proteins lacking enzymatic activity. L.E. SAMELSON reviews certain issues common to various signaling systems, and focuses on the role of adapters in TCR-mediated activation. A. VEILLETTE *et al.* summarize the signaling machinery involved in immunoreceptor-mediated cell activation, and cover the current knowledge regarding the negative regulation of immune cell activation.

The field of **Lymphocyte Surface Antigens and Activation Mechanisms** is examined in two chapters. T cell activation is dependent upon signals delivered through the antigen-specific T cell receptor and accessory receptors on the T cell. The CD28/CTLA-4/ B7-1/B7-2 family provides a paradigm to define new related immune pathways. B.M. CARRENO & M. COLLINS review new pathways for costimulation and inhibition of the B7 family of ligands and its receptors, and discuss how integration of signals through this family of costimulatory and inhibitory receptors and their ligands may be critical for activation of immune responses and tolerance. N. ISAKOV & A. ALTMAN discuss the selective expression of the novel protein Kinase C (PKC) isoform, PKC-θ, in T cells, as well as its essential role in T cell antigen receptor (TCR)-triggered activation of mature T lymphocytes.

Much information has been obtained on the area of **Lymphocyte Development and Differentiation.** As pointed out by T. HONJO *et al.,* one of the most striking facts of the complete human genome sequencing is that the human genome may contain as few as 30,000 genes, only twofold more than those in the fruit fly or worm genomes. One strategy to overcome such a small number of genes is somatic alteration of genetic information after birth. The authors first compare recent advances in molecular mechanisms of class switch recombination and somatic hypermutation. Next, a unified model of regulation of these two different types of genetic alteration mechanisms by activation-induced cytidine deaminase (AID), a putative RNA editing enzyme, is discussed. B-1a ($CD5^+$) cells can be distinguished from all other B cells by surface phenotype and have a number of characteristic properties. *In vitro*, they are long lived, refractory to activation through B cell receptor (BCR) ligation, and, in contrast to B-2 cells, proliferate by treatment with phorbol esters. In a very interesting review, R. BERLAND and H.H. WORTIS focus on origins and role of B-1 cells in the production of natural serum IgM, in the production of IgA in the mucosal immune system, and autoimmunity. The function of $CD5^+$ molecule as a negative regulator of BCR signaling that may help prevent inappropriate activation of autoreactive B-1a cells is also discussed. Self-renewing, hematopoietic stem cells (HSC) are multipotent, capable of generating erythroid, myeloid, dendritic, and lymphoid cell lineages. B and T lymphocytes arise from HSCs through the coordinated action of a class of transcription factors known as the helix-loop-helix proteins (HLH). M.W. QUONG *et al.* summarize recent data and examine the various functions of class I HLH proteins, also known as E proteins, and their antagonists throughout lymphoid maturation. Finally, the role of one of the E proteins (E47) as a tumor supressor is also discussed. The cell´s DNA must be packaged and organized in a manner compatible with a number of nuclear events, including differential gene transcription, DNA replication, gene recombination, and cell division. In a given cell type, decondensed chromatin is primarily associated with genes that must be accessible to the machinery involved in transcription and recombination.

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

The transitions between condensed and decondensed chromatin are thought to be critical for regulating these processes. By other hand, the acquisition of a more condensed chromatin structure is often associated with gene silencing. S.T. SMALE AND A.G. FISHER review recent progress toward understanding the role of chromatin structure and gene regulation in the immune system. In typical primary immune responses, the elimination of effector T cells at the end of the response is incomplete and a small proportion of T cells survive to become long-lived memory cells. In a didactic and up-to-date chapter, J. SPRENT & C.D. SURH first consider some of the relevant features of naïve T cells in unstimulated animals. After that, the authors review the origin and differentiation of memory T cells and the factors controlling the long-term survival of these cells.

The area of **Regulation of Immune Response** is reviewed in three chapters. The immune system has for many years been known to be influenced by glucocorticoids. This physiological regulation of the immune system by glucocorticoids is only one part of reciprocal regulation between the CNS and immune system through which the CNS signals the immune system via hormonal and neuronal pathways and the immune system signals the CNS through cytokines. J.I. WEBSTER *et al.* review the regulation of the immune response via the neuroendocrine system, focusing on the effects of interruptions of this regulatory loop at multiple levels in predisposition and expression of immune diseases and on mechanisms of glucocorticoid effects on immune cells and molecules. Innate immune cells such as dendritic cells (DC) must be activated in order to trigger the generation of optimal adaptative immune responses. These cells display a set of pattern recognition receptors (PPRs), which have a general ability to detect certain molecular structures present in pathogens but not in vertebrate genomic DNAs. Manipulation of PPR-activated pathways may be useful both for the purposes of activating therapeutic responses in cancer or some infectious diseases and also for preventing undesirable immune activation in other human diseases. In a very up-to-date chapter, A.M. KRIEG discusses a recently described PPR ligand - the unmethylated CpG dinucleotides - that are prevalent in pathogens but are suppressed and methylated in vertebrate genomic DNAs. The author also reviews the immune recognition of CpG motifs as a defense mechanism, types of CpGDNA, cellular immunology of CpG and induction of Th1-type immune responses, mechanisms of action, therapeutic applications of CpGDNA in treatment of cancer, allergic diseases, and adverse effects of CpGDNA. Innate immunity is an evolutionarily ancient part of the host defense mechanisms. It covers many areas of host defense against pathogenic microbes, including the recognition of pathogen-associated molecular patterns (PAMPs). Whereas the mechanism of generating receptors in the adaptative immune system involves great variability and rearrangement of receptor gene segments, the innate immune recognition relies on a limited number of germline-encoded receptors. In an excellent chapter, C.A.A JANEWAY & R.M. MEDZHITOV review the mechanisms of recognition that are truly innate, such that the genes encoded in the germline DNA and do not require the gene rearrangement essential to adaptative immune recognition.

In the field of **MHC**, P. GUERMONPREZ *et al.* summarize recent advances in the cell biology of antigen uptake and presentation and focus on the extraordinary efficiency of dendritic cells for T cell stimulation, initiation of immune response and induction of tolerance. Finally, the use of dendritic cells for active immunotherapy is discussed. Heat shock proteins (HSPs) are abundant soluble intracellular proteins, present in all cells, that appeared at very dawn of life. Members of the HSP family appear to play a key role in fundamental immunological phenomena such as activation of antigen presenting cells, indirect presentation, and chaperoning of peptides during antigen presentation. In an attractive review, P. SRIVASTAVA first focuses on differences and similarities between HSPs and the MHC proteins. Next, the author reviews the primordial functions of the HSPs in innate immunity. At the end, the many paths where the functions of the MHC proteins and the HSPs converge are discussed in a very didactic way. Gene-chips contain thousands of nucleotide sequences that allow simultaneous analyses of the complex mixture of RNAs transcribed in cells. Analogous to gene-chips, the peptides displayed by MHC molecules represent the entire ensemble of polypeptides expressed within a cell. The MHC molecules and the sets of peptides they display can therefore be considered nature gene-chips that are probed by the CD8+T cell repertoire. The pathway that generates the peptide-receptive MHC I involves several steps and key components. In a interesting issue, N. SHASTRI *et al.* focus on the less well understood aspects of the pathway that generates antigenic peptides and suggest a general model for the peptide/MHC I antigen processing pathway.

The study of animal models of mucosal inflammation as a means to probe the pathogenesis of inflammatory bowel disease (IBD) extends back a half century. These historically important models revealed the critical role of mucosal microflora in the pathogenesis of mucosal inflammation and the related role of barrier function as a bulwark against extensive stimulation of the mucosal immune system by the microflora. In a very interesting chapter, W. STROBER *et al.* discuss newer models of mucosal inflammation that reflect a wide variety of causes. Nevertheless, as emphasized by the authors, the resulting inflammation that develops is almost always channeled into a final common pathway of inflammation, mediated by either an excessive Th1 response associated with excessive IL-12/IFN-γ/TNF-α secretion or an excessive Th2 response associated with increased IL-4/IL-5 secretion.

Two chapters are dedicated to **Cytokines.** Several cell types involved in immune responses interact with and cross-regulate each other, and the target cells respond using signal transduction pathways to mediate gene expression and immune function. MAP kinases are among the most ancient and evolutionarily conserved signal transduction pathways, and are widely used throughout evolution in many physiological processes. C. DONG *et al.* focus on recent progress on the function and regulation of MAP kinases in different components or phases of immune responses, with particular focus on the studies achieved through mouse genetic approaches. The TNF-family RNAK-L (RANK-L, TRANCE, ODF) and its receptor RANK are key regulators of bone remodeling, and they are essential for the development and activation of osteoclasts. These recently described molecules have also critical functions in immunity and couple lymphoid cells with other organ systems such as bone morphogenesis and mammary gland formation in pregnancy. L.E. THEILL *et al*. review the biological functions of RANK-L, its receptor RANK, and the decay receptor OPG. Interventions involving these proteins for development of new therapies for osteoporosis, tooth loss, arthritis, or bone metastases in cancer are also discussed.

The two dominant mechanisms of contact-dependent lymphocyte-mediated cytotoxicity are the granule exocytosis and the Fas pathways. The biological significance of these pathways in various *in vivo* settings, the molecular components of these pathways, and the possible therapeutic interventions to control autoimmune diseases and graft vs. host disease through these two cytotoxic systems are focused by J.H. RUSSELL & T.J. LEY in a very interesting chapter. Phagocyte-microbe contact is accompanied by intracellular signals that trigger cellular processes as cytoskeletal rearrangement, alterations in membrane trafficking, activation of microbial killing mechanisms, production of pro-and anti-inflammatory cytokines and chemokines, activation of apoptosis, and production of molecules required for efficient antigen presentation to the adaptative immune system. In an excellent review, D.M. UNDERHILL & A. OZINSKY examine this complexity focusing their discussion specifically on phagocytosis of microbes.

Finally, the excellent prefatory chapter written by Charles A. JANEWAY, Jr "A trip through my life with an immunological theme" is obligatory to all readers. This volume 20 of the **Annual Review of Immunology** offers a broad of recent information on selected topics in Basic Immunology, and is mostly targeted to posgraduates and researchers in various fields of Immunology.

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