Therapeutic Immunology

edited by

K. FRANK AUSTEN

STEVEN J. BURAKOFF

FRED S. ROSEN

TERRY B. STROM

b

Blackwell Science

Therapeutic Immunology

edited by

K. FRANK AUSTEN, MD
Theodore Bevier Bayles Professor of Medicine, Harvard Medical School; Chairman of Rheumatology and Immunology, Brigham and Women's Hospital, Boston, Massachusetts

STEVEN J. BURAKOFF, MD
Professor of Pediatrics, Harvard Medical School; Chief of Pediatric Oncology, Dana Farber Cancer Institute, Boston, Massachusetts

FRED S. ROSEN, MD
James L. Gamble Professor of Pediatrics, Harvard Medical School; President, The Center for Blood Research, Boston, Massachusetts

TERRY B. STROM, MD
Professor of Medicine, Harvard Medical School; Director of Immunology, Beth Israel Hospital, Boston, Massachusetts

Blackwell
Science

Blackwell Science

Editorial offices:
238 Main Street, Cambridge, Massachusetts 02142, USA
Osney Mead, Oxford OX2 0EL, England
25 John Street, London WC1N 2BL, England
23 Ainslie Place, Edinburgh EH3 6AJ, Scotland
54 University Street, Carlton, Victoria 3053, Australia
Arnette Blackwell SA, 1 rue de Lille, 75007 Paris, France
Blackwell Wissenschafts-Verlag GmbH
Kurfürstendamm 57, 10707 Berlin, Germany
Feldgasse 13, A-1238 Vienna, Austria

Distributors:

North America
Blackwell Science, Inc.
238 Main Street
Cambridge, Massachusetts 02142
(Telephone orders: 800-215-1000 or 617-876-7000)

Australia
Blackwell Science Pty Ltd
54 University Street
Carlton, Victoria 3053
(Telephone orders: 03-347-0300
fax: 03-349-3016)

Outside North America and Australia
Blackwell Science, Ltd.
c/o Marston Book Services, Ltd.
P.O. Box 87
Oxford OX2 0DT
England
(Telephone orders: 44-1865-791155)

Acquisitions: Victoria Reeders
Development: Kathleen Broderick
Production: Tracey Solon
Manufacturing: Karen Feeney
Printed and bound by: Braun-Brumfield, Inc.

Printed in the United States of America
96 97 98 99 5 4 3 2

Notice: The indications and dosages of all drugs in this book have been recommended in the medical literature and conform to the practices of the general medical community. The medications described do not necessarily have specific approval by the Food and Drug Administration for use in the diseases and dosages for which they are recommended. The package insert for each drug should be consulted for use and dosage as approved by the FDA. Because standards of usage change, it is advisable to keep abreast of revised recommendations, particularly those concerning new drugs.

Library of Congress Cataloging-in-Publication Data

Therapeutic immunology / [edited by] K. Frank Austen . . . [et al.].
p. cm.
Includes bibliographical references and index.
ISBN 0-86542-375-X (alk. paper)
1. Immunotherapy. I. Austen, K. Frank (Karl Frank)
[DNLM: 1. Immunotherapy. 2. Immune System—drug effects. QW 940 T398 1996]
RM275.T44 1996
615'.37—dc20
DNLM/DLC
for Library of Congress 95-51338
CIP

Therapeutic Immunology

Contributors

Abul K. Abbas, MD
Professor of Pathology, Harvard Medical School; Brigham and Women's Hospital, Boston, Massachusetts

Donna M. Ambrosino, MD
Associate Professor of Pediatrics, Harvard Medical School; Clinical Associate, Dana Farber Cancer Institute, Boston, Massachusetts

William P. Arend, MD
Professor of Medicine, University of Colorado School of Medicine; Attending Physician, University Hospital, Denver, Colorado

Kevin P. Barton, MD
Instructor, Department of Medicine, Division of Biological Sciences, University of Chicago, Pritzker School of Medicine; Attending Physician, University of Chicago Hospitals, Chicago, Illinois

Baruj Benacerraf, MD
Fabyan Professor of Pathology Emeritus, Harvard Medical School; Dana Farber Cancer Institute, Boston, Massachusetts

Barbara E. Bierer, MD
Associate Professor of Medicine, Harvard Medical School; Director of Pediatric Bone Marrow Transplantation, Dana Farber Cancer Institute, Boston, Massachusetts

Kurt J. Bloch, MD
Professor of Medicine, Harvard Medical School; Chief of Allergy and Immunology, Massachusetts General Hospital, Boston, Massachusetts

Suzanne Bornschein-Church, MD
Clinical and Research Fellow, Harvard University; Clinical and Research Fellow, Massachusetts General Hospital, Boston, Massachusetts

David M. Briscoe, MD
Attending Pediatric Nephrologist, Children's Hospital, Boston, Massachusetts

Michael R. Bristow, MD, PhD
Division of Cardiology, University of Colorado School of Medicine, Denver, Colorado

George W. Carter, PhD
Vice President of Immunoscience Research, Abbott Laboratories, North Chicago, Illinois

Henry N. Claman, MD
Distinguished Professor of Medicine and Immunology, University of Colorado School of Medicine; University of Colorado Health Sciences Center, Denver, Colorado

Ramzi S. Cotran, MD
S.B. Mallory Professor of Pathology, Harvard Medical School; Chairman of Pathology, Brigham and Women's Hospital, Boston, Massachusetts

John R. David, MD
Professor of Tropical Public Health, Harvard School of Public Health; Senior Physician, Brigham and Women's Hospital, Boston, Massachusetts

H. Joachim Deeg, MD
Professor of Medicine, University of Washington School of Medicine; Member, Fred Hutchinson Cancer Research Center, Seattle, Washington

David L. DeWitt, MD
Assistant Professor of Biochemistry, Michigan State University College of Human Medicine, Lansing, Michigan

John P. Doweiko, MD
Instructor in Medicine, Harvard Medical School; Attending Physician, Division of Hematology/Oncology and Infectious Disease, New England Deaconess Hospital, Boston, Massachusetts

Richard L. Edelson, MD
Professor and Chairman of Dermatology, Yale University School of Medicine; Chief of Dermatology, Yale–New Haven Hospital, New Haven, Connecticut

Martha M. Eibl, MD
Professor of Immunology, University of Vienna, Consultant Immunologist of the Pediatric Hospitals of the City of Vienna, Austria

Q. G. Eichbaum, PhD
Postdoctoral Fellow, Division of Hematology and Infectious Diseases, Children's Hospital, Boston, Massachusetts

R.A.B. Ezekowitz, MBChB, DPhil
Charles Wilder Professor of Pediatrics, Harvard Medical School; Chief of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts

James L.M. Ferrara, MD
Associate Professor of Pediatrics, Harvard Medical School; Attending Physician in Pediatric Oncology and Bone Marrow Transplantation, Dana Farber Cancer Institute, Children's Hospital, Brigham and Women's Hospital, Boston, Massachusetts

A.W. Ford-Hutchinson, PhD
Vice President of Research, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec

Barbara S. Fox, PhD
Vice President of Discovery Research, ImmunoLogic Pharmaceutical Corporation, Waltham, Massachusetts

David A. Fruman, PhD
Postdoctoral Fellow, Division of Pediatric Oncology, Dana Farber Cancer Institute, Boston, Massachusetts

Stephen T. Furlong, PhD
Assistant Professor of Medicine, Harvard Medical School; Associate Immunobiologist, Brigham and Women's Hospital, Boston, Massachusetts

Raif S. Geha, MD
Prince Turki bin Abdul Aziz Professor of Pediatrics, Harvard Medical School; Chief of Immunology, Children's Hospital, Boston, Massachusetts

Daryl K. Granner, MD
Professor and Chairman of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee

Philip D. Greenberg, MD
Professor of Medicine and Immunology, University of Washington School of Medicine; Head, Program in Immunology, Fred Hutchinson Cancer Research Center, Seattle, Washington

Julia L. Greenstein, PhD
BioTransplant, Inc., Charlestown, Massachusetts

S.V. Griffin, MA, MRCP
Honorary Registrar, Department of Medicine, Cambridge University Medical School, Addenbrooke's Hospital, Cambridge, United Kingdom

Robert Gristwood, BSc, PhD
Head of Biology Research and Development, Chiroscience Limited, Cambridge, United Kingdom

Jerome E. Groopman, MD
Professor of Medicine, Harvard Medical School; Chief of Hematology/Oncology, New England Deaconess Hospital, Boston, Massachusetts

David A. Hafler, MD
Associate Professor of Neurology, Harvard Medical School; Physician in Neurology, Brigham and Women's Hospital, Boston, Massachusetts

Gerald A. Higgs, PhD
Head of Discovery Projects, Celltech Therapeutics Limited, Berkshire, United Kingdom

Stephen T. Holgate, MD, DSc, FRCP
MRC Clinical Professor of Immunopharmacology, Southampton University Medical School; Honorary Consultant Physician, Southampton General Hospital, Southampton, Hampshire, United Kingdom

Luca Inverardi, MD
Associate Professor of Medicine, Diabetes Research Institute, University of Miami School of Medicine, Miami, Florida

Judith R. Jaeger, PhD
Director of Clinical Research/Immunology, Clinical Program Director/Cell Adhesion, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut

Elizabeth M. Jaffee, MD
Assistant Professor of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Roger L. Jenkins, MD, FACS
Associate Clinical Professor of Surgery, Harvard Medical School; Director of Hepatology and Liver Transplantation, New England Deaconess Hospital, Boston, Massachusetts

Srinivas V. Kaveri, DVM, MD
Charge de Recherche CNRS, Hôpital Broussais, Paris, France

Michel D. Kazatchkine, MD
Professor of Immunology, Université Pierre et Marie Curie; Head, Clinical Immunology, Hôpital Broussais, Paris, France

Ralph A. Kelly, MD
Assistant Professor of Medicine, Harvard Medical School; Associate Physician, Brigham and Women's Hospital, Boston, Massachusetts

Lloyd B. Klickstein, MD, PhD
Instructor in Medicine, Harvard Medical School; Department of Rheumatology, Brigham and Women's Hospital, Boston, Massachusetts

M. Thirumala Krishna, MBBS, MRCP (UK)
Clinical Research Fellow, University Medicine, University of Southampton; Honorary Registrar, Department of Medicine, Southampton General Hospital, Southampton, United Kingdom

Laura R. Lark, PhD
Postdoctoral Fellow, Department of Microbiology, University of Texas Southwestern Medical Center at Dallas, Texas

Jeffrey A. Ledbetter, PhD
Autoimmunity Department Director, Bristol-Myers-Squibb Pharmaceutical Research Institute, Seattle, Washington

Jeffrey M. Leiden, MD, PhD
Professor of Medicine, Division of Biological Sciences, University of Chicago Pritzker School of Medicine; Chief of Cardiology, University of Chicago Hospitals, Chicago, Illinois

Norman L. Letvin, MD
Professor of Medicine, Harvard Medical School; Chief of Viral Pathogenesis, Beth Israel Hospital, Boston, Massachusetts

Peter S. Linsley, PhD
Senior Research Fellow, Bristol-Myers-Squibb Pharmaceutical Research Institute, Seattle, Washington

C.M. Lockwood, FRCP, MRCPath
Wellcome Reader in the School of Medicine, University of Cambridge; Honorary Consultant Physician, Cambridge, United Kingdom

Richard P. MacDermott, MD
Lecturer of Medicine, Harvard Medical School, Boston; Chief of Gastroenterology Section, Lahey Hitchcock Medical Center, Burlington, Massachusetts

Amadeo Marcos-Alvarez, MD
Visiting Fellow, Hepatology Surgery and Liver Transplantation, New England Deaconess Hospital, Boston, Massachusetts

Kenneth L. Melmon, MD
Professor of Medicine, Associate Dean for Postgraduate Medical Education, Stanford University School of Medicine, Stanford, California

Steven J. Mentzer, MD
Associate Professor, Harvard Medical School; Director of Lung Transplant Program, Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts

Francis D. Moore, Jr., MD
Associate Professor of Surgery, Harvard Medical School; Attending Surgeon, Brigham and Women's Hospital, Boston, Massachusetts

David G. Nathan, MD
Robert A. Stranahan Professor, Harvard Medical School; Physician-in-Chief, Children's Hospital, Boston, Massachusetts

Jean Nichols, PhD
Seragen, Inc., Hopkinton, Massachusetts

Christopher F. Nicodemus, MD
Clinical Instructor of Rheumatology and Immunology, Brigham and Women's Hospital, Boston; Vice President of Medical Affairs, ImmunoLogic Pharmaceutical Corporation, Waltham, Massachusetts

Robert B. Nussenblatt, MD
Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, Maryland

Drew M. Pardoll, MD
Associate Professor of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland

Victor L. Perez, MD
Research Fellow, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts

William P. Peters, MD, PhD
Director of Bone Marrow Transplant Center, Duke University Medical Center, Durham, North Carolina

William P. Petros, PharmD
Clinical Associate of Medicine, Duke University Medical Center, Durham, North Carolina

Alberto Pugliese
Research Assistant Professor of Medicine, Diabetes Research Institute, University of Miami School of Medicine, Miami, Florida

C.D. Pusey, BA, MB, MA, MSc, FRCP
Professor of Renal Medicine, Royal Postgraduate Medical School; Honorary Consultant Physician, Hammersmith Hospital, London, United Kingdom

Dale G. Renlund, MD
Professor of Medicine, University of Utah School of Medicine; Medical Director, Utah Transplantation Affiliated Hospitals Cardiac Transplant Program, Salt Lake City, Utah

Camillo Ricordi, MD
Professor of Surgery, University of Miami School of Medicine; Chief of Cellular Transplantation; Co-Director of Diabetes Research Institute, Miami, Florida

Stanley R. Riddell
Associate Professor, University of Washington School of Medicine; Associate Member, Fred Hutchinson Cancer Research Center, Seattle, Washington

I.W. Rodger, PhD
Senior Director of Pharmacology, Merck Frosst Centre for Therapeutic Research, Kirkland, Quebec

Robert Rothlein, PhD
Section Leader, Research and Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut

Robert H. Rubin, MD, FACP, FCCP
Osborne Chair in Health Sciences, Harvard–MIT Division of Health Sciences and Technology, Cambridge; Chief of Transplantation Infectious Diseases, Massachusetts General Hospital, Boston, Massachusetts

Tomasz Sablinski, MD, PhD
Instructor of Surgery, Harvard Medical School; Assistant in Immunology (Surgery), Massachusetts General Hospital, Boston, Massachusetts

David H. Sachs, MD
Paul S. Russell/Warner-Lambert Professor of Surgery, Harvard Medical School; Director of Transplantation, Biology Research Center, Massachusetts General Hospital, Boston, Massachusetts

Michael E. Shapiro, MD
Chief of Transplantation, Department of Surgery, Beth Israel Hospital, Boston, Massachusetts

Colin A. Sieff, MB, BCh, FRCPath
Associate Professor of Pediatrics, Harvard Medical School; Attending Hematologist, Children's Hospital, Boston, Massachusetts

Kendall A. Smith, MD
Chief of Allergy and Immunology, Professor of Medicine, Cornell University Medical College; Attending Physician, The New York Hospital, New York, New York

Thomas W. Smith, MD
Professor of Medicine, Harvard Medical School; Chief of Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts

William L. Smith, PhD
Professor and Chairperson of Biochemistry, Michigan State University College of Human Medicine, Lansing, Michigan

Alfred D. Steinberg, MD
Principal Scientist, Mitre Corporation, McLean, Virginia

A. Christopher Stevens, MD
Instructor in Medicine, Harvard Medical School; Associate in Medicine, Division of Gastroenterology, Beth Israel Hospital, Boston, Massachusetts

Per-Erik Strömstedt, PhD
Postdoctoral Fellow, Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, Tennessee

David J. Sugarbaker, MD
Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts

Manikkam Suthanthiran, MD
Professor of Medicine, Biochemistry and Surgery, Chief of Nephrology, Cornell University Medical College; Chief of Transplantation Medicine and Extracorporeal Therapy, The New York Hospital, New York, New York

David O. Taylor, MD
Assistant Professor of Medicine, Division of Cardiology, University of Utah School of Medicine, Salt Lake City, Utah

Gerald R. Thrush, PhD
Instructor of Microbiology, University of Texas Southwestern Medical Center at Dallas, Texas

Stephen A. Tilles, MD
Assistant Professor of Medicine, Division of Allergy and Clinical Immunology, Oregon Health Sciences University School of Medicine; Director of Asthma and Allergy Clinic, Oregon Health Sciences Center, Portland, Oregon

Nina E. Tolkoff-Rubin, MD
Associate Professor of Medicine, Harvard Medical School; Director of Hemodialysis and CAPD Units, Massachusetts General Hospital, Boston, Massachusetts

David E. Trentham, MD
Associate Professor of Medicine, Harvard Medical School; Chief of Division of Rheumatology, Beth Israel Hospital, Boston, Massachusetts

Giorgio Trinchieri, MD
Professor, Wistar Institute, Philadelphia, Pennsylvania

Ellen S. Vitetta, PhD
Professor of Microbiology, Director of Cancer Immunobiology Center, University of Texas Southwestern Medical Center at Dallas, Texas

E. Sally Ward, PhD
Assistant Professor of Microbiology and Cancer Immunobiology Center, University of Texas Southwestern Medical Center at Dallas, Texas

A. Thomas Waytes, MD, PhD
Clinical Assistant Professor of Internal Medicine, Wayne State University School of Medicine, Detroit; Medical Director, Immuno-U.S., Inc., Rochester; Medical Staff, Department of Medicine, Veterans Administration Medical Center, Allen Park, Michigan

Michael E. Weinblatt, MD
Associate Professor of Medicine, Harvard Medical School; Vice Chairman of Rheumatology, Brigham and Women's Hospital, Boston, Massachusetts

Howard L. Weiner, MD
Co-Director of Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts

Hermann M. Wolf, MD
Research Associate, Institute of Immunology, University of Vienna, Austria

Amy Crum Vander Woude, MD
Fellow in Hematology-Oncology, Harvard Medical School; Division of Hematology-Oncology, Brigham and Women's Hospital, Boston, Massachusetts

Preface

In the past several decades we have made monumental advances in our understanding of the workings of the immune system. The cellular constituents of the immune system have been identified, often through an appreciation of cell-specific surface protein markers. Often these "phenotypic markers" prove to represent proteins that provide critical cell-specific functional attributes. The precise identity and function of cell surface and secreted proteins have been studied exhaustively. The secreted factors, both preformed and newly synthesized, profoundly alter the microenvironment in which cell–cell and cell–stromal bilateral interactions occur. This line of inquiry has yielded detailed and perhaps unforeseen insights into the remarkable complexity of the immune system.

In very recent years, a more refined and exacting knowledge of the immune system has been garnered through a structure/function analysis of important immune system proteins, which increasingly reveal the role individual genes play in immune system recognition and the attendant responses.

It was natural to anticipate that conceptual breakthroughs in understanding the afferent and effect limbs of the immune response would rapidly translate from the bench to the bedside. In fact, the advances at the bench were not closely followed by dramatic changes in the clinic. Until recently most therapeutic advances were derived from bold and inspired empiricism or even serendipity, rather than basic conceptual understandings. The initial clinical deployment of corticosteroids, antimetabolites, radiomimetics, and organ transplantation preceded the definition of the distinctive cell-specific surface phenotypic markers of T cells and B cells and of stromal and hematopoietic cytokines. Nonetheless, a large community of immunologist physician/scientists (including the editors) fervently believed that given a solid understanding of the basic workings of the immune system, new therapies would follow through conceptual design. We believe that we are now at this stage—"our time" has come. The pace at which new and increasingly effective therapies have entered the clinic has quickened. It would appear that sophisticated molecular approaches are responsible. This perception has driven our efforts to produce *Therapeutic Immunology.* Our library shelves are well stacked with excellent works concerning basic immunology, disease-oriented clinical immunology, and organ-directed immunopathology. Less attention has been paid to the therapies themselves. We hope this book will provide a framework for understanding the mechanism by which therapies—old, recent, incipient or embryonic, and anticipated—manipulate the immune system to benefit the patient.

The task of organizing and editing a text with multiple authors in order to address the range of therapeutic interventions for diseases of immunologic origin is complex and intimidating. We deeply appreciate the support that we have received from the staff of our individual offices. We thank Victoria Reeders, Acquisitions Editor; Kathleen Broderick, Development Editor; and Karen Feeney, Book Production Manager, at Blackwell Science, for their support and wise counsel. We are most appreciative of Ms. Arlene Stolper Simon for the countless hours she spent editing various chapters as well as the index, and in reviewing proofs. Finally, we are particularly appreciative of the prodigious effort that the authors provided in order to share their knowledge with our readers, and to initiate this volume that directs our attention to a key aspect of immunologic diseases, namely their management.

K.F.A.
S.J.B.
F.S.R.
T.B.S.

Contents

I

INTRODUCTION

CHAPTER ONE

The Immune System

Baruj Benacerraf

The immune system directs defense mechanisms to foreign, harmful invaders while preserving autologous cells and tissues from injury. The defense mechanisms include neutralization of toxins by antibody, phagocytosis of opsonized microorganisms by macrophages and polymorphonuclear leukocytes, triggering of inflammatory phenomena through the release of active mediators from T cells and mast cells, lysis of opsonized cells and bacteria by molecules of the complement system, and killing and lysis of target cells by specific killer T cells and natural killer (NK) cells.

Nature had to resolve major problems to construct an efficient immune system, including 1) how to package in a single antibody or T-cell receptor the structure to mediate defense mechanisms, such as phagocytosis or lysis, as well as the specificity necessary to recognize and react with the universe of foreign molecules; 2) how to produce rapidly on initial or repeated contacts antibody molecules capable of reacting with up to a million or more foreign molecules that the organism had never encountered before; and 3) how to protect autologous cells and tissues against such a powerful and all-encompassing recognition system, which must learn how to differentiate self from nonself.

Two distinct immunologic systems with different recognition characteristics have evolved to mediate immune phenomena.

1. The antibodies or immunoglobulin molecules, which react specifically with antigens in body fluids and which are produced by B lymphocytes and plasma cells for this purpose.

2. The immune cells or T (thymus-derived) lymphocytes, which recognize and react with antigen on the surface of live, autologous, or foreign cells.

This latter system is also concerned with regulation of the immune system through the synthesis and secretion of lymphokines, and with the fundamental responsibility of distinguishing self from nonself.

These two systems differ in their immunologic specificities. Antibodies bind to determinants contributed by the native conformation of the antigen.

T-cell receptors are specific for internal sequential determinants of protein antigens, which are generated inside cells by a mechanism generally referred to as "antigen processing" and which involve the denaturation and unfolding of the antigen molecule by enzymatic action. In addition, most T-cell receptors are restricted to recognize these peptides on the surface of cells only when associated with transplantation antigens of the major histocompatibility complex (MHC), a process referred to as "presentation."

Because optimal immune responses to protein antigens, whether cellular or humoral, require the involvement of antigen-specific helper T cells, the phenomena of antigen processing and presentation are fundamental requirements to initiate immune responses.

MAJOR HISTOCOMPATIBILITY COMPLEX

There are two classes of MHC molecules. Class I MHC molecules, which are expressed on the surface membrane of all cells, are destined to present peptides generated in the cytosol from internally synthesized proteins, displaying in this manner the identity of the cell to the immune system. In contrast, class II MHC molecules, which are expressed only on antigen-presenting cells, macrophages, dendritic cells, and B cells, are specialized in the presentation of peptides generated from foreign antigens that pass through lysosomes and endosomes (Fig 1.1). The structure of

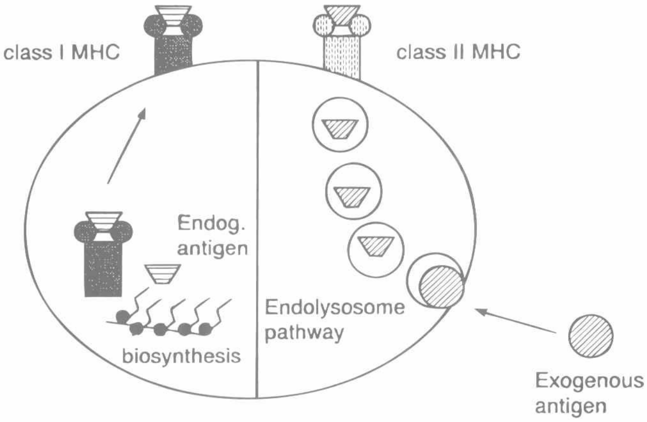

FIGURE 1.1 *Schematic representation of an antigen-presenting cell engaged in the processing of 1) foreign antigens through the phagolysosome pathway to generate the immunogenic peptides bound to class II major histocompatibility complex (MHC) molecules and 2) internal proteins processed in the cytoplasm to generate peptides bound by class I MHC molecules. The complexes of peptides and MHC molecules are then expressed on the cell membrane. (Endog. = endogenous.)*

the two classes of MHC molecules differs slightly in a manner related to their distinctive functions as well as to the optimal size of the peptides they bind.

The commitment of T lymphocytes to recognize foreign antigens only when associated with MHC molecules occurs in the thymus where the immune system learns to differentiate self from nonself. In the thymus, T cells specific for autologous MHC molecules are initially stimulated to expand clonally. Then those cells specific for self MHC molecules associated with autologous peptides are deleted. Only cells remain with a high affinity for self MHC molecules plus foreign peptides or for alloantigens of the MHC of the species.

Another most important aspect of MHC molecules is their considerable polymorphism, which is why we reject tissue from each other. The existence of a highly polymorphic MHC complex and the commitment of T cells to recognize antigen only in the context of autologous MHC molecules has had two important consequences: 1) the linkage of certain immunologic diseases to select human leukocyte antigens, the human MHC and 2) the survival of the species against any conceivable attack by potentially immunogenic infectious agents. Certain individuals would always be expected to be immunologically better adapted to survive the challenge.

Cells of the immune system

The cells of the immune system are, first, those concerned with antigen processing and presentation, macrophages, dendritic cells, and Langerhans' cells. These cells are not immunologically specific.

The functions of macrophages are phagocytosis, digestion, and destruction of phagocytized microorganisms, especially when macrophages are activated; antigen processing and presentation to T cells in the context of class II histocompatibility antigens; and synthesis and secretion of inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).

Interleukin-1 is produced when the cell is activated by T cells, antigen-antibody (Ag-Ab) complexes, or bacterial products. Interleukin-1 is an important inflammatory molecule. It induces fever and the synthesis of important defense molecules such as complement components C2, C3, C4, and C5, factor B, interferon, and important enzymes.

Macrophages are, therefore, critically important both as the initiators of immune responses by presenting antigen appropriately to T cells and as the effectors of important defense mechanisms.

Second, there are immunologically specific cells, or lymphocytes. Lymphocytes can be subdivided into two classes: B lymphocytes and T lymphocytes. B lymphocytes synthesize immunoglobulins and express them as receptors for soluble intact antigens. T lymphocytes consist of regulating cells, helper and suppressor T cells, and effector T cells, such as cytolytic T cells (CTLs), which destroy target cells bearing antigens for which they are specific. T cells recognize antigen on the surface of other cells, especially macrophages and dendritic cells. As stated earlier, T cells have receptors for gene products of the MHC. They recognize and react with foreign antigens only when presented as peptides bound to autologous MHC molecules.

The major markers and distribution of human T cells are listed in Table 1.1.

Third, there are plasma cells, which derive from activated B lymphocytes. They do not divide. They lose surface immunoglobulin during differentiation, but actively secrete monoclonal antibody of unique specificity and a single isotype. They are short-lived cells unless malignant, as in myelomas, and specialize as antibody producers and secretors.

Fourth, there are NK cells, which are not immunologically specific. Natural killer cells have strong Fc receptors for immunoglobulin G (IgG); they can kill antibody-coated nucleated cells. Natural killer cells can also bind to and kill some tumor or virally infected cells in the absence of antibody.

Other important effector cells activated by immune mediators are 1) the polymorphonuclear leukocytes, which are especially effective against antibody-coated gram-positive pyogenic organisms; 2) the eosinophils, which are especially effective in immunity against parasitic infections; and 3) the mast cells, which release

Table 1.1. Major Markers and Distribution of Human T Cells

SURFACE MOLECULE	DISTRIBUTION
CD3	Mature thymocytes All peripheral T cells
CD4	Majority of thymocytes 60% of peripheral T cells All helper T cells Restricted to class II MHC molecules
CD8	Majority of thymocytes 30% of peripheral T cells 100% of suppressor and cytolytic T cells Restricted to class I MHC molecules

MHC = major histocompatibility complex.

Table 1.2. Comparative Properties of B, T, and NK Cells

VARIABLE	B CELLS	NK CELLS	T CELLS
Amount in blood	5–10%	5–10%	80–90%
Surface IgM, IgD	++++	–	–
Surface IgG	Very few	+	–
Binding of monomeric Ig	–	+	–
Stability of surface Ig	Stable	Labile	–

Ig = immunoglobulin; NK = natural killer.

vasoactive amines when activated by IgE antibody and antigen.

Humoral immunity

After the injection of antigen, several days elapse before specific antibodies can be detected in the serum. The serum level of these antibodies, which belong to the IgM class, rises to a peak in a few days and then declines. This constitutes the primary antibody response.

When weeks or months later antigen is again injected, a hastened secondary or anamnestic antibody response occurs; antibody rises to a much higher serum level, and declines more slowly after the peak. Moreover, the antibodies belong to the IgG class rather than the IgM class. There has been a switch in antibody class. Both primary and secondary antibody responses are very heterogeneous, in regard to both specificity and affinity of the antibodies. However, the secondary response antibodies have a much greater affinity for the antigen than the primary response antibodies. Thereby, the immune system displays an ability to learn how to produce better and more specific antibodies.

Primary and secondary responses reflect the clonal expansion of B lymphocytes bearing immunoglobulin (antibody) receptors uniquely specific for the antigen and their differentiation into plasma cells that are capable of producing and secreting large amounts of antibody. This antibody is of identical specificity as the antibody receptor on the original precursor B lymphocyte that was selected by the interaction with the antigen. There are more than a million distinct B lymphocytes bearing different antibodies for the antigens to select from in a single individual.

Clonal selection theory of Burnet

To explain the great diversity of antibodies capable of reacting with the enormous numbers of antigens in our environment, Burnet proposed that genetic mechanisms exist to code for and produce antibodies of widely different specificities, but that antibody-producing cells are clonally committed during differentiation to produce a single homogeneous antibody of unique specificity—a monoclonal antibody.

Furthermore, this process operates at random, so that an enormous variety of monoclonal antibodies are produced previous to the introduction of any antigen, each antibody by a different clone. The antigen, in the course of immunization, selects specific lymphocyte clones by interacting with their immunoglobulin receptors and activates them to replicate and expand the population of antigen-stimulated clones. The differentiation of the B cells then proceeds to antibody-secreting plasma cells or memory cells. Burnet's theory has been verified to be absolutely correct in every aspect.

A most useful, practical application of the clonal selection theory of Burnet is the development, many years later, by Kohler and Milstein of the monoclonal antibody technique, which has received widespread application in biology and medicine.

Significance of immunologic specificity

The specificity of antigen-antibody reactions is based on the spatial complementarity of the antibody-combining site with the antigen determinant.