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BOOK REVIEW*

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In this volume, two important chapters focus on the area of **Immunoglobulins and B Cell Receptors.** Serum antibody composition is the result of tightly regulated differentiation of B lymphocytes into antibody secreting cells (ASCs), plasma blasts, and plasma cells. To maintain humoral memory, ASCs can be recruited to a pool of long-lived plasma cells. Survival of the plasma cells is dependent of defined signals provided in a limited number of survival niches in the body, most prominently in the bone marrow. Thus, competition between newly generated plasma blasts and old plasma cells for occupancy of survival niches allows the immune system to maintain a stable humoral immunological memory over long periods, to react to new pathogenic challenges, and to adapt to humoral memory in response to these antigens. **R.A. MANZ *et al.*** review current concepts on the biology of ASCs with respect to their contribution to the maintenance of serum antibody levels, humoral immunity, and humoral memory. **H. JUMAA *et al.*** discuss recent progress in unravelling the molecular mechanisms of signalling pathways that control simultaneously proliferation and differentiation of early B cells.

Three chapters are dedicated to **T Lymphocyte and NK Receptors.** The T cell antigen receptor (TCR) delivers signals that are crucial at distinct stages of T cell development in the thymus, as well as for the activation and differentiation of mature T cells into effector and memory cells in the periphery. Recent studies discussed by **M.E. CALL & K.W. WUCHERPFENNIG** established the great importance of the cell membrane environment for protein-protein and protein-lipid interactions that are critical for the assembly and function of the TCR-CD3 complex. Natural killer (NK) cells discriminate between normal cells and abnormal cells by using a repertoire of cell surface receptors that control their activation, proliferation, and effector functions. NK recognition includes the initial binding to potential target cells, interactions between activating and inhibitory receptors with ligands available on the target, and the interaction of signals transmitted by these receptors, which determines whether the NK cell detaches and moves on or stays and respond. In an excellent chapter, **L.L. LANIER** focuses on the structure, signal transduction, and biological function of the activating and inhibitory NK receptors, with particular emphasis on those receptors with defined physiological ligands. Different classes of NK receptors defined by their ligand specificity, e.g. receptors for MHC class I, receptors for MHC class I-related ligands, and receptors for host-encoded non-MHC ligands are discussed in this exciting review. The Tec family nonreceptor tyrosine kinases have recently been recognized as key mediators of antigen receptor signalling in lymphocytes. This family consists of five family members, which are expressed primarily in hematopoietic cells. In T cells, three major Tec kinases are expressed, all of which are tyrosine phosphorylated upon TCR stimulation. In a very interesting issue, **L.J. BERG *et al.*** cover Tec family kinases as important regulators of TCR signalling that contribute to activation of phospholipase C-γ. Recent studies suggesting that Tec family kinases also regulate actin cytoskeletal reorganization and cellular adhesion following TCR stimulation are also discussed.

The field of **MHC and Antigen Processing and Presentation** is covered in two chapters. Plasmocitoid dendritic cell precursors (pDCs), also known as type I interferon-producing cells (IPCs) display plasma cell morphology, and selectively express Toll-like receptor (TLR)-7 and TLR-9. Upon viral infections, pDCs/IPCs rapidly produce large amounts of type 1 interferon, which not only have direct inhibitory effects on viral replication but also contribute to the activation of NK cells, B cells, T cells, and mature DCs, leading to the induction and expansion of an antiviral immune response. After producing large amounts of type 1 IFN, pDC/IPCs rapidly differentiate into mature DCs and may contribute to T cell regulation. Isolation and characterization of human pDC/IPCs and regulation of T cell-mediated immune responses by pDC/IPCs are discussed by **Y-J LIU** in a very interesting review. The past several years have yielded great advances in our understanding of the cells biology and biochemistry of antigen processing and presentation. **E.S. TROMBETTA & I. MELLMAN** summarize what we have learned about the functional attributes of antigen-presenting cells (APCs), with special emphasis on dendritic cells. Their overall organization, regulation, and intracellular transport that both facilitate and modulate the processing of protein antigens are discussed in a very didactic manner.

Two chapters in this volume deal with **Lymphocyte Surface Antigens. JP-Y TING *et al.*** review the Cartepiller (CLR) family of proteins, a new discovered family that appears to have its evolutionary roots in plants and is likely an ancient family of genes. CLR is important in controlling inflammation and apoptosis and likely has wide impact not only in the immune system and organs/tissues rich with inflammatory cells, but also may serve functions in nonimmune cells. Pathways in the B7:CD28 family have key roles in regulating T cell activation and tolerance and are promising therapeutic targets. Five new B7 family members (ICOS ligand, PD-L1, PD-L2, B7-H3 and B7-H4), that are expressed on professional antigen-presenting cells as well as on cells within nonlymphoid organs, were recently identified. **R.J.GREENWALD *et al.*** focus on recent advances in our understanding of the functions of pathways in the B7:CD28 family. First, they discuss recently identified immune and nonimmune function of B7-1 and B7-2. Next, the authors summarize our current

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

understanding of the new B7 family members in regulating T cell activation and tolerance in peripheral tissue. Finally, their therapeutic potential in autoimmunity, asthma and allergy, infectious diseases, and transplantation is discussed.

In 2005, the important area of **Cytokines** is covered in five chapters. TNF and its receptors have a diverse and complex set of interaction with the immune system. They can influence inflammation and innate immunity, lymphoid organization, or activation of antigen-presenting cells (APCs), or they can provide direct signals to T cells. **T.H. WATTS** focuses on several members of the TNFR/TNF ligand superfamily that play a direct role in T cell responses subsequent to initial T cell activation. Their potential therapeutic applications, including cancer, infectious disease, transplantation, and autoimmunity are also discussed. That secondary lymphoid organs are sites for immune response initiation has long been known. Naïve B and T cells continually enter secondary lymphoid organs from the blood and migrate within minutes to the juxtaposed B cell follicles and T cell zones, respectively. In a very interesting chapter, **J.G. CYSTER** first reviews the roles of chemokines in cell homing to lymphoid follicles and T cell zones, and in facilitating interactions between cells during the initiation of adaptive immunity. Next, the author focuses on another type of soluble mediator, a lysophospholipid (sphingosine-1-phosphate, (S1P), in lymphoid trafficking. Finally, the author reviews information emerging on the requirements from cell egress from secondary lymphoid organs and thymus. The multiple subtypes of α-interferons and single β-interferon belong to the type I family of interferons (IFNs) and are central to a vast array of immunological functions. The broad effects of IFN-α/β include innate immunity, and almost every aspect of cellular and humoral adaptive immune responses. In the last years, a clear picture of several aspects of their biology has emerged, including signalling processes, priming capacity, cross-talk among themselves and other cytokines, receptors and ligands involved in their production, and their major cellular producers. In an excellent chapter, **A.N. THEOFILOPOULOS *et al.*** review select aspects of the biology of IFN-α/β related to these recent advances, with focus on their role in systemic and organ-specific autoimmune diseases like systemic lupus erythematosus and insulin-dependent diabetes mellitus, respectively. Lymphotoxins (LTα and LTβ) together with the two related cytokines, tumor necrosis factor (TNF) and LIGHT (LT-related inducible ligand that competes for glycoprotein D binding to herpesvirus entry mediator on T cells), form an integrated signalling network necessary for efficient innate and adaptive immune responses (TL/TNF/LIGHT network). In the clinic, TNF/LTα have proven to be important targets for suppressing inflammation in certain autoimmune diseases, including rheumatoid arthritis and inflammatory bowel syndrome, but not others, such as multiple sclerosis. In an up-to-date issue, **C.F. WARE** first discusses the structural and functional features of the LT/TNF/LIGHT signalling systems. Next, the author reviews clinical results using LT/TNF/ inhibitors in various human autoimmune diseases. Finally, side effects of TNF inhibitors which include increased susceptibility to certain infectious diseases are discussed in a very didactic manner. Complement system activation has recently been implicated in the pathogenesis of many inflammatory and immunological diseases. The complement activation exerts its harmful roles through the generation of complement protein split products, especially C3a and C5a. Accumulating data suggest that C5a is one of the most patent inflammatory peptides. **R-F GUO & P.A. WARD** describe actions of C5a, focusing on its roles in innate immunity and molecular and cellular events that lead to the inflammatory sequelae. Human and animal experimental data describing the cellular and molecular mechanisms of C5a in the development of inflammatory disorders, sepsis, acute lung injury, ischemic-reperfusion injury, and asthma are also discussed.

The area of **Lymphocyte Development and Differentiation** has been the target for several publications in previous volumes of this scientific series and much information has been obtained on this field. The splenic marginal zone (MZ) is primarily made up of marginal zone B cells (MZ B cells), specialized macrophages, and reticular cells. In rodents, MZ B cells are now recognized as a distinct naïve B lineage, separate from mature follicular (FO) B cells and B-1 cells. In humans, most MZ B cells are thought to represent a memory population. In a didactic and informative review, **S. PILLAI *et al.*** review the mechanisms involved in the entry of B lymphocytes into the MZ and their subsequent retention in this area. Next, the authors focus on the functions of these cells in both innate and adaptive immunity. Finally, the biology of human MZ B cells and their relevance to disease are considered. Helper T cell-regulated B cell immunity progresses in an ordered cascade of cellular development that culminates in the production of antigen-specific memory B cells. In a very interesting chapter, **L.J. McHEYSER–WILLIAMS & M.G. McHEYSER–WILLIAMS** provide an overview of the cellular and molecular regulators of this dynamic process with emphasis on the multiple memory B cell fates that develop *in vivo*. T cell development, as a process, incorporate multiple stages at which different choices are available to the cells, extending over many cell cycles and a long period of time. Moreover, T cell development is guided by a complex set of key regulators throughout the process, in different combinations. **E.V. ROTHENBERG & T. TAGHON** describe the modes of action of the major T-lineage-defining transcription factors and the signal pathways that activate them during intrathymic differentiation from pluripotent precursors. DNA is degraded during programmed cell death (apoptosis) that accompanies mammalian development. By the other hand, as pointed out by **S. NAGATA**, there are "living" or at least "functional" cells that not carry DNA, like erythrocytes and lens fiber cells in the eyes. In these cell populations, DNA is removed or degraded at the final stage of their differentiation into mature cells by recently identified specific DNases. Additionally, mice deficient in the respective DNase develop anemia and cataract, indicating that DNA degradation is an essential step for differentiation of erythroid cells and lens fiber cells. In a very interesting chapter, the author reviews how DNA is degraded during apoptosis, erythroid cell differentiation, and lens cell differentiation. There are several features of natural killer T (NKT) cells that have emerged from studies carried out during the previous decade. Despite this progress, knowledge of the natural antigens they recognize and their physiologic role remain incomplete. **M. KRONENBERG** reviews the known properties of mouse and human NKT cells and focuses on recent findings and on important unresolved questions concerning the development, specificity, and function of these unique T lymphocyte. The Notch pathway is a key regulator of developmental choices, differentiation, and function throughout the hematolymphoid system. The diverse functions of Notch are mediated through a conserved signalling pathway in which transmembrane receptors undergo regulated proteolysis and nuclear translocation to activate transcription. The state-of-the-art of regulation of development, differentiation, and

functions of peripheral T and B cells by the Notch pathway is presented by **I. MAILLARD *et al.***

Three exciting chapters deal with **Phagocytosis and Inflammation.** Neutrophils constitute the first line of defense of the innate immune system by phagocytosing, killing, and digesting bacteria and fungi. During the past few years, there were many evidences implicating a major primary role for the granule proteins in the killing process, with a less direct but still facilitating and activating role for the respiratory burst through the NADPH oxidase. This raises the question of the connection between these two processes. In a very up to-date chapter, **A.W. SEGAL** reviews recent progress in our understanding of the relationship between the oxidase and granule enzyme activation in the killing process. Innate defense mechanisms consist of a cellular and a humoral arm. Like the cellular arm, the humoral arm is also diverse: it includes collectins (mannose–binding lectin, surfactant protein A and D, C1q), ficolins, and pentraxins. C reactive protein (CRP) and serum amyloid P (SAP) component are classic short pentraxins produced in the liver. Long pentraxins, including the prototype PTX3, are produced by a variety of cells and tissues, most notably dendritic cells and macrophages, in response to Toll-like receptor engagement and inflammatory cytokines. Current research suggests that PTX3 acts as a functional ancestor of antibodies, recognizing microbes, activating complement, and facilitating pathogen recognition by phagocytes. In a very interesting review, **C. GARLAND *et al.*** summarize current understanding of the structure and function of pentraxins with focus on the more recently discovered long pentraxin PTX3, and on the classic short pentraxins CRP and SAP. Macrophages express a broad range of plasma membrane receptors that mediate their interactions with natural and altered-self components of the host as well as a range of microorganisms. Their ability to recognize a wide range of ligands, and to responde appropriately, is central to macrophage functions in homeostasis as well as host defense in innate and acquired immunity, autoimmunity, inflammation, and immunopathology. The role of classic opsonins (antibody and complement) and of a range of microbial ligands by Toll-like receptors and families of cytosolic proteins (e.g. NODs, NALPs) has been well documented. **P.R. TAYLOR *et al.*** review less well-known receptor families implicated in nonopsonic recognition, mediating either cell adhesion or phagocytosis.

The important area of **Autoimmunity** is covered in two chapters. The nonobese diabetic mouse (NOD) strain is an excellent model of autoimmune type 1 diabetes (T1D), which shares many similarities to type 1a diabetes in human subjects. **M.S. ANDERSON & J.A. BLUESTONE** first summarize recent advances in our understanding of disease development and progression in the NOD mice. Next, the authors highlight how these findings will lead to potential therapies for the treatment of autoimmune diabetes. Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). It leads to substantial disability through deficits of sensation and of motor, autonomic, and neurocognitive function. MS is still considered a $CD4^+$Th1-mediated autoimmune disease. Damage of the target tissue (CNS) is, however, most likely mediated by other components of the immune system, such as antibodies, complement, $CD8^+$T cells, and factors produced by innate immune cells. In a very exciting chapter, **M. SOSPEDRA & R. MARTIN**, as pointed out by the authors themselves, deviate from their review 12 years ago and consider the role of the CNS in targeting the disease process, in interactions with the immune system, and in the long-term course of MS.

The field of **ALLERGY** includes only one chapter by **S.J. GALLI *et al.*** covering current progress in mast cells knowledge. First, the authors summarize current understanding of the positive and negative regulation of signaling in mast cells via the FcεRI, including recent work indicating that the mast cell functional properties can be modified by action of IgE in the absence of known antigen. Next, they advance the hypothesis that mast cells also may contribute to the initiation and regulation of acquired immune responses. Finally, the authors illustrate how mast cell knockin mice have been used to identify and characterize the potentially diverse contributions of mast cells to the induction, expression, and regulation of IgE– associated and other acquired immune responses.

Two chapters in this volume deal with **Immunology of Infectious Diseases and Vaccines.** Malaria remains one of the world's greatest public health challengers and the immune response to the malaria parasite is very complex. Although there is evidence from human and animal model systems that cellular mediated immunity (CMI) can control parasite load, the factors that regulate CMI are poorly understood. **M.F. GOOD *et al.*** analyze the contribution of cellular immune responses to both protection from malaria and pathogenesis. $CD8^+$T cells play a critical role in antiviral immunity by exerting direct antiviral activity against infected cells. As pointed out by **J.W. YEWDELL & S.M. MANSOUR HAERYFAR** in their chapter, understanding of antiviral $TCD8^+$ responses requires answering the following questions: Which cells present antigen? Where and when does this occur? In a very didactic manner, the authors focus on recent progress obtained by *in vivo* studies in mice to understand the basis for activation of naïve $TCD8^+$ in virus infections.

Finally, in his prefatory chapter, **Tadamitsu Kishimoto** summarizes his 40 years of research in immunology. He spent part of his professional life studying one of the factors derived from culture supernatant of T cells that induces proliferation and differentiation of B cells, interleukin–6 (IL– 6). He "feels exceptionally fortunate that his life´s work not only revealed the framework of cytokine signaling, but also led to the development of a new therapy for chronic inflammatory diseases".

This volume 23 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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