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BOOK REVIEW

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Two chapters in this volume deal with **Immunology of Infectious Diseases.** Circulating monocytes are increasingly implicated as essential players in defense against a range of microbial pathogens by supplying tissues with macrophage and dendritic cells precursors. In humans and mice, monocytes either specifically traffic into inflamed tissues or, in the absence of overt inflammation, constitutively maintain tissue macrophage/ dendritic cells populations. Inflammatory monocytes respond rapidly to microbial stimuli by secreting cytokines and antimicrobial factors, express the CCR2 chemokine receptor, and traffic to sites of microbial infection in response to monocyte chemoattractant protein (MCP)-1 (CCL2) secretion. In a very interesting issue, the *in vivo* mechanisms that promote chemokine secretion, monocyte differentiation and trafficking, and finally monocyte-mediated microbial killing remain active are focused by **N.V. SERBINA *et al.***

Generally, two major genetic approaches in the mouse have been used to identify host proteins and biochemical pathways that affect host response to many pathogens. The forward genetics, the more recent strategy, is an experimental approach in which gene mapping and positional cloning are used to elucidate the molecular mechanisms underlying phenotypic differences between two individuals for a given trait. This approach has been highly successful for the study of inbred mouse strains that show differences in innate susceptibility to several microbes and has revealed genes, proteins, and signaling pathways that play critical roles in the immune response to a large number of infectious agents. In a very interesting chapter, **S.M. VIDAL *et al.*** describe some of the most informative examples of such discoveries, with an emphasis on the implications of the discovered genes and proteins for our evolving understanding of innate or acquired immune defenses.

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. In 2008, this important area is covered in seven chapters. Primary immune responses are initiated in secondary lymphoid organs that develop during embryogenesis or in the first few weeks after birth and are situated throughout the body at strategic sites where antigens from pathogens are most likely to be encountered. Its development occurs according to a highly coordinated series of interactions orchestrated by homeostatic chemokines, cytokines, and growth factors that attract hematopoietic cells to sites of future lymphoid organ development and promote their survival and differentiation. **T.D. RANDALL *et al.*** describe the current paradigm of secondary lymphoid organ development and discuss the differences in the timing, molecular interactions, and cell types involved in the development of each secondary lymphoid organ.

It is broadly recognized that thymus structure is key to the intrathymic selection of a selftolerant and self-MHC-restricted T cell antigen receptor (TCR) repertoire. A look at the evolution of the immune system strongly suggests that medulla-cortex organization is functionally important because, as soon as there was a thymus, this architectural hallmark of the thymus was present. In a very didactic way, **H. RODEWALD** focuses on significant recent advances in the field of thymus organogenesis, starting with a brief primer on the embryological origin of the thymus in phylogeny and concluding with the recently identified functional second thymus in mice, located in the neck.

Introduced to the field of immunology in 2002, two-photon microscopy has proved to be the method of choice for visualizing living cells deep within native tissue environments, and it is now revealing an elegant cellular choreograph of cell motility, antigen capture, and cell-cell interactions in a variety of *in vivo* settings. In a very interesting review, **M.D. CAHALAN & I. PARKER** first discuss the technology of two-photon microscopy as applied to immunoimaging and then focus on its applications to live-cell imaging of immune cells in the lymph node under basal conditions and in response to antigenic challenge.

The impaired growth of retroviruses, including HIV-1, in foreign and sometimes even in their natural hosts often stems from the action of potent host-encoded "viral restriction factors" that form important protective components of the innate immune system. The discovery of APOBEC3G and related cytidine deaminases as one class of host restriction factors and of the action of HIV-1 Vif as a specific APOBEC3G antagonist have stimulated scientific interest. The antiviral mechanisms of the APOBEC3 family are not clear but appear to involve their intrinsic RNA binding and deaminase activities. **Ya-Lin CHIU & W.C. GREENE** summarize current understanding of the mechanism of action of the APOBEC3 family of enzymes, the impact of these enzymes on viral evolution and disease progression, and their roles in controlling the replication of exogenous retroviruses.

In the B cell lineage, Blimp-1 (B lymphocyte–induced maturation protein-1) is required for development of immunoglobulin-secreting cells and for maintenance of long-lived plasma cells (LLPCs). Blimp-1, discovered 16 years ago as a transcriptional repressor of the IFNβ promoter, is reviewed by **G. MARTINS** & **K. CALAMEIN** in a very up-to-date issue.

Prior to antigen exposure, mice and humans constantly recreate a highly diverse repertoire of antigen-binding sites in pro- and pre-B cells in the bone marrow through the rearrangement of germ line immunoglobulin (Ig) variable (V), diversity (D), and joining (J) elements to form the heavy (H) and light (L) chain V regions in the Ig genes. Once an antigen appears, however, cognate mature B cells are stimulated to proliferate, differentiate, and migrate to germinal centers in secondary lymphoid organs, where they begin to express large amounts of activation-induced cytidine deaminase (AID), which initiates somatic hypermutation (SHM) of the antibody V regions that encode the antigen-binding sites. **J.U. PELED *et al.*** discuss SHM of the V region genes in mice and humans focusing on how the different enzymatic systems that are involved in SHM are organized and regulated. The authors first describe general features of SHM, followed by each of the mutation and repair systems involved

in V region hypermutation, and then they address the issue of the overall regulation of SHM. Finally, in a separate and very up-to-date chapter, **J. STAVNEZER *et al.*** discuss in detail the mechanism and regulation of class switch recombination.

In 2008, the important area of **Cytokines** is covered in three chapters. In the past two decades, major progress has been made in understanding the critical role of the interferon regulatory factor (IRF) family of transcription factors (IRFs) in the control of cell growth, cell survival, and oncogenesis. Since the first review in this Annual Review of Immunology series (2001), the crucial involvement of many IRFs in innate immune responses elicited by pattern recognition receptors (PRRs) has been clarified in greater detail. In his second review about this issue, **T. TANIGUCHI** focuses on current literature on how IRFs orchestrate and control homeostatic mechanisms of host defense. In addition to its contributions to immunity, the role of several IRFs in the regulation of the cell cycle and apoptosis and its implications for understanding susceptibility to and progression of several cancers is also discussed.

Early data support a central role for interleukin (IL)-2 in protective immune responses. It was quite surprising, therefore, that after the genes for IL-2 or two subunits of the IL-2R, IL-2Rα (CD25) and IL-2Rβ (CD122), were individually inactivated in mice by gene targeting, the resulting phenotype is not immunodeficiency, as predicted, but rather a very serious lymphoproliferative and autoimmune disorder. There is now much evidence that a defect in CD4+CD25+ Foxp3+ T regulatory (Treg) cell production is the main reason for lethal autoimmunity associated with IL-2/IL-2R deficiency. This cell population suppresses potentially autoreactive peripheral T cells that escape thymic negative selection. Emerging findings, however, suggest an essential role for IL-2 in immune memory. In a very exciting chapter, **T.R. MALEK** first introduces the basics of the IL-2/IL-2R system. After, current understanding of the dual role of IL-2 in maintaining tolerance and contributing to immunity *in vivo* with emphasis on T regulatory cell production and homeostasis is reviewed.

Interleukin-21 (IL-21), a potent immunomodulatory type I cytokine, was first observed to be produced by CD4+ Tcells and to modulate the proliferation and effector function of other lymphoid cells. Subsequently, however, IL-21 was observed to act on multiple nonlymphoid lineages as well and to be produced by innate immune natural killer T (NKT) cells and the more recently identified Th17 lineage. In an excellent issue, **R. SPOLSKI & W.J. LEONARD** review IL-21 biology and focus on its strong antitumor action via its effects on both NK and CD8+ T cells and also on its implications for cancer and autoimmunity.

Much information has been obtained on the area of **Autoimmunity.** Rheumatoid Arthritis (RA) is often denoted an autoimmune disease, largely based on the presence of rheumatoid factors (RF). However, the presence of RF is not specific for RA and no experimental studies have demonstrated any proarthritogenic effects of RF. However, other data favor a possible role for autoimmune reactions in the disease. Over the past 10 years, there has been a major development in the field of immunity focused on antibodies to citrullinated proteins (ACPA), i.e., to peptides posttranslationally modified by the conversion of peptidylarginine to peptidylcitrulline. These antibodies are highly specific serological markers for RA, i.e., they exist in around 2% of normal populations, are also quite rare in other inflammatory conditions, and can be found in approximately 60% of RA patients. Recent studies on anticitrulline immunity, summarized by **L. KLARESKOG *et al.,*** demonstrate that RA should be subdivided into at least two distinct subsets (ACPA-positive and ACPA-negative disease) and that we might be able to devise immunotherapies specifically adapted to each arthritis subpopulations.

Although several autoimmune diseases are characterized by the presence of autoantibodies produced by autoreactive B cells, genetic and animal models point to a central role of autoreactive T cells as the primary mediators of autoimmune disease. Many genes identified as causing or predisposing to autoimmunity encode proteins that are involved in cell signal transduction. Protein tyrosine phosphatases (PTPs) are important regulators of many cellular functions and a growing number of PTPs have been implicated in human disease conditions, such as developmental defects, neoplastic disorders, immunodeficiency, and autoimmunity. **T. VANG *et al.*** first review the involvement of PTPs in human autoimmunity; next, they focus on the possible involvement of additional PTPs in susceptibility to autoimmune and inflammatory diseases. Finally, the possibility that PTPs regulating the immune system may serve as therapeutic targets is discussed.

Although mast cells have long been recognized as central players in allergy, recent evidence that these cells are activated by complement and can modulate both B and T cell responses suggests that mast cells can play also a central role in autoimmunity. In an excellent and challenging review, **B.A. SAYED *et al.*** first focus on key features of mast cells and describe the range of autoimmune diseases in which mast cells have been implicated. The defined and hypothesized mechanisms of mast cell action are then discussed, including the seemingly paradoxical antiinflammatory role of these cells in promoting tolerance. Finally, the genetically determined heterogeneity of mast cells and the implications for disease susceptibility are discussed in a very didactic way.

Two chapters are dedicated to **Regulation of the immune response.** One of the fundamental discoveries of modern immunology was the finding that antibody responses require "help" from Th2 cells which produce cytokines such as IL-4 and direct B cells to undergo Ig isotype switching to IgG and IgE. It is now apparent that a subset of nonpolarized CD4+ T cells termed follicular B helper T cells (TFH cells or T follicular helper cells) are the true helper cells for antibody responses, although other T cells such as Th2 cells, γδ T cells, and NKT cells may also contribute. TFH cells are distinguishable from Th1 and Th2 cells by several criteria, including chemokine receptor expression (CXCR5), location/migration (B cell follicles), and function (B cell help). Central to the function of CD4+ T cells is IL-21, a "helper" cytokine produced by TFH cells that potently stimulates the differentiation of B cells into antibody-forming cells through IL-21R. In an up-to-date issue, **C. KING *et al.*** first focus on some of the controversial questions concerning TFH cell differentiation, the relation of TFH cells to other T cell subsets such as Th2 and/or Th17, and the influence of several molecules that are highly expressed by TFH cells and most likely participate in T cell–dependent B cell differentiation. Finally, the authors argue that dysregulation of TFH cell function, and over- or underexpression of TFH cell-associated molecules such as ICOS or IL-21, most likely contributes to the pathogenesis of certain autoimmune diseases or immunodeficiencies.

Immune responses to foreign and self-antigens require specific and balanced responses to clear pathogens and tumors and yet maintain

tolerance. Induction and maintenance of T cell tolerance requires inhibitory signals delivered by programmed death 1 (PD-1) and its ligands, PD-L1 and PD-L2, on nonhematopoietic cells that can limit effector T cell responses and protect tissues from immune-mediated tissue damage. **M.E. KEIR *et al*** review recent advances in our understanding of the roles played by PD-1 and its ligands in regulating T cell activation and tolerance and consider the therapeutic potential of manipulation of PD-1 and its ligands.

Two important chapters are dedicated to the area of **Inflammation.** The two major clinical indications for intravenous IgG (IVIG) therapeutic application are IgG replacement therapy in primary and secondary immunodeficiencies and antiinflammation therapy in a variety of acute and chronic autoimmune diseases. Whereas the mechanism of IVIG activity in IgG replacement therapy may be explained by the presence of so-called natural or by the presence of common pathogen-specific IgG antiantibodies derived from previously immunized or vaccinated serum donors, the explanation of the anti-inflammatory activity in autoimmune diseases is unclear. In a very informative chapter, **F. NIMMERJAHN & J.V. RAVETCH** start with a description of the drug IVIG, summarize the clinical use of IVIG for different diseases and discuss recent data on the molecular mechanisms, with an emphasis on results obtained in *in vivo* model systems that might explain how this potent drug mediates its activity *in vivo*.

Although important for immunity, aberrant accumulation of T cells in the lung is seen in numerous noninfectious pulmonary inflammatory diseases such as asthma, where T lymphocytes in the lung are believed to orchestrate an abnormal inflammatory process. The hallmark of asthma is prominent chronic inflammation with accumulation of activated effector Tcells around the airways and in the airway lumen associated with reversible airway dysfunction. In a very interesting chapter, **B.D. MEDOFF *et al.*** summarize recent advances in mechanisms of T cell homing into the lung during asthma and present a paradigm for the mechanisms that control the movement of these cells into and out of the airways.

Recent data suggest that actin filaments play a dual role in **T cell activation**, enhancing cell activation by promoting conjugate formation and the assembly of signaling complexes, but also downregulating activation, perhaps by facilitating molecular movements that culminate in the internalization of the TCR regulatory proteins. The roles of actin filaments in T cell function and on the interplay between cytoskeletal changes and the signaling events associated with T cell activation are reviewed by **J. BURKHARDT *et al.***

The area of **MHC** is reviewed in two very up-to-date chapters. The rules for the conserved reaction of αβ T cell receptors (TCRs) with MHC proteins plus peptides are poorly understood, probably because thymocytes bearing TCRs with the strongest MHC reactivity are lost by negative selection. Thus, only TCRs with an attenuated ability to react with MHC appear on mature T cells. It is not clear until now if evolution had selected TCRs that reacted in some predictable way with MHC. **P. MARRACK *et al***. describe relatively evolutionarily conserved amino acids in the TCR complementarity-determining regions (CDR) 1 and CDR2 that are often used to bind exposed areas of the MHCα helices.

The specialized capacities of dendritic cells (DCs) for acquiring, processing, retaining, and finally presenting peptides on major histocompatibility complex molecules are critical properties that account in part for their superior role in antigen presentation. Unlike other antigen-presenting cells, like macrophages, DCs are specialized for homing efficiently to the T cell zones of lymphoid organs for optimal interactions with T lymphocytes. Thus, the pathways and mechanisms that govern how DCs migrate to lymphoid and nonlymphoid tissues figure importantly in immune responses. **G.J. RANDOLPH *et al.*** compare the distinct migratory patterns of dendritic cell subsets and their precursors and discuss how the highly regulated patterns of DC migration *in vivo* may affect their roles in immunity.

The field of **Cytotoxic cells** includes one excellent chapter by **D. CHOWDHURY & J. LIEBERMAN.** The granzymes (granule enzymes) are a family of highly homologous serine proteases contained in granules of cytotoxic T lymphocytes and natural killer cells that are released during granule exocytosis. Their major role is to induce cell death to eliminate viruses and tumor cells. The granzymes may also play a role in immune regulation by controlling the survival of activated lymphocytes and may also regulate inflammation by acting on extracellular substrates. The authors review what is known about the biochemistry, gene regulation, cell biology, functions, and inhibitors of the granzyme family and focus on recent studies that implicate granzymes in immune regulation and extracellular proteolytic functions in inflammation.

Finally, the prefatory chapter "Doing What I Like" by **K. Frank AUSTEN** summarizes his wonderful scientific journey and is obligatory to all readers.

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 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.

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