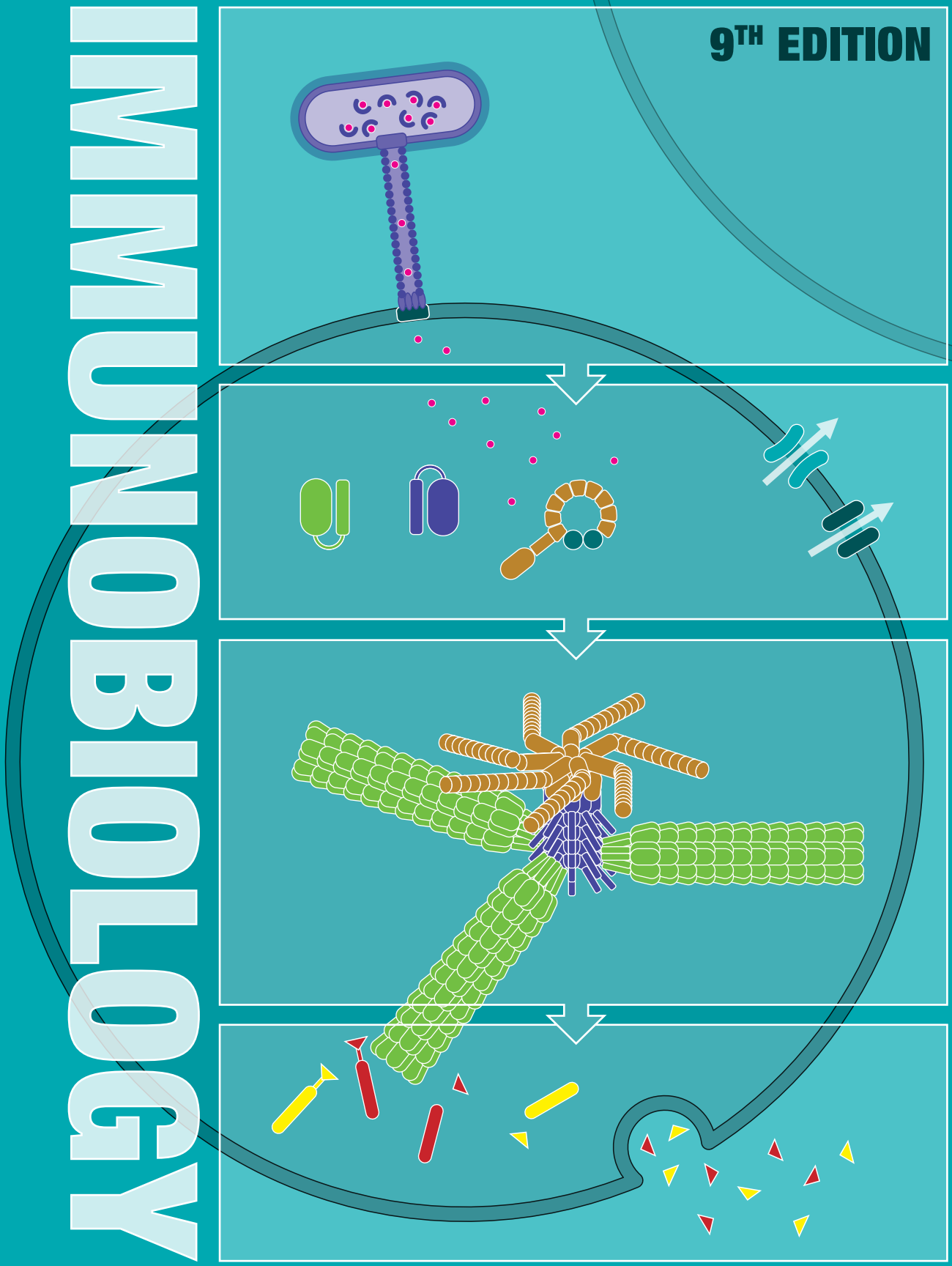
JANEWAY'S

IMMUNOBIOLOGY

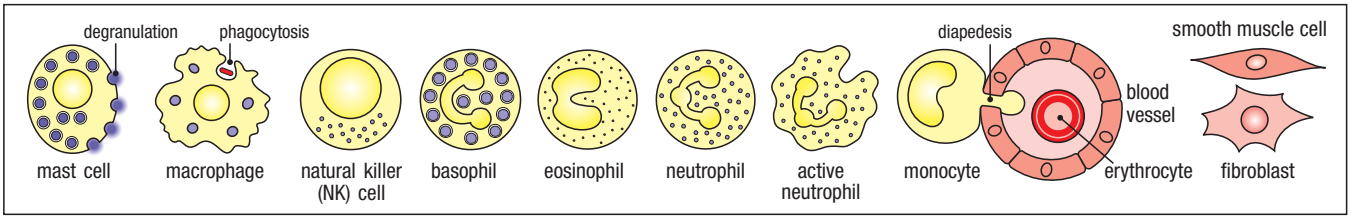
9TH EDITION

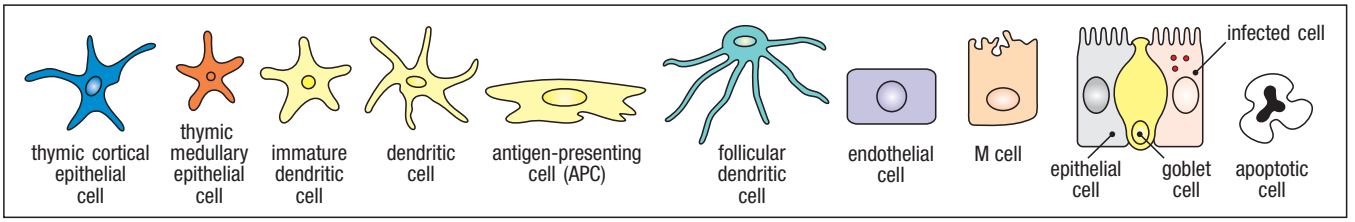


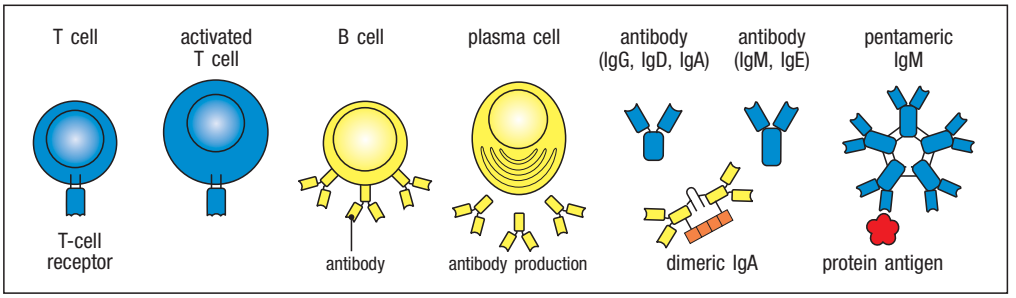
KENNETH MURPHY & CASEY WEAVER

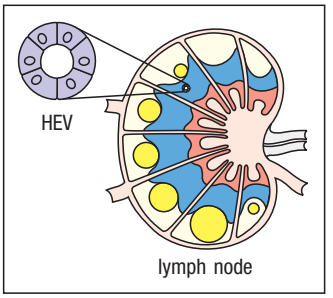
GS
Garland Science

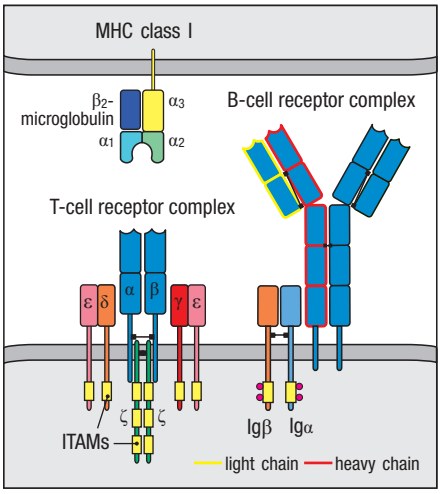
Icons used throughout the book

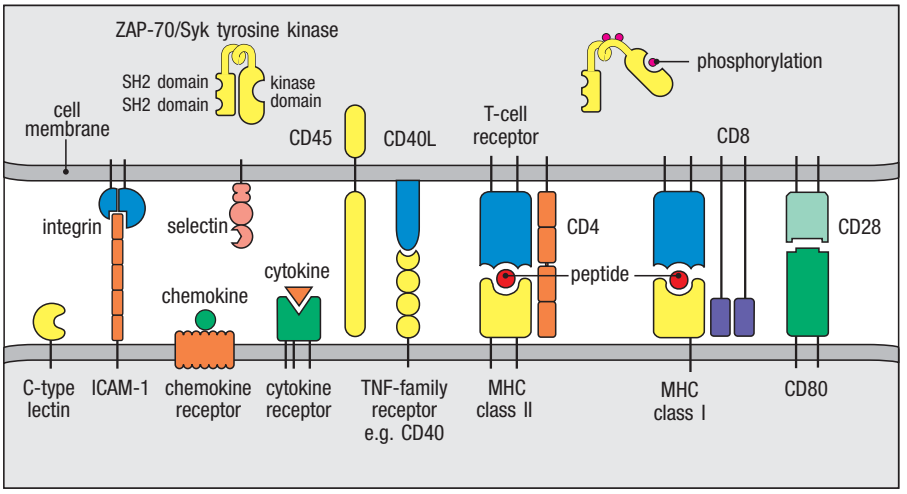


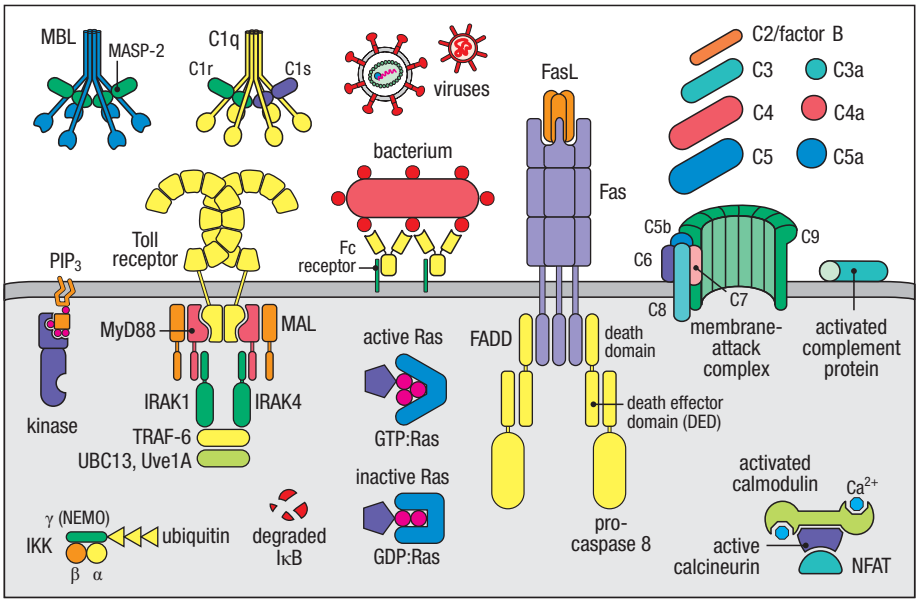


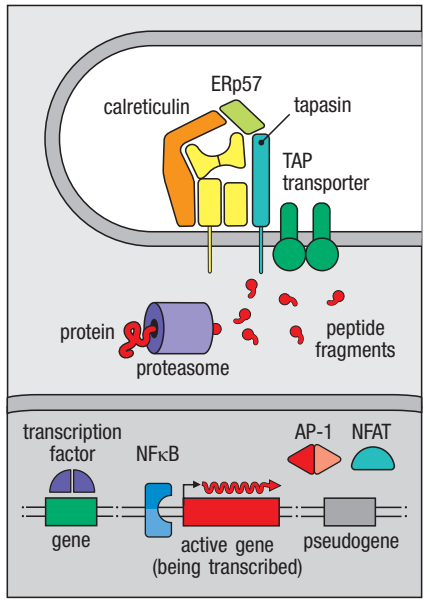












JANEWAY'S

IMMUNO BIOLOGY

9TH EDITION

This page intentionally left blank
to match pagination of print book

JANEWAY'S IMMUNO BIOLOGY

9TH EDITION

Kenneth Murphy
Washington University School of Medicine, St. Louis

Casey Weaver
University of Alabama at Birmingham, School of Medicine

With contributions by:
Allan Mowat
University of Glasgow

Leslie Berg
University of Massachusetts Medical School

David Chaplin
University of Alabama at Birmingham, School of Medicine

With acknowledgment to:
Charles A. Janeway Jr.

Paul Travers
MRC Centre for Regenerative Medicine, Edinburgh

Mark Walport

Garland Science
Taylor & Francis Group
NEW YORK AND LONDON

Vice President: Denise Schanck
Development Editor: Monica Toledo
Associate Editor: Allie Bochicchio
Assistant Editor: Claudia Acevedo-Quiñones
Text Editor: Elizabeth Zayetz
Production Editor: Deepa Divakaran
Typesetter: Deepa Divakaran and EJ Publishing Services
Illustrator and Design: Matthew McClements, Blink Studio, Ltd.
Copyeditor: Richard K. Mickey
Proofreader: Sally Livitt
Permission Coordinator: Sheri Gilbert
Indexer: Medical Indexing Ltd.

ISBN 978-0-8153-4505-3 978-0-8153-4551-0 (International Paperback)

Library of Congress Cataloging-in-Publication Data
Names: Murphy, Kenneth (Kenneth M.), author. | Weaver, Casey, author.
Title: Janeway's immunobiology / Kenneth Murphy, Casey Weaver ; with contributions by Allan Mowat, Leslie Berg, David Chaplin ; with acknowledgment to Charles A. Janeway Jr., Paul Travers, Mark Walport.
Other titles: Immunobiology
Description: 9th edition. | New York, NY : Garland Science/Taylor & Francis Group, LLC, [2016] | Includes bibliographical references and index.
Identifiers: LCCN 2015050960| ISBN 9780815345053 (pbk.) | ISBN 9780815345510 (pbk.-ROW) | ISBN 9780815345503 (looseleaf)
Subjects: | MESH: Immune System--physiology | Immune System--physiopathology | Immunity | Immunotherapy
Classification: LCC QR181 | NLM QW 504 | DDC 616.07/9--dc23
LC record available at http://lccn.loc.gov/2015050960

Published by Garland Science, Taylor & Francis Group, LLC, an informa business, 711 Third Avenue, New York, NY, 10017, USA, and 3 Park Square, Milton Park, Abingdon, OX14 4RN, UK.

Printed in the United States of America

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

Garland Science
Taylor & Francis Group
NEW YORK AND LONDON

Visit our web site at http://www.garlandscience.com

Preface

Janeway's Immunobiology is intended for undergraduate and graduate courses and for medical students, but its depth and scope also make it a useful resource for trainees and practicing immunologists. Its narrative takes the host's perspective in the struggle with the microbial world—a viewpoint distinguishing 'immunology' from 'microbiology'. Other facets of immunology, such as autoimmunity, immunodeficiencies, allergy, transplant rejection, and new aspects of cancer immunotherapy are also covered in depth, and a companion book, *Case Studies in Immunology*, provides clinical examples of immune-related disease. In *Immunobiology*, symbols in the margin indicate where the basic immunological concepts related to *Case Studies* are discussed.

The ninth edition retains the previous organization of five major sections and sixteen chapters, but reorganizes content to clarify presentation and eliminate redundancies, updating each chapter and adding over 100 new figures. The first section (Chapters 1–3) includes the latest developments in innate sensing mechanisms and covers new findings in innate lymphoid cells and the concept of 'immune effector modules' that is used throughout the rest of the book. Coverage of chemokine networks has been updated throughout (Chapters 3 and 11). The second section (Chapters 4–6) adds new findings for γ:δ T cell recognition and for the targeting of activation-induced cytidine deaminase (AID) class switch recombination. The third section (Chapters 7 and 8) is extensively updated and covers new material on integrin activation, cytoskeletal reorganization, and Akt and mTOR signaling. The fourth section enhances coverage of CD4 T cell subsets (Chapter 9), including follicular helper T cells that regulate switching and affinity maturation (Chapter 10). Chapter 11 now organizes innate and adaptive responses to pathogens around the effector module concept, and features new findings for tissue-resident memory T cells. Chapter 12 has been thoroughly updated to keep pace with the quickly advancing field of mucosal immunity. In the last section, coverage of primary and secondary immunodeficiencies has been reorganized and updated with an expanded treatment of immune evasion by pathogens and HIV/AIDS (Chapter 13). Updated and more detailed consideration of allergy and allergic diseases are presented in Chapter 14, and for autoimmunity and transplantation in Chapter 15. Finally, Chapter 16 has expanded coverage of new breakthroughs in cancer immunotherapy, including 'checkpoint blockade' and chimeric antigen receptor (CAR) T-cell therapies.

End-of-chapter review questions have been completely updated in the ninth edition, posed in a variety of formats, with answers available online. Appendix I: The Immunologist's Toolbox has undergone a comprehensive revitalization with the addition of many new techniques, including the CRISPR/Cas9 system and mass spectrometry/proteomics. Finally, a new Question Bank has been created to aid instructors in the development of exams that require the student to reflect upon and synthesize concepts in each chapter.

Once again, we benefited from the expert revision of Chapter 12 by Allan Mowat, and from contributions of two new contributors, David Chaplin and Leslie Berg. David's combined clinical and basic immunologic strengths greatly improved Chapter 14, and Leslie applied her signaling expertise to Chapters 7 and 8, and Appendix I, and her strength as an educator in creating the new Question Bank for instructors. Many people deserve special thanks. Gary Grajales wrote all end-of-chapter questions. New for this edition, we enlisted input from our most important audience and perhaps best critics—students of immunology-in-training who provided feedback on drafts of individual chapters, and Appendices II–IV. We benefitted from our thoughtful colleagues who reviewed the eighth edition. They are credited in the Acknowledgments section; we are indebted to them all.

We have the good fortune to work with an outstanding group at Garland Science. We thank Monica Toledo, our development editor, who coordinated the entire project, guiding us gently but firmly back on track throughout the process, with efficient assistance from Allie Bochicchio and Claudia Acevedo-Quiñones. We thank Denise Schanck, our publisher, who, as always, contributed her guidance, support, and wisdom. We thank Adam Sendroff, who is instrumental in relaying information about the book to immunologists around the world. As in all previous editions, Matt McClements has contributed his genius—and patience—re-interpreting authors' sketches into elegant illustrations. We warmly welcome our new text editor Elizabeth Zayetz, who stepped in for Eleanor Lawrence, our previous editor, and guiding light. The authors wish to thank their most important partners—Theresa and Cindy Lou—colleagues in life who have supported this effort with their generosity of time, their own editorial insights, and their infinite patience.

As temporary stewards of Charlie's legacy, *Janeway's Immunobiology*, we hope this ninth edition will continue to inspire—as he did—students to appreciate immunology's beautiful subtlety. We encourage all readers to share with us their views on where we have come up short, so the next edition will further approach the asymptote. Happy reading!

Kenneth Murphy
Casey Weaver

Resources for Instructors and Students

The teaching and learning resources for instructors and students are available online. The homework platform is available to interested instructors and their students. Instructors will need to set up student access in order to use the dashboard to track student progress on assignments. The instructor's resources on the Garland Science website are password-protected and available only to adopting instructors. The student resources on the Garland Science website are available to everyone. We hope these resources will enhance student learning and make it easier for instructors to prepare dynamic lectures and activities for the classroom.

Online Homework Platform with Instructor Dashboard

Instructors can obtain access to the online homework platform from their sales representative or by emailing science@garland.com. Students who wish to use the platform must purchase access and, if required for class, obtain a course link from their instructor.

The online homework platform is designed to improve and track student performance. It allows instructors to select homework assignments on specific topics and review the performance of the entire class, as well as individual students, via the instructor dashboard. The user-friendly system provides a convenient way to gauge student progress, and tailor classroom discussion, activities, and lectures to areas that require specific remediation. The features and assignments include:

- *Instructor Dashboard* displays data on student performance: such as responses to individual questions and length of time spent to complete assignments.
- *Tutorials* explain essential or difficult concepts and are integrated with a variety of questions that assess student engagement and mastery of the material.

The tutorials were created by Stacey A. Gorski, University of the Sciences in Philadelphia.

Instructor Resources

Instructor Resources are available on the Garland Science Instructor's Resource Site, located at www.garlandscience.com/instructors. The website provides access not only to the teaching resources for this book but also to all other Garland Science textbooks. Adopting instructors can obtain access to the site from their sales representative or by emailing science@garland.com.

Art of Janeway's Immunobiology, Ninth Edition

The images from the book are available in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. Figures are searchable by figure number, by figure name, or by keywords used in the figure legend from the book.

Figure-Integrated Lecture Outlines

The section headings, concept headings, and figures from the text have been integrated into PowerPoint® presentations. These will be useful for instructors who would like a head start creating lectures for their course. Like all of our PowerPoint® presentations, the lecture outlines can be customized. For example, the content of these presentations can be combined with videos and questions from the book or Question Bank, in order to create unique lectures that facilitate interactive learning.

Animations and Videos

The animations and videos that are available to students are also available on the Instructor's Website in two formats. The WMV-formatted movies are created for instructors who wish to use the movies in PowerPoint® presentations on Windows® computers; the QuickTime-formatted movies are for use in PowerPoint® for Apple computers or Keynote® presentations. The movies can easily be downloaded using the 'download' button on the movie preview page. The movies are related to specific chapters and callouts to the movies are highlighted in color throughout the textbook.

Question Bank

Written by Leslie Berg, University of Massachusetts Medical School, the Question Bank includes a variety of question formats: multiple choice, fill-in-the-blank, true-false, matching, essay, and challenging synthesis questions. There are approximately 30–40 questions per chapter, and a large number of the multiple-choice questions will be suitable for use with personal response systems (that is, clickers). The Question Bank provides a comprehensive sampling of questions that require the student to reflect upon and integrate information, and can be used either directly or as inspiration for instructors to write their own test questions.

Student Resources

The resources for students are available on the *Janeway's Immunobiology* Student Website, located at students.garlandscience.com.

Answers to End-of-Chapter Questions

Answers to the end-of-chapter questions are available to students for self-testing.

Animations and Videos

There are over 40 narrated movies, covering a range of immunology topics, which review key concepts and illuminate the experimental process.

Flashcards

Each chapter contains flashcards, built into the student website, that allow students to review key terms from the text.

Glossary

The comprehensive glossary of key terms from the book is online and can be searched or browsed.

Acknowledgments

We would like to thank the following experts who read parts or the whole of the eighth edition chapters and provided us with invaluable advice in developing this new edition.

Chapter 2: Teizo Fujita, Fukushima Prefectural General Hygiene Institute; Thad Stappenbeck, Washington University; Andrea J. Tenner, University of California, Irvine.

Chapter 3: Shizuo Akira, Osaka University; Mary Dinauer, Washington University in St. Louis; Lewis Lanier, University of California, San Francisco; Gabriel Nuñez, University of Michigan Medical School; David Raulet, University of California, Berkeley; Caetano Reis e Sousa, Cancer Research UK; Tadatsugu Taniguchi, University of Tokyo; Eric Vivier, Université de la Méditerranée Campus de Luminy; Wayne Yokoyama, Washington University.

Chapter 4: Chris Garcia, Stanford University; Ellis Reinherz, Harvard Medical School; Robyn Stanfield, The Scripps Research Institute; Ian Wilson, The Scripps Research Institute.

Chapter 5: Michael Lieber, University of Southern California Norris Cancer Center; Michel Neuberger, University of Cambridge; David Schatz, Yale University School of Medicine; Barry Sleckman, Washington University School of Medicine, St. Louis; Philip Tucker, University of Texas, Austin.

Chapter 6: Sebastian Amigorena, Institut Curie; Siamak Bahram, Centre de Recherche d'Immunologie et d'Hematologie; Peter Cresswell, Yale University School of Medicine; Mitchell Kronenberg, La Jolla Institute for Allergy & Immunology; Philippa Marrack, National Jewish Health; Hans-Georg Rammensee, University of Tuebingen, Germany; Jose Villadangos, University of Melbourne; Ian Wilson, The Scripps Research Institute.

Chapter 7: Oreste Acuto, University of Oxford; Francis Chan, University of Massachusetts Medical School; Vigo Heissmeyer, Helmholtz Center Munich; Steve Jameson, University of Minnesota; Pamela L. Schwartzberg, NIH; Art Weiss, University of California, San Francisco.

Chapter 8: Michael Cancro, University of Pennsylvania School of Medicine; Robert Carter, University of Alabama; Ian Crispe, University of Washington; Kris Hogquist, University of Minnesota; Eric Huseby, University of Massachusetts Medical School; Joonsoo Kang, University of Massachusetts Medical School; Ellen Robey, University of California, Berkeley; Nancy Ruddle, Yale University School of Medicine; Juan Carlos Zúñiga-Pflücker, University of Toronto.

Chapter 9: Francis Carbone, University of Melbourne; Shane Crotty, La Jolla Institute of Allergy and Immunology; Bill Heath, University of Melbourne, Victoria; Marc Jenkins, University of Minnesota; Alexander Rudensky, Memorial Sloan Kettering Cancer Center; Shimon Sakaguchi, Osaka University.

Chapter 10: Michael Cancro, University of Pennsylvania School of Medicine; Ann Haberman, Yale University School of Medicine; John Kearney, University of Alabama at Birmingham; Troy Randall, University of Alabama at Birmingham; Jeffrey Ravetch, Rockefeller University; Haley Tucker, University of Texas at Austin.

Chapter 11: Susan Kaech, Yale University School of Medicine; Stephen McSorley, University of California, Davis.

Chapter 12: Nadine Cerf-Bensussan, Université Paris Descartes-Sorbonne, Paris; Thomas MacDonald, Barts and London School of Medicine and Dentistry; Maria Rescigno, European Institute of Oncology; Michael Russell, University at Buffalo; Thad Stappenbeck, Washington University.

Chapter 13: Mary Collins, University College London; Paul Goepfert, University of Alabama at Birmingham; Paul Klenerman, University of Oxford; Warren Leonard, National Heart, Lung, and Blood Institute, NIH; Luigi Notarangelo, Boston Children's Hospital; Sarah Rowland-Jones, Oxford University; Harry Schroeder, University of Alabama at Birmingham.

Chapter 14: Cezmi A. Akdis, Swiss Institute of Allergy and Asthma Research; Larry Borish, University of Virginia Health System; Barry Kay, National Heart and Lung Institute; Harald Renz, Philipps University Marburg; Robert Schleimer, Northwestern University; Dale Umetsu, Genentech.

Chapter 15: Anne Davidson, The Feinstein Institute for Medical Research; Robert Fairchild, Cleveland Clinic; Rikard Holmdahl, Karolinska Institute; Fadi Lakkis, University of Pittsburgh; Ann Marshak-Rothstein, University of Massachusetts Medical School; Carson Moseley, University of Alabama at Birmingham; Luigi Notarangelo, Boston Children's Hospital; Noel Rose, Johns Hopkins Bloomberg School of Public Health; Warren Shlomchik, University of Pittsburgh School of Medicine; Laurence Turka, Harvard Medical School.

Chapter 16: James Crowe, Vanderbilt University; Glenn Dranoff, Dana–Farber Cancer Institute; Thomas Gajewski, University of Chicago; Carson Moseley, University of Alabama at Birmingham; Caetano Reis e Sousa, Cancer Research UK.

Appendix I: Lawrence Stern, University of Massachusetts Medical School.

We would also like to specially acknowledge and thank the students: Alina Petris, University of Manchester; Carlos Briseno, Washington University in St. Louis; Daniel DiToro, University of Alabama at Birmingham; Vivek Durai, Washington University in St. Louis; Wilfredo Garcia, Harvard University; Nichole Escalante, University of Toronto; Kate Jackson, University of Manchester; Isil Mirzanli, University of Manchester; Carson Moseley, University of Alabama at Birmingham; Daniel Silberger, University of Alabama at Birmingham; Jeffrey Singer, University of Alabama at Birmingham; Deepica Stephen, University of Manchester; Mayra Cruz Tleugabulova, University of Toronto.

This page intentionally left blank
to match pagination of print book

Contents

PART I AN INTRODUCTION TO IMMUNOBIOLOGY AND INNATE IMMUNITY

Chapter 1 Basic Concepts in Immunology 1
Chapter 2 Innate Immunity: The First Lines of Defense 37
Chapter 3 The Induced Response of Innate Immunity 77

PART II THE RECOGNITION OF ANTIGEN

Chapter 4 Antigen Recognition by B-cell and T-cell Receptors 139
Chapter 5 The Generation of Lymphocyte Antigen Receptors 173
Chapter 6 Antigen Presentation to T Lymphocytes 213

PART III THE DEVELOPMENT OF MATURE LYMPHOCYTE RECEPTOR REPERTOIRES

Chapter 7 Lymphocyte Receptor Signaling 257
Chapter 8 The Development of B and T Lymphocytes 295

PART IV THE ADAPTIVE IMMUNE RESPONSE

Chapter 9 T-cell-Mediated Immunity 345
Chapter 10 The Humoral Immune Response 399
Chapter 11 Integrated Dynamics of Innate and Adaptive Immunity 445
Chapter 12 The Mucosal Immune System 493

PART V THE IMMUNE SYSTEM IN HEALTH AND DISEASE

Chapter 13 Failures of Host Defense Mechanisms 533
Chapter 14 Allergy and Allergic Diseases 601
Chapter 15 Autoimmunity and Transplantation 643
Chapter 16 Manipulation of the Immune Response 701

APPENDICES

I The Immunologist's Toolbox 749
II CD antigens 791
III Cytokines and their Receptors 811
IV Chemokines and their Receptors 814

Biographies 816
Glossary 818
Index 855

Detailed Contents

PART I AN INTRODUCTION TO IMMUNO-BIOLOGY AND INNATE IMMUNITY

Chapter 1 Basic Concepts in Immunology 1

The origins of vertebrate immune cells. 2

Principles of innate immunity. 3

1-1 Commensal organisms cause little host damage while pathogens damage host tissues by a variety of mechanisms. 3

1-2 Anatomic and chemical barriers are the first defense against pathogens. 5

1-3 The immune system is activated by inflammatory inducers that indicate the presence of pathogens or tissue damage. 6

1-4 The myeloid lineage comprises most of the cells of the innate immune system. 7

1-5 Sensor cells express pattern recognition receptors that provide an initial discrimination between self and nonself. 8

1-6 Sensor cells induce an inflammatory response by producing mediators such as chemokines and cytokines. 9

1-7 Innate lymphocytes and natural killer cells are effector cells that share similarities with lymphoid lineages of the adaptive immune system. 11

Summary. 11

Principles of adaptive immunity. 11

1-8 The interaction of antigens with antigen receptors induces lymphocytes to acquire effector and memory activity. 12

1-9 Antibodies and T-cell receptors are composed of constant and variable regions that provide distinct functions. 13

1-10 Antibodies and T-cell receptors recognize antigens by fundamentally different mechanisms. 14

1-11 Antigen-receptor genes are assembled by somatic gene rearrangements of incomplete receptor gene segments. 15

1-12 Lymphocytes activated by antigen give rise to clones of antigen-specific effector cells that mediate adaptive immunity. 15

1-13 Lymphocytes with self-reactive receptors are normally eliminated during development or are functionally inactivated. 16

1-14 Lymphocytes mature in the bone marrow or the thymus and then congregate in lymphoid tissues throughout the body. 17

1-15 Adaptive immune responses are initiated by antigen and antigen-presenting cells in secondary lymphoid tissues. 18

1-16 Lymphocytes encounter and respond to antigen in the peripheral lymphoid organs. 19

1-17 Mucosal surfaces have specialized immune structures that orchestrate responses to environmental microbial encounters. 22

1-18 Lymphocytes activated by antigen proliferate in the peripheral lymphoid organs, generating effector cells and immunological memory. 23

Summary. 24

The effector mechanisms of immunity. 25

1-19 Innate immune responses can select from several effector modules to protect against different types of pathogens. 26

1-20 Antibodies protect against extracellular pathogens and their toxic products. 27

1-21 T cells orchestrate cell-mediated immunity and regulate B-cell responses to most antigens. 29

1-22 Inherited and acquired defects in the immune system result in increased susceptibility to infection. 31

1-23 Understanding adaptive immune responses is important for the control of allergies, autoimmune disease, and the rejection of transplanted organs. 32

1-24 Vaccination is the most effective means of controlling infectious diseases. 33

Summary. 34

Summary to Chapter 1. 34

Questions. 35

References. 36

Chapter 2 Innate Immunity: The First Lines of Defense 37

Anatomic barriers and initial chemical defenses. 38

2-1 Infectious diseases are caused by diverse living agents that replicate in their hosts. 38

2-2 Epithelial surfaces of the body provide the first barrier against infection. 42

2-3 Infectious agents must overcome innate host defenses to establish a focus of infection. 44

2-4 Epithelial cells and phagocytes produce several kinds of antimicrobial proteins. 45

Summary. 48

The complement system and innate immunity. 49

2-5 The complement system recognizes features of microbial surfaces and marks them for destruction by coating them with C3b. 50

2-6 The lectin pathway uses soluble receptors that recognize microbial surfaces to activate the complement cascade. 53

2-7 The classical pathway is initiated by activation of the C1 complex and is homologous to the lectin pathway. 56

2-8 Complement activation is largely confined to the surface on which it is initiated. 57

2-9 The alternative pathway is an amplification loop for C3b formation that is accelerated by properdin in the presence of pathogens. 58

2-10 Membrane and plasma proteins that regulate the formation and stability of C3 convertases determine the extent of complement activation. 60

2-11 Complement developed early in the evolution of multicellular organisms. 61
2-12 Surface-bound C3 convertase deposits large numbers of C3b fragments on pathogen surfaces and generates C5 convertase activity. 62
2-13 Ingestion of complement-tagged pathogens by phagocytes is mediated by receptors for the bound complement proteins. 63
2-14 The small fragments of some complement proteins initiate a local inflammatory response. 65
2-15 The terminal complement proteins polymerize to form pores in membranes that can kill certain pathogens. 66
2-16 Complement control proteins regulate all three pathways of complement activation and protect the host from their destructive effects. 67
2-17 Pathogens produce several types of proteins that can inhibit complement activation. 71
Summary. 72
Summary to Chapter 2. 73
Questions. 74
References. 75

Chapter 3 The Induced Responses of Innate Immunity 77

Pattern recognition by cells of the innate immune system. 77
3-1 After entering tissues, many microbes are recognized, ingested, and killed by phagocytes. 78
3-2 G-protein-coupled receptors on phagocytes link microbe recognition with increased efficiency of intracellular killing. 81
3-3 Microbial recognition and tissue damage initiate an inflammatory response. 85
3-4 Toll-like receptors represent an ancient pathogen-recognition system. 87
3-5 Mammalian Toll-like receptors are activated by many different pathogen-associated molecular patterns. 88
3-6 TLR-4 recognizes bacterial lipopolysaccharide in association with the host accessory proteins MD-2 and CD14. 92
3-7 TLRs activate NFκB, AP-1, and IRF transcription factors to induce the expression of inflammatory cytokines and type I interferons. 92
3-8 The NOD-like receptors are intracellular sensors of bacterial infection and cellular damage. 96
3-9 NLRP proteins react to infection or cellular damage through an inflammasome to induce cell death and inflammation. 98
3-10 The RIG-I-like receptors detect cytoplasmic viral RNAs and activate MAVS to induce type I interferon production and pro-inflammatory cytokines. 101
3-11 Cytosolic DNA sensors signal through STING to induce production of type I interferons. 103
3-12 Activation of innate sensors in macrophages and dendritic cells triggers changes in gene expression that have far-reaching effects on the immune response. 104
3-13 Toll signaling in *Drosophila* is downstream of a distinct set of pathogen-recognition molecules. 105
3-14 TLR and NOD genes have undergone extensive diversification in both invertebrates and some primitive chordates. 106
Summary. 106

Induced innate responses to infection. 107
3-15 Cytokines and their receptors fall into distinct families of structurally related proteins. 107
3-16 Cytokine receptors of the hematopoietin family are associated with the JAK family of tyrosine kinases, which activate STAT transcription factors. 109
3-17 Chemokines released by macrophages and dendritic cells recruit effector cells to sites of infection. 111
3-18 Cell-adhesion molecules control interactions between leukocytes and endothelial cells during an inflammatory response. 113
3-19 Neutrophils make up the first wave of cells that cross the blood vessel wall to enter an inflamed tissue. 116
3-20 TNF-α is an important cytokine that triggers local containment of infection but induces shock when released systemically. 118
3-21 Cytokines made by macrophages and dendritic cells induce a systemic reaction known as the acute-phase response. 118
3-22 Interferons induced by viral infection make several contributions to host defense. 121
3-23 Several types of innate lymphoid cells provide protection in early infection. 124
3-24 NK cells are activated by type I interferon and macrophage-derived cytokines. 125
3-25 NK cells express activating and inhibitory receptors to distinguish between healthy and infected cells. 126
3-26 NK-cell receptors belong to several structural families, the KIRs, KLRs, and NCRs. 128
3-27 NK cells express activating receptors that recognize ligands induced on infected cells or tumor cells. 130
Summary. 131
Summary to Chapter 3. 131
Questions. 132
References. 133

PART II THE RECOGNITION OF ANTIGEN

Chapter 4 Antigen Recognition by B-cell and T-cell Receptors 139

The structure of a typical antibody molecule. 140
4-1 IgG antibodies consist of four polypeptide chains. 141
4-2 Immunoglobulin heavy and light chains are composed of constant and variable regions. 142
4-3 The domains of an immunoglobulin molecule have similar structures. 142
4-4 The antibody molecule can readily be cleaved into functionally distinct fragments. 144
4-5 The hinge region of the immunoglobulin molecule allows flexibility in binding to multiple antigens. 145
Summary. 145

The interaction of the antibody molecule with specific antigen. 146
4-6 Localized regions of hypervariable sequence form the antigen-binding site. 146
4-7 Antibodies bind antigens via contacts in CDRs that are complementary to the size and shape of the antigen. 147
4-8 Antibodies bind to conformational shapes on the surfaces of antigens using a variety of noncovalent forces. 148
4-9 Antibody interaction with intact antigens is influenced by steric constraints. 150
4-10 Some species generate antibodies with alternative structures. 151
Summary. 152
Antigen recognition by T cells. 152
4-11 The TCRα:β heterodimer is very similar to a Fab fragment of immunoglobulin. 153
4-12 A T-cell receptor recognizes antigen in the form of a complex of a foreign peptide bound to an MHC molecule. 155
4-13 There are two classes of MHC molecules with distinct subunit compositions but similar three-dimensional structures. 155
4-14 Peptides are stably bound to MHC molecules, and also serve to stabilize the MHC molecule on the cell surface. 158
4-15 MHC class I molecules bind short peptides of 8–10 amino acids by both ends. 158
4-16 The length of the peptides bound by MHC class II molecules is not constrained. 160
4-17 The crystal structures of several peptide:MHC:T-cell receptor complexes show a similar orientation of the T-cell receptor over the peptide:MHC complex. 161
4-18 The CD4 and CD8 cell-surface proteins of T cells directly contact MHC molecules and are required to make an effective response to antigen. 163
4-19 The two classes of MHC molecules are expressed differentially on cells. 166
4-20 A distinct subset of T cells bears an alternative receptor made up of γ and δ chains. 166
Summary. 167
Summary to Chapter 4. 168
Questions. 169
References. 170
Chapter 5 The Generation of Lymphocyte Antigen Receptors 173
Primary immunoglobulin gene rearrangement. 174
5-1 Immunoglobulin genes are rearranged in the progenitors of antibody-producing cells. 174
5-2 Complete genes that encode a variable region are generated by the somatic recombination of separate gene segments. 175
5-3 Multiple contiguous V gene segments are present at each immunoglobulin locus. 176
5-4 Rearrangement of V, D, and J gene segments is guided by flanking DNA sequences. 178
5-5 The reaction that recombines V, D, and J gene segments involves both lymphocyte-specific and ubiquitous DNA-modifying enzymes. 179
5-6 The diversity of the immunoglobulin repertoire is generated by four main processes. 184
5-7 The multiple inherited gene segments are used in different combinations. 184
5-8 Variable addition and subtraction of nucleotides at the junctions between gene segments contributes to the diversity of the third hypervariable region. 185
Summary. 186
T-cell receptor gene rearrangement. 187
5-9 The T-cell receptor gene segments are arranged in a similar pattern to immunoglobulin gene segments and are rearranged by the same enzymes. 187
5-10 T-cell receptors concentrate diversity in the third hypervariable region. 189
5-11 γ:δ T-cell receptors are also generated by gene rearrangement. 190
Summary. 191
Structural variation in immunoglobulin constant regions. 191
5-12 Different classes of immunoglobulins are distinguished by the structure of their heavy-chain constant regions. 192
5-13 The constant region confers functional specialization on the antibody. 193
5-14 IgM and IgD are derived from the same pre-mRNA transcript and are both expressed on the surface of mature B cells. 194
5-15 Transmembrane and secreted forms of immunoglobulin are generated from alternative heavy-chain mRNA transcripts. 195
5-16 IgM and IgA can form polymers by interacting with the J chain. 197
Summary. 198
Evolution of the adaptive immune response. 198
5-17 Some invertebrates generate extensive diversity in a repertoire of immunoglobulin-like genes. 198
5-18 Agnathans possess an adaptive immune system that uses somatic gene rearrangement to diversify receptors built from LRR domains. 200
5-19 RAG-dependent adaptive immunity based on a diversified repertoire of immunoglobulin-like genes appeared abruptly in the cartilaginous fishes. 202
5-20 Different species generate immunoglobulin diversity in different ways. 203
5-21 Both α:β and γ:δ T-cell receptors are present in cartilaginous fishes. 206
5-22 MHC class I and class II molecules are also first found in the cartilaginous fishes. 206
Summary. 207
Summary to Chapter 5. 207
Questions. 208
References. 209
Chapter 6 Antigen Presentation to T Lymphocytes 213
The generation of α:β T-cell receptor ligands. 214
6-1 Antigen presentation functions both in arming effector T cells and in triggering their effector functions to attack pathogen-infected cells. 214

6-2 Peptides are generated from ubiquitinated proteins in the cytosol by the proteasome. 216
6-3 Peptides from the cytosol are transported by TAP into the endoplasmic reticulum and further processed before binding to MHC class I molecules. 218
6-4 Newly synthesized MHC class I molecules are retained in the endoplasmic reticulum until they bind a peptide. 219
6-5 Dendritic cells use cross-presentation to present exogenous proteins on MHC class I molecules to prime CD8 T cells. 222
6-6 Peptide:MHC class II complexes are generated in acidified endocytic vesicles from proteins obtained through endocytosis, phagocytosis, and autophagy. 223
6-7 The invariant chain directs newly synthesized MHC class II molecules to acidified intracellular vesicles. 225
6-8 The MHC class II-like molecules HLA-DM and HLA-DO regulate exchange of CLIP for other peptides. 226
6-9 Cessation of antigen processing occurs in dendritic cells after their activation through reduced expression of the MARCH-1 E3 ligase. 229
Summary. 230

The major histocompatibility complex and its function. 231
6-10 Many proteins involved in antigen processing and presentation are encoded by genes within the MHC. 231
6-11 The protein products of MHC class I and class II genes are highly polymorphic. 234
6-12 MHC polymorphism affects antigen recognition by T cells by influencing both peptide binding and the contacts between T-cell receptor and MHC molecule. 235
6-13 Alloreactive T cells recognizing nonself MHC molecules are very abundant. 239
6-14 Many T cells respond to superantigens. 240
6-15 MHC polymorphism extends the range of antigens to which the immune system can respond. 241
Summary. 242

Generation of ligands for unconventional T-cell subsets. 242
6-16 A variety of genes with specialized functions in immunity are also encoded in the MHC. 243
6-17 Specialized MHC class I molecules act as ligands for the activation and inhibition of NK cells and unconventional T-cell subsets. 245
6-18 Members of the CD1 family of MHC class I-like molecules present microbial lipids to invariant NKT cells. 246
6-19 The nonclassical MHC class I molecule MR1 presents microbial folate metabolites to MAIT cells. 248
6-20 γ:δ T cells can recognize a variety of diverse ligands. 249
Summary. 250
Summary to Chapter 6. 250
Questions. 251
References. 252

PART III THE DEVELOPMENT OF MATURE LYMPHOCYTE RECEPTOR REPERTOIRES

Chapter 7 Lymphocyte Receptor Signaling 257

General principles of signal transduction and propagation. 257
7-1 Transmembrane receptors convert extracellular signals into intracellular biochemical events. 258
7-2 Intracellular signal propagation is mediated by large multiprotein signaling complexes. 260
7-3 Small G proteins act as molecular switches in many different signaling pathways. 262
7-4 Signaling proteins are recruited to the membrane by a variety of mechanisms. 262
7-5 Post-translational modifications of proteins can both activate and inhibit signaling responses. 263
7-6 The activation of some receptors generates small-molecule second messengers. 264
Summary. 265

Antigen receptor signaling and lymphocyte activation. 265
7-7 Antigen receptors consist of variable antigen-binding chains associated with invariant chains that carry out the signaling function of the receptor. 266
7-8 Antigen recognition by the T-cell receptor and its co-receptors transduces a signal across the plasma membrane to initiate signaling. 267
7-9 Antigen recognition by the T-cell receptor and its co-receptors leads to phosphorylation of ITAMs by Src-family kinases, generating the first intracellular signal in a signaling cascade. 268
7-10 Phosphorylated ITAMs recruit and activate the tyrosine kinase ZAP-70. 270
7-11 ITAMs are also found in other receptors on leukocytes that signal for cell activation. 270
7-12 Activated ZAP-70 phosphorylates scaffold proteins and promotes PI 3-kinase activation. 271
7-13 Activated PLC-γ generates the second messengers diacylglycerol and inositol trisphosphate that lead to transcription factor activation. 272
7-14 Ca^{2+} entry activates the transcription factor NFAT. 273
7-15 Ras activation stimulates the mitogen-activated protein kinase (MAPK) relay and induces expression of the transcription factor AP-1. 274
7-16 Protein kinase C activates the transcription factors NFκB and AP-1. 276
7-17 PI 3-kinase activation upregulates cellular metabolic pathways via the serine/threonine kinase Akt. 277
7-18 T-cell receptor signaling leads to enhanced integrin-mediated cell adhesion. 278
7-19 T-cell receptor signaling induces cytoskeletal reorganization by activating the small GTPase Cdc42. 279
7-20 The logic of B-cell receptor signaling is similar to that of T-cell receptor signaling, but some of the signaling components are specific to B cells. 279
Summary. 282

Co-stimulatory and inhibitory receptors modulate antigen receptor signaling in T and B lymphocytes. 282
7-21 The cell-surface protein CD28 is a required co-stimulatory signaling receptor for naive T-cell activation. 283
7-22 Maximal activation of PLC-γ, which is important for transcription factor activation, requires a co-stimulatory signal induced by CD28. 284
7-23 TNF receptor superfamily members augment T-cell and B-cell activation. 284

7-24 Inhibitory receptors on lymphocytes downregulate immune responses by interfering with co-stimulatory signaling pathways. 286
7-25 Inhibitory receptors on lymphocytes downregulate immune responses by recruiting protein or lipid phosphatases. 287
Summary. 288
Summary to Chapter 7. 289
Questions. 290
References. 291

Chapter 8 The Development of B and T Lymphocytes 295

Development of B lymphocytes. 296
8-1 Lymphocytes derive from hematopoietic stem cells in the bone marrow. 297
8-2 B-cell development begins by rearrangement of the heavy-chain locus. 299
8-3 The pre-B-cell receptor tests for successful production of a complete heavy chain and signals for the transition from the pro-B cell to the pre-B cell stage. 302
8-4 Pre-B-cell receptor signaling inhibits further heavy-chain locus rearrangement and enforces allelic exclusion. 303
8-5 Pre-B cells rearrange the light-chain locus and express cell-surface immunoglobulin. 304
8-6 Immature B cells are tested for autoreactivity before they leave the bone marrow. 305
8-7 Lymphocytes that encounter sufficient quantities of self antigens for the first time in the periphery are eliminated or inactivated. 308
8-8 Immature B cells arriving in the spleen turn over rapidly and require cytokines and positive signals through the B-cell receptor for maturation and long-term survival. 309
8-9 B-1 B cells are an innate lymphocyte subset that arises early in development. 312
Summary. 313

Development of T lymphocytes. 315
8-10 T-cell progenitors originate in the bone marrow, but all the important events in their development occur in the thymus. 315
8-11 Commitment to the T-cell lineage occurs in the thymus following Notch signaling. 317
8-12 T-cell precursors proliferate extensively in the thymus, but most die there. 317
8-13 Successive stages in the development of thymocytes are marked by changes in cell-surface molecules. 319
8-14 Thymocytes at different developmental stages are found in distinct parts of the thymus. 321
8-15 T cells with α:β or γ:δ receptors arise from a common progenitor. 322
8-16 T cells expressing γ:δ T-cell receptors arise in two distinct phases during development. 322
8-17 Successful synthesis of a rearranged β chain allows the production of a pre-T-cell receptor that triggers cell proliferation and blocks further β-chain gene rearrangement. 324
8-18 T-cell α-chain genes undergo successive rearrangements until positive selection or cell death intervenes. 326
Summary. 328

Positive and negative selection of T cells. 328
8-19 Only thymocytes whose receptors interact with self peptide:self MHC complexes can survive and mature. 328
8-20 Positive selection acts on a repertoire of T-cell receptors with inherent specificity for MHC molecules. 329
8-21 Positive selection coordinates the expression of CD4 or CD8 with the specificity of the T-cell receptor and the potential effector functions of the T cell. 330
8-22 Thymic cortical epithelial cells mediate positive selection of developing thymocytes. 331
8-23 T cells that react strongly with ubiquitous self antigens are deleted in the thymus. 332
8-24 Negative selection is driven most efficiently by bone marrow-derived antigen-presenting cells. 334
8-25 The specificity and/or the strength of signals for negative and positive selection must differ. 334
8-26 Self-recognizing regulatory T cells and innate T cells develop in the thymus. 335
8-27 The final stage of T-cell maturation occurs in the thymic medulla. 336
8-28 T cells that encounter sufficient quantities of self antigens for the first time in the periphery are eliminated or inactivated. 336
Summary. 337
Summary to Chapter 8. 337
Questions. 339
References. 340

PART IV THE ADAPTIVE IMMUNE RESPONSE 345

Chapter 9 T-cell-Mediated Immunity 345

Development and function of secondary lymphoid organs—sites for the initiation of adaptive immune responses. 347
9-1 T and B lymphocytes are found in distinct locations in secondary lymphoid tissues. 347
9-2 The development of secondary lymphoid tissues is controlled by lymphoid tissue inducer cells and proteins of the tumor necrosis factor family. 349
9-3 T and B cells are partitioned into distinct regions of secondary lymphoid tissues by the actions of chemokines. 350
9-4 Naive T cells migrate through secondary lymphoid tissues, sampling peptide:MHC complexes on dendritic cells. 351
9-5 Lymphocyte entry into lymphoid tissues depends on chemokines and adhesion molecules. 352
9-6 Activation of integrins by chemokines is responsible for the entry of naive T cells into lymph nodes. 353
9-7 The exit of T cells from lymph nodes is controlled by a chemotactic lipid. 355
9-8 T-cell responses are initiated in secondary lymphoid organs by activated dendritic cells. 356
9-9 Dendritic cells process antigens from a wide array of pathogens. 358

9-10 Microbe-induced TLR signaling in tissue-resident dendritic cells induces their migration to lymphoid organs and enhances antigen processing. 361
9-11 Plasmacytoid dendritic cells produce abundant type I interferons and may act as helper cells for antigen presentation by conventional dendritic cells. 363
9-12 Macrophages are scavenger cells that can be induced by pathogens to present foreign antigens to naive T cells. 363
9-13 B cells are highly efficient at presenting antigens that bind to their surface immunoglobulin. 364
Summary. 366

Priming of naive T cells by pathogen-activated dendritic cells. 366
9-14 Cell-adhesion molecules mediate the initial interaction of naive T cells with antigen-presenting cells. 367
9-15 Antigen-presenting cells deliver multiple signals for the clonal expansion and differentiation of naive T cells. 368
9-16 CD28-dependent co-stimulation of activated T cells induces expression of interleukin-2 and the high-affinity IL-2 receptor. 368
9-17 Additional co-stimulatory pathways are involved in T-cell activation. 369
9-18 Proliferating T cells differentiate into effector T cells that do not require co-stimulation to act. 370
9-19 CD8 T cells can be activated in different ways to become cytotoxic effector cells. 372
9-20 CD4 T cells differentiate into several subsets of functionally different effector cells. 372
9-21 Cytokines induce the differentiation of naive CD4 T cells down distinct effector pathways. 375
9-22 CD4 T-cell subsets can cross-regulate each other's differentiation through the cytokines they produce. 377
9-23 Regulatory CD4 T cells are involved in controlling adaptive immune responses. 379
Summary. 380

General properties of effector T cells and their cytokines. 380
9-24 Effector T-cell interactions with target cells are initiated by antigen-nonspecific cell-adhesion molecules. 381
9-25 An immunological synapse forms between effector T cells and their targets to regulate signaling and to direct the release of effector molecules. 381
9-26 The effector functions of T cells are determined by the array of effector molecules that they produce. 383
9-27 Cytokines can act locally or at a distance. 383
9-28 T cells express several TNF-family cytokines as trimeric proteins that are usually associated with the cell surface. 386
Summary. 386

T-cell-mediated cytotoxicity. 387
9-29 Cytotoxic T cells induce target cells to undergo programmed cell death via extrinsic and intrinsic pathways of apoptosis. 387
9-30 The intrinsic pathway of apoptosis is mediated by the release of cytochrome *c* from mitochondria. 389
9-31 Cytotoxic effector proteins that trigger apoptosis are contained in the granules of CD8 cytotoxic T cells. 390
9-32 Cytotoxic T cells are selective serial killers of targets expressing a specific antigen. 391
9-33 Cytotoxic T cells also act by releasing cytokines. 392
Summary. 392
Summary to Chapter 9. 392
Questions. 393
References. 395

Chapter 10 The Humoral Immune Response 399

B-cell activation by antigen and helper T cells. 400
10-1 Activation of B cells by antigen involves signals from the B-cell receptor and either T_{FH} cells or microbial antigens. 400
10-2 Linked recognition of antigen by T cells and B cells promotes robust antibody responses. 402
10-3 B cells that encounter their antigens migrate toward the boundaries between B-cell and T-cell areas in secondary lymphoid tissues. 403
10-4 T cells express surface molecules and cytokines that activate B cells, which in turn promote T_{FH}-cell development. 406
10-5 Activated B cells differentiate into antibody-secreting plasmablasts and plasma cells. 406
10-6 The second phase of a primary B-cell immune response occurs when activated B cells migrate into follicles and proliferate to form germinal centers. 408
10-7 Germinal center B cells undergo V-region somatic hypermutation, and cells with mutations that improve affinity for antigen are selected. 410
10-8 Positive selection of germinal center B cells involves contact with T_{FH} cells and CD40 signaling. 412
10-9 Activation-induced cytidine deaminase (AID) introduces mutations into genes transcribed in B cells. 413
10-10 Mismatch and base-excision repair pathways contribute to somatic hypermutation following initiation by AID. 414
10-11 AID initiates class switching to allow the same assembled V_H exon to be associated with different C_H genes in the course of an immune response. 415
10-12 Cytokines made by T_{FH} cells direct the choice of isotype for class switching in T-dependent antibody responses. 418
10-13 B cells that survive the germinal center reaction eventually differentiate into either plasma cells or memory cells. 419
10-14 Some antigens do not require T-cell help to induce B-cell responses. 419
Summary. 421

The distributions and functions of immunoglobulin classes. 422
10-15 Antibodies of different classes operate in distinct places and have distinct effector functions. 423
10-16 Polymeric immunoglobulin receptor binds to the Fc regions of IgA and IgM and transports them across epithelial barriers. 425
10-17 The neonatal Fc receptor carries IgG across the placenta and prevents IgG excretion from the body. 426

10-18 High-affinity IgG and IgA antibodies can neutralize toxins and block the infectivity of viruses and bacteria. 426
10-19 Antibody:antigen complexes activate the classical pathway of complement by binding to C1q. 429
10-20 Complement receptors and Fc receptors both contribute to removal of immune complexes from the circulation. 430
Summary. 431
The destruction of antibody-coated pathogens via Fc receptors. 432
10-21 The Fc receptors of accessory cells are signaling receptors specific for immunoglobulins of different classes. 432
10-22 Fc receptors on phagocytes are activated by antibodies bound to the surface of pathogens and enable the phagocytes to ingest and destroy pathogens. 433
10-23 Fc receptors activate NK cells to destroy antibody-coated targets. 435
10-24 Mast cells and basophils bind IgE antibody via the high-affinity Fcε receptor. 436
10-25 IgE-mediated activation of accessory cells has an important role in resistance to parasite infection. 437
Summary. 438
Summary to Chapter 10. 439
Questions. 440
References. 441
Chapter 11 Integrated Dynamics of Innate and Adaptive Immunity 445
Integration of innate and adaptive immunity in response to specific types of pathogens. 446
11-1 The course of an infection can be divided into several distinct phases. 446
11-2 The effector mechanisms that are recruited to clear an infection depend on the infectious agent. 449
Summary. 452
Effector T cells augment the effector functions of innate immune cells. 452
11-3 Effector T cells are guided to specific tissues and sites of infection by changes in their expression of adhesion molecules and chemokine receptors. 453
11-4 Pathogen-specific effector T cells are enriched at sites of infection as adaptive immunity progresses. 457
11-5 T_H1 cells coordinate and amplify the host response to intracellular pathogens through classical activation of macrophages. 458
11-6 Activation of macrophages by T_H1 cells must be tightly regulated to avoid tissue damage. 460
11-7 Chronic activation of macrophages by T_H1 cells mediates the formation of granulomas to contain intracellular pathogens that cannot be cleared. 461
11-8 Defects in type 1 immunity reveal its important role in the elimination of intracellular pathogens. 461
11-9 T_H2 cells coordinate type 2 responses to expel intestinal helminths and repair tissue injury. 462
11-10 T_H17 cells coordinate type 3 responses to enhance the clearance of extracellular bacteria and fungi. 465
11-11 Differentiated effector T cells continue to respond to signals as they carry out their effector functions. 466
11-12 Effector T cells can be activated to release cytokines independently of antigen recognition. 467
11-13 Effector T cells demonstrate plasticity and cooperativity that enable adaptation during anti-pathogen responses. 468
11-14 Integration of cell- and antibody-mediated immunity is critical for protection against many types of pathogens. 469
11-15 Primary CD8 T-cell responses to pathogens can occur in the absence of CD4 T-cell help. 470
11-16 Resolution of an infection is accompanied by the death of most of the effector cells and the generation of memory cells. 471
Summary. 472
Immunological memory. 473
11-17 Immunological memory is long lived after infection or vaccination. 473
11-18 Memory B-cell responses are more rapid and have higher affinity for antigen compared with responses of naive B cells. 475
11-19 Memory B cells can reenter germinal centers and undergo additional somatic hypermutation and affinity maturation during secondary immune responses. 476
11-20 MHC tetramers identify memory T cells that persist at an increased frequency relative to their frequency as naive T cells. 477
11-21 Memory T cells arise from effector T cells that maintain sensitivity to IL-7 or IL-15. 478
11-22 Memory T cells are heterogeneous and include central memory, effector memory, and tissue-resident subsets. 480
11-23 CD4 T-cell help is required for CD8 T-cell memory and involves CD40 and IL-2 signaling. 482
11-24 In immune individuals, secondary and subsequent responses are mainly attributable to memory lymphocytes. 484
Summary. 485
Summary to Chapter 11. 486
Questions. 487
References. 488
Chapter 12 The Mucosal Immune System 493
The nature and structure of the mucosal immune system. 493
12-1 The mucosal immune system protects the internal surfaces of the body. 493
12-2 Cells of the mucosal immune system are located both in anatomically defined compartments and scattered throughout mucosal tissues. 496
12-3 The intestine has distinctive routes and mechanisms of antigen uptake. 499
12-4 The mucosal immune system contains large numbers of effector lymphocytes even in the absence of disease. 500
12-5 The circulation of lymphocytes within the mucosal immune system is controlled by tissue-specific adhesion molecules and chemokine receptors. 501

12-6 Priming of lymphocytes in one mucosal tissue may induce protective immunity at other mucosal surfaces. 502
12-7 Distinct populations of dendritic cells control mucosal immune responses. 503
12-8 Macrophages and dendritic cells have different roles in mucosal immune responses. 505
12-9 Antigen-presenting cells in the intestinal mucosa acquire antigen by a variety of routes. 505
12-10 Secretory IgA is the class of antibody associated with the mucosal immune system. 506
12-11 T-independent processes can contribute to IgA production in some species. 509
12-12 IgA deficiency is relatively common in humans but may be compensated for by secretory IgM. 509
12-13 The intestinal lamina propria contains antigen-experienced T cells and populations of unusual innate lymphoid cells. 510
12-14 The intestinal epithelium is a unique compartment of the immune system. 511
Summary. 514
The mucosal response to infection and regulation of mucosal immune responses. 514
12-15 Enteric pathogens cause a local inflammatory response and the development of protective immunity. 515
12-16 Pathogens induce adaptive immune responses when innate defenses have been breached. 518
12-17 Effector T-cell responses in the intestine protect the function of the epithelium. 518
12-18 The mucosal immune system must maintain tolerance to harmless foreign antigens. 519
12-19 The normal intestine contains large quantities of bacteria that are required for health. 520
12-20 Innate and adaptive immune systems control microbiota while preventing inflammation without compromising the ability to react to invaders. 521
12-21 The intestinal microbiota plays a major role in shaping intestinal and systemic immune function. 522
12-22 Full immune responses to commensal bacteria provoke intestinal disease. 524
Summary. 525
Summary to Chapter 12. 525
Questions. 526
References. 527

PART V THE IMMUNE SYSTEM IN HEALTH AND DISEASE

Chapter 13 Failures of Host Defense Mechanisms 533
Immunodeficiency diseases. 533
13-1 A history of repeated infections suggests a diagnosis of immunodeficiency. 534
13-2 Primary immunodeficiency diseases are caused by inherited gene defects. 534
13-3 Defects in T-cell development can result in severe combined immunodeficiencies. 535
13-4 SCID can also be due to defects in the purine salvage pathway. 538
13-5 Defects in antigen receptor gene rearrangement can result in SCID. 538
13-6 Defects in signaling from T-cell antigen receptors can cause severe immunodeficiency. 539
13-7 Genetic defects in thymic function that block T-cell development result in severe immunodeficiencies. 539
13-8 Defects in B-cell development result in deficiencies in antibody production that cause an inability to clear extracellular bacteria and some viruses. 541
13-9 Immune deficiencies can be caused by defects in B-cell or T-cell activation and function that lead to abnormal antibody responses. 543
13-10 Normal pathways for host defense against different infectious agents are pinpointed by genetic deficiencies of cytokine pathways central to type 1/T_H1 and type 3/T_H17 responses. 546
13-11 Inherited defects in the cytolytic pathway of lymphocytes can cause uncontrolled lympho-proliferation and inflammatory responses to viral infections. 548
13-12 X-linked lymphoproliferative syndrome is associated with fatal infection by Epstein–Barr virus and with the development of lymphomas. 550
13-13 Immunodeficiency is caused by inherited defects in the development of dendritic cells. 551
13-14 Defects in complement components and complement-regulatory proteins cause defective humoral immune function and tissue damage. 552
13-15 Defects in phagocytic cells permit widespread bacterial infections. 553
13-16 Mutations in the molecular regulators of inflammation can cause uncontrolled inflammatory responses that result in 'autoinflammatory disease.' 556
13-17 Hematopoietic stem cell transplantation or gene therapy can be useful to correct genetic defects. 557
13-18 Noninherited, secondary immunodeficiencies are major predisposing causes of infection and death. 558
Summary. 559
Evasion and subversion of immune defenses. 560
13-19 Extracellular bacterial pathogens have evolved different strategies to avoid detection by pattern recognition receptors and destruction by antibody, complement, and antimicrobial peptides. 560
13-20 Intracellular bacterial pathogens can evade the immune system by seeking shelter within phagocytes. 563
13-21 Immune evasion is also practiced by protozoan parasites. 565
13-22 RNA viruses use different mechanisms of antigenic variation to keep a step ahead of the adaptive immune system. 566
13-23 DNA viruses use multiple mechanisms to subvert NK-cell and CTL responses. 568
13-24 Some latent viruses persist *in vivo* by ceasing to replicate until immunity wanes. 571
Summary. 573
Acquired immune deficiency syndrome. 573
13-25 HIV is a retrovirus that establishes a chronic infection that slowly progresses to AIDS. 574

13-26 HIV infects and replicates within cells of the immune system. 576
13-27 Activated CD4 T cells are the major source of HIV replication. 578
13-28 There are several routes by which HIV is transmitted and establishes infection. 579
13-29 HIV variants with tropism for different co-receptors play different roles in transmission and progression of disease. 580
13-30 A genetic deficiency of the co-receptor CCR5 confers resistance to HIV infection. 582
13-31 An immune response controls but does not eliminate HIV. 583
13-32 Lymphoid tissue is the major reservoir of HIV infection. 585
13-33 Genetic variation in the host can alter the rate of disease progression. 585
13-34 The destruction of immune function as a result of HIV infection leads to increased susceptibility to opportunistic infection and eventually to death. 587
13-35 Drugs that block HIV replication lead to a rapid decrease in titer of infectious virus and an increase in CD4 T cells. 588
13-36 In the course of infection HIV accumulates many mutations, which can result in the outgrowth of drug-resistant variants. 590
13-37 Vaccination against HIV is an attractive solution but poses many difficulties. 591
13-38 Prevention and education are important in controlling the spread of HIV and AIDS. 592
Summary. 593
Summary to Chapter 13. 594
Questions. 594
References. 595

Chapter 14 Allergy and Allergic Diseases 601

IgE and IgE-mediated allergic diseases. 602
14-1 Sensitization involves class switching to IgE production on first contact with an allergen. 603
14-2 Although many types of antigens can cause allergic sensitization, proteases are common sensitizing agents. 605
14-3 Genetic factors contribute to the development of IgE-mediated allergic disease. 607
14-4 Environmental factors may interact with genetic susceptibility to cause allergic disease. 609
14-5 Regulatory T cells can control allergic responses. 611
Summary. 612

Effector mechanisms in IgE-mediated allergic reactions. 612
14-6 Most IgE is cell-bound and engages effector mechanisms of the immune system by pathways different from those of other antibody isotypes. 613
14-7 Mast cells reside in tissues and orchestrate allergic reactions. 613
14-8 Eosinophils and basophils cause inflammation and tissue damage in allergic reactions. 616
14-9 IgE-mediated allergic reactions have a rapid onset but can also lead to chronic responses. 617
14-10 Allergen introduced into the bloodstream can cause anaphylaxis. 619
14-11 Allergen inhalation is associated with the development of rhinitis and asthma. 621
14-12 Allergy to particular foods causes systemic reactions as well as symptoms limited to the gut. 624
14-13 IgE-mediated allergic disease can be treated by inhibiting the effector pathways that lead to symptoms or by desensitization techniques that aim at restoring biological tolerance to the allergen. 625
Summary. 627

Non-IgE-mediated allergic diseases. 628
14-14 Non-IgE dependent drug-induced hypersensitivity reactions in susceptible individuals occur by binding of the drug to the surface of circulating blood cells. 628
14-15 Systemic disease caused by immune-complex formation can follow the administration of large quantities of poorly catabolized antigens. 628
14-16 Hypersensitivity reactions can be mediated by T_H1 cells and CD8 cytotoxic T cells. 630
14-17 Celiac disease has features of both an allergic response and autoimmunity. 634
Summary. 636
Summary to Chapter 14. 636
Questions. 637
References. 638

Chapter 15 Autoimmunity and Transplantation 643

The making and breaking of self-tolerance. 643
15-1 A critical function of the immune system is to discriminate self from nonself. 643
15-2 Multiple tolerance mechanisms normally prevent autoimmunity. 645
15-3 Central deletion or inactivation of newly formed lymphocytes is the first checkpoint of self-tolerance. 646
15-4 Lymphocytes that bind self antigens with relatively low affinity usually ignore them but in some circumstances become activated. 647
15-5 Antigens in immunologically privileged sites do not induce immune attack but can serve as targets. 648
15-6 Autoreactive T cells that express particular cytokines may be nonpathogenic or may suppress pathogenic lymphocytes. 649
15-7 Autoimmune responses can be controlled at various stages by regulatory T cells. 650
Summary. 652

Autoimmune diseases and pathogenic mechanisms. 652
15-8 Specific adaptive immune responses to self antigens can cause autoimmune disease. 652
15-9 Autoimmunity can be classified into either organ-specific or systemic disease. 653
15-10 Multiple components of the immune system are typically recruited in autoimmune disease. 654
15-11 Chronic autoimmune disease develops through positive feedback from inflammation, inability to clear the self antigen, and a broadening of the autoimmune response. 657

15-12 Both antibody and effector T cells can cause tissue damage in autoimmune disease. 659
15-13 Autoantibodies against blood cells promote their destruction. 661
15-14 The fixation of sublytic doses of complement to cells in tissues stimulates a powerful inflammatory response. 661
15-15 Autoantibodies against receptors cause disease by stimulating or blocking receptor function. 662
15-16 Autoantibodies against extracellular antigens cause inflammatory injury. 663
15-17 T cells specific for self antigens can cause direct tissue injury and sustain autoantibody responses. 665
Summary. 668
The genetic and environmental basis of autoimmunity. 669
15-18 Autoimmune diseases have a strong genetic component. 669
15-19 Genomics-based approaches are providing new insight into the immunogenetic basis of autoimmunity. 670
15-20 Many genes that predispose to autoimmunity fall into categories that affect one or more tolerance mechanisms. 674
15-21 Monogenic defects of immune tolerance. 674
15-22 MHC genes have an important role in controlling susceptibility to autoimmune disease. 676
15-23 Genetic variants that impair innate immune responses can predispose to T-cell-mediated chronic inflammatory disease. 678
15-24 External events can initiate autoimmunity. 679
15-25 Infection can lead to autoimmune disease by providing an environment that promotes lymphocyte activation. 680
15-26 Cross-reactivity between foreign molecules on pathogens and self molecules can lead to antiself responses and autoimmune disease. 680
15-27 Drugs and toxins can cause autoimmune syndromes. 682
15-28 Random events may be required for the initiation of autoimmunity. 682
Summary. 682
Responses to alloantigens and transplant rejection. 683
15-29 Graft rejection is an immunological response mediated primarily by T cells. 683
15-30 Transplant rejection is caused primarily by the strong immune response to nonself MHC molecules. 684
15-31 In MHC-identical grafts, rejection is caused by peptides from other alloantigens bound to graft MHC molecules. 685
15-32 There are two ways of presenting alloantigens on the transplanted donor organ to the recipient's T lymphocytes. 686
15-33 Antibodies that react with endothelium cause hyperacute graft rejection. 688
15-34 Late failure of transplanted organs is caused by chronic injury to the graft. 688
15-35 A variety of organs are transplanted routinely in clinical medicine. 689
15-36 The converse of graft rejection is graft-versus-host disease. 691
15-37 Regulatory T cells are involved in alloreactive immune responses. 692
15-38 The fetus is an allograft that is tolerated repeatedly. 693
Summary. 694
Summary to Chapter 15. 694
Questions. 695
References. 696
Chapter 16 Manipulation of the Immune Response 701
Treatment of unwanted immune responses. 701
16-1 Corticosteroids are powerful anti-inflammatory drugs that alter the transcription of many genes. 702
16-2 Cytotoxic drugs cause immunosuppression by killing dividing cells and have serious side-effects. 703
16-3 Cyclosporin A, tacrolimus, rapamycin, and JAK inhibitors are effective immunosuppressive agents that interfere with various T-cell signaling pathways. 704
16-4 Antibodies against cell-surface molecules can be used to eliminate lymphocyte subsets or to inhibit lymphocyte function. 706
16-5 Antibodies can be engineered to reduce their immunogenicity in humans. 707
16-6 Monoclonal antibodies can be used to prevent allograft rejection. 708
16-7 Depletion of autoreactive lymphocytes can treat autoimmune disease. 710
16-8 Biologics that block TNF-α, IL-1, or IL-6 can alleviate autoimmune diseases. 711
16-9 Biologic agents can block cell migration to sites of inflammation and reduce immune responses. 712
16-10 Blockade of co-stimulatory pathways that activate lymphocytes can be used to treat autoimmune disease. 713
16-11 Some commonly used drugs have immunomodulatory properties. 713
16-12 Controlled administration of antigen can be used to manipulate the nature of an antigen-specific response. 714
Summary. 714
Using the immune response to attack tumors. 716
16-13 The development of transplantable tumors in mice led to the discovery of protective immune responses to tumors. 716
16-14 Tumors are 'edited' by the immune system as they evolve and can escape rejection in many ways. 717
16-15 Tumor rejection antigens can be recognized by T cells and form the basis of immunotherapies. 720
16-16 T cells expressing chimeric antigen receptors are an effective treatment in some leukemias. 723
16-17 Monoclonal antibodies against tumor antigens, alone or linked to toxins, can control tumor growth. 724
16-18 Enhancing the immune response to tumors by vaccination holds promise for cancer prevention and therapy. 726
16-19 Checkpoint blockade can augment immune responses to existing tumors. 727
Summary. 728

Fighting infectious diseases with vaccination. 729
16-20 Vaccines can be based on attenuated pathogens or material from killed organisms. 730
16-21 Most effective vaccines generate antibodies that prevent the damage caused by toxins or that neutralize the pathogen and stop infection. 731
16-22 Effective vaccines must induce long-lasting protection while being safe and inexpensive. 732
16-23 Live-attenuated viral vaccines are usually more potent than 'killed' vaccines and can be made safer by the use of recombinant DNA technology. 732
16-24 Live-attenuated vaccines can be developed by selecting nonpathogenic or disabled bacteria or by creating genetically attenuated parasites (GAPs). 734
16-25 The route of vaccination is an important determinant of success. 735
16-26 *Bordetella pertussis* vaccination illustrates the importance of the perceived safety of a vaccine. 736
16-27 Conjugate vaccines have been developed as a result of linked recognition between T and B cells. 737
16-28 Peptide-based vaccines can elicit protective immunity, but they require adjuvants and must be targeted to the appropriate cells and cell compartment to be effective. 738
16-29 Adjuvants are important for enhancing the immunogenicity of vaccines, but few are approved for use in humans. 739
16-30 Protective immunity can be induced by DNA-based vaccination. 740
16-31 Vaccination and checkpoint blockade may be useful in controlling existing chronic infections. 741
Summary. 742
Summary to Chapter 16. 742
Questions. 743
References. 744

APPENDICES

Appendix I The Immunologist's Toolbox 749
A-1. Immunization. 749
A-2 Antibody responses. 752
A-3 Affinity chromatography. 753
A-4 Radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), and competitive inhibition assay. 753
A-5 Hemagglutination and blood typing. 755
A-6 Coombs tests and the detection of rhesus incompatibility. 756
A-7 Monoclonal antibodies. 757
A-8 Phage display libraries for antibody V-region production. 758
A-9 Generation of human monoclonal antibodies from vaccinated individuals. 759
A-10 Microscopy and imaging using fluorescent dyes. 760
A-11 Immunoelectron microscopy. 761
A-12 Immunohistochemistry. 762
A-13 Immunoprecipitation and co-immunoprecipitation. 762
A-14 Immunoblotting (Western blotting). 764
A-15 Use of antibodies in the isolation and characterization of multiprotein complexes by mass spectrometry. 764
A-16 Isolation of peripheral blood lymphocytes by density-gradient fractionation. 766
A-17 Isolation of lymphocytes from tissues other than blood. 766
A-18 Flow cytometry and FACS analysis. 767
A-19 Lymphocyte isolation using antibody-coated magnetic beads. 770
A-20 Isolation of homogeneous T-cell lines. 770
A-21 Limiting-dilution culture. 771
A-22 ELISPOT assay. 773
A-23 Identification of functional subsets of T cells based on cytokine production or transcription factor expression. 773
A-24 Identification of T-cell receptor specificity using peptide:MHC tetramers. 776
A-25 Biosensor assays for measuring the rates of association and dissociation of antigen receptors for their ligands. 777
A-26 Assays of lymphocyte proliferation. 778
A-27 Measurements of apoptosis. 779
A-28 Assays for cytotoxic T cells. 780
A-29 Assays for CD4 T cells. 782
A-30 Transfer of protective immunity. 782
A-31 Adoptive transfer of lymphocytes. 783
A-32 Hematopoietic stem-cell transfers. 784
A-33 *In vivo* administration of antibodies. 785
A-34 Transgenic mice. 786
A-35 Gene knockout by targeted disruption. 786
A-36 Knockdown of gene expression by RNA interference (RNAi). 790

Appendix II CD antigens 791
Appendix III Cytokines and their Receptors 811
Appendix IV Chemokines and their Receptors 814
Biographies 816
Photograph Acknowledgments 817
Glossary 818
Index 855

PART I
AN INTRODUCTION TO IMMUNOBIOLOGY AND INNATE IMMUNITY

1 Basic Concepts in Immunology
2 Innate Immunity: The First Lines of Defense
3 The Induced Response of Innate Immunity

Basic Concepts in Immunology

1

Immunology is the study of the body's defense against infection. We are continually exposed to microorganisms, many of which cause disease, and yet become ill only rarely. How does the body defend itself? When infection does occur, how does the body eliminate the invader and cure itself? And why do we develop long-lasting immunity to many infectious diseases encountered once and overcome? These are the questions addressed by immunology, which we study to understand our body's defenses against infection at the cellular and molecular levels.

The beginning of immunology as a science is usually attributed to **Edward Jenner** for his work in the late 18th century (Fig. 1.1). The notion of immunity—that surviving a disease confers greater protection against it later—was known since ancient Greece. **Variolation**—the inhalation or transfer into superficial skin wounds of material from smallpox pustules—had been practiced since at least the 1400s in the Middle East and China as a form of protection against that disease and was known to Jenner. Jenner had observed that the relatively mild disease of cowpox, or vaccinia, seemed to confer protection against the often fatal disease of smallpox, and in 1796, he demonstrated that inoculation with cowpox protected the recipient against smallpox. His scientific proof relied on the deliberate exposure of the inoculated individual to infectious smallpox material two months after inoculation. This scientific test was his original contribution.

Jenner called the procedure **vaccination**. This term is still used to describe the inoculation of healthy individuals with weakened or attenuated strains of disease-causing agents in order to provide protection from disease. Although Jenner's bold experiment was successful, it took almost two centuries for smallpox vaccination to become universal. This advance enabled the World Health Organization to announce in 1979 that smallpox had been eradicated (Fig. 1.2), arguably the greatest triumph of modern medicine.

Jenner's strategy of vaccination was extended in the late 19th century by the discoveries of many great microbiologists. **Robert Koch** proved that infectious diseases are caused by specific microorganisms. In the 1880s, **Louis Pasteur**

IN THIS CHAPTER

The origins of vertebrate immune cells.

Principles of innate immunity.

Principles of adaptive immunity.

The effector mechanisms of immunity.

Fig. 1.1 Edward Jenner. Portrait by John Raphael Smith. Reproduced courtesy of Yale University, Harvey Cushing/John Hay Whitney Medical Library.

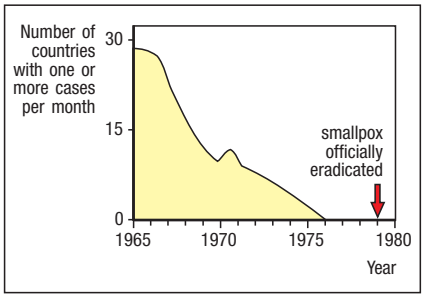


Fig. 1.2 The eradication of smallpox by vaccination. After a period of 3 years in which no cases of smallpox were recorded, the World Health Organization was able to announce in 1979 that smallpox had been eradicated, and vaccination stopped (upper panel). A few laboratory stocks have been retained, however, and some fear that these are a source from which the virus might reemerge. Ali Maow Maalin (lower panel) contracted and survived the last case of smallpox in Somalia in 1977. Photograph courtesy of Dr. Jason Weisfeld.

devised a vaccine against cholera in chickens, and developed a rabies vaccine that proved to be a spectacular success upon its first trial in a boy bitten by a rabid dog.

These practical triumphs led to a search for vaccination's mechanism of protection and to the development of the science of immunology. In the early 1890s, **Emil von Behring** and **Shibasaburo Kitasato** discovered that the serum of animals immune to diphtheria or tetanus contained a specific 'antitoxic activity' that could confer short-lived protection against the effects of diphtheria or tetanus toxins in people. This activity was later determined to be due to the proteins we now call **antibodies**, which bind specifically to the toxins and neutralize their activity. That these antibodies might have a crucial role in immunity was reinforced by **Jules Bordet's** discovery in 1899 of **complement**, a component of serum that acts in conjunction with antibodies to destroy pathogenic bacteria.

A specific response against infection by potential pathogens, such as the production of antibodies against a particular pathogen, is known as **adaptive immunity**, because it develops during the lifetime of an individual as an adaptation to infection with that pathogen. Adaptive immunity is distinguished from **innate immunity**, which was already known at the time von Behring was developing serum therapy for diphtheria chiefly through the work of the great Russian immunologist **Elie Metchnikoff,** who discovered that many microorganisms could be engulfed and digested by phagocytic cells, which thus provide defenses against infection that are nonspecific. Whereas these cells—which Metchnikoff called 'macrophages'—are always present and ready to act, adaptive immunity requires time to develop but is highly specific.

It was soon clear that specific antibodies could be induced against a vast range of substances, called **antigens** because they could stimulate *anti*body *gen*eration. **Paul Ehrlich** advanced the development of an **antiserum** as a treatment for diphtheria and developed methods to standardize therapeutic serums. Today the term antigen refers to any substance recognized by the adaptive immune system. Typically antigens are common proteins, glycoproteins, and polysaccharides of pathogens, but they can include a much wider range of chemical structures, for example, metals such as nickel, drugs such as penicillin, and organic chemicals such as the urushiol (a mix of pentadecylcatechols) in the leaves of poison ivy. Metchnikoff and Ehrlich shared the 1908 Nobel Prize for their respective work on immunity.

This chapter introduces the principles of innate and adaptive immunity, the cells of the immune system, the tissues in which they develop, and the tissues through which they circulate. We then outline the specialized functions of the different types of cells by which they eliminate infection.

The origins of vertebrate immune cells.

The body is protected from infectious agents, their toxins, and the damage they cause by a variety of effector cells and molecules that together make up the **immune system**. Both innate and adaptive immune responses depend upon the activities of white blood cells or **leukocytes**. Most cells of the immune system arise from the **bone marrow**, where many of them develop and mature. But some, particularly certain tissue-resident macrophage populations (for example, the microglia of the central nervous system), originate from the yolk sack or fetal liver during embryonic development. They seed tissues before birth and are maintained throughout life as independent, self-renewing populations. Once mature, immune cells reside within peripheral tissues, circulate in the bloodstream, or circulate in a specialized system of vessels called

the **lymphatic system**. The lymphatic system drains extracellular fluid and immune cells from tissues and transports them as **lymph** that is eventually emptied back into the blood system.

All the cellular elements of blood, including the red blood cells that transport oxygen, the platelets that trigger blood clotting in damaged tissues, and the white blood cells of the immune system, ultimately derive from the **hematopoietic stem cells (HSCs)** of the bone marrow. Because these can give rise to all the different types of blood cells, they are often known as **pluripotent** hematopoietic stem cells. The hematopoietic stem cells give rise to cells of more limited developmental potential, which are the immediate progenitors of red blood cells, platelets, and the two main categories of white blood cells, the **lymphoid** and **myeloid** lineages. The different types of blood cells and their lineage relationships are summarized in Fig. 1.3.

Principles of innate immunity.

In this part of the chapter we will outline the principles of innate immunity and describe the molecules and cells that provide continuous defense against invasion by pathogens. Although the white blood cells known as **lymphocytes** possess the most powerful ability to recognize and target pathogenic microorganisms, they need the participation of the innate immune system to initiate and mount their offensive. Indeed, the adaptive immune response and innate immunity use many of the same destructive mechanisms to eliminate invading microorganisms.

1-1 Commensal organisms cause little host damage while pathogens damage host tissues by a variety of mechanisms.

We recognize four broad categories of disease-causing microorganisms, or **pathogens**: **viruses**, **bacteria** and archaea, **fungi**, and the unicellular and multicellular eukaryotic organisms collectively termed **parasites** (Fig. 1.4). These microorganisms vary tremendously in size and in how they damage host tissues. The smallest are viruses, which range from five to a few hundred nanometers in size and are obligate intracellular pathogens. Viruses can directly kills cells by inducing lysis during their replication. Somewhat larger are intracellular bacteria and mycobacteria. These can kill cells directly or damage cells by producing toxins. Many single-celled intracellular parasites, such as members of the *Plasmodium* genus that cause malaria, also directly kill infected cells. Pathogenic bacteria and fungi growing in extracellular spaces can induce shock and sepsis by releasing toxins into the blood or tissues. The largest pathogens—parasitic worms, or helminths—are too large to infect host cells but can injure tissues by forming cysts that induce damaging cellular responses in the tissues into which the worms migrate.

Not all microbes are pathogens. Many tissues, especially the skin, oral mucosa, conjunctiva, and gastrointestinal tract, are constantly colonized by microbial communities—called the **microbiome**—that consist of archaea, bacteria, and fungi but cause no damage to the host. These are also called **commensal microorganisms**, since they can have a symbiotic relationship with the host. Indeed, some commensal organisms perform important functions, as in the case of the bacteria that aid in cellulose digestion in the stomachs of ruminants. The difference between commensal organisms and pathogens lies in whether they induce damage. Even enormous numbers of microbes in the intestinal microbiome normally cause no damage and are confined within the intestinal lumen by a protective layer of mucus, whereas pathogenic bacteria can penetrate this barrier, injure intestinal epithelial cells, and spread into the underlying tissues.

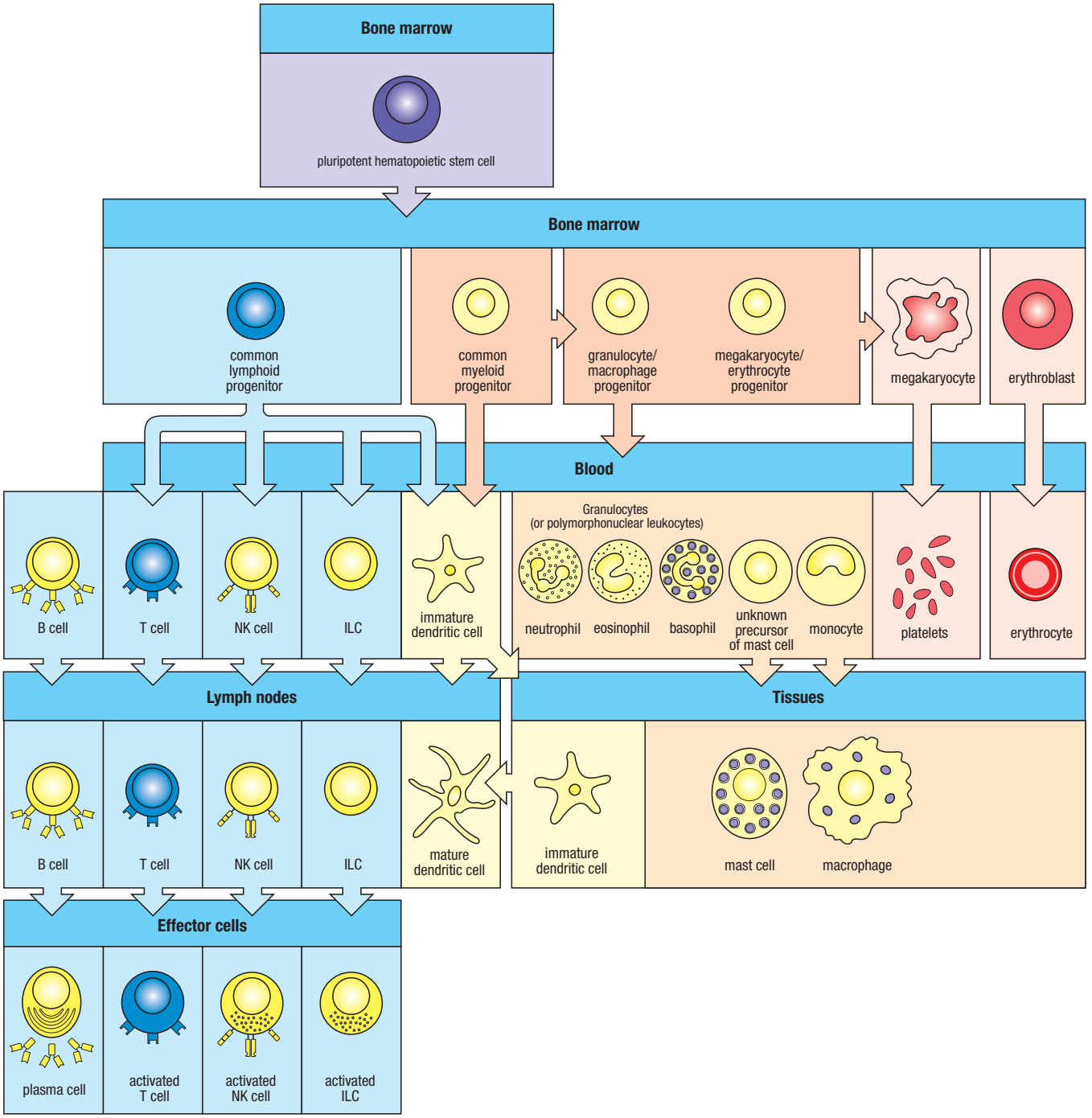


Fig. 1.3 All the cellular elements of the blood, including the cells of the immune system, arise from pluripotent hematopoietic stem cells in the bone marrow. These pluripotent cells divide to produce two types of stem cells. A common lymphoid progenitor gives rise to the lymphoid lineage (blue background) of white blood cells or leukocytes—the innate lymphoid cells (ILCs) and natural killer (NK) cells and the T and B lymphocytes. A common myeloid progenitor gives rise to the myeloid lineage (pink and yellow backgrounds), which comprises the rest of the leukocytes, the erythrocytes (red blood cells), and the megakaryocytes that produce platelets important in blood clotting. T and B lymphocytes are distinguished from the other leukocytes by having antigen receptors and from each other by their sites of differentiation—the thymus and bone marrow, respectively. After encounter with antigen, B cells differentiate into antibody-secreting plasma cells, while T cells differentiate into effector T cells with a variety of functions. Unlike T and B cells, ILCs and NK cells lack antigen specificity. The remaining leukocytes are the monocytes, the dendritic cells, and the neutrophils, eosinophils, and basophils. The last three of these circulate in the blood and are termed granulocytes, because of the cytoplasmic granules whose staining gives these cells a distinctive appearance in blood smears, or polymorphonuclear leukocytes, because of their irregularly shaped nuclei. Immature dendritic cells (yellow background) are phagocytic cells that enter the tissues; they mature after they have encountered a potential pathogen. The majority of dendritic cells are derived from the common myeloid progenitor cells, but some may also arise from the common lymphoid progenitor. Monocytes enter tissues, where they differentiate into phagocytic macrophages or dendritic cells. Mast cells also enter tissues and complete their maturation there.

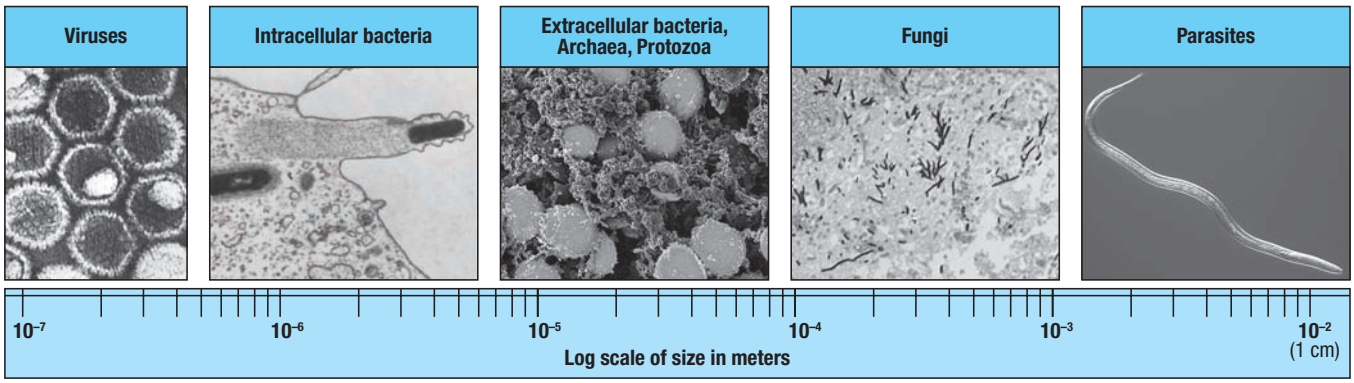


Fig. 1.4 Pathogens vary greatly in size and lifestyle. Intracellular pathogens include viruses, such as herpes simplex (first panel), and various bacteria, such as *Listeria monocytogenes* (second panel). Many bacteria, such as *Staphylococcus aureus* (third panel), or fungi, such as *Aspergillus fumigates* (fourth panel), can grow in the extracellular spaces and directly invade through tissues, as do some archaea and protozoa (third panel). Many parasites, such as the nematode *Strongyloides stercoralis* (fifth panel), are large multicellular organisms that can move throughout the body in a complex life cycle. Second panel courtesy of Dan Portnoy. Fifth panel courtesy of James Lok.

1-2 Anatomic and chemical barriers are the first defense against pathogens.

The host can adopt three strategies to deal with the threat posed by microbes: **avoidance**, **resistance**, and **tolerance**. Avoidance mechanisms prevent exposure to microbes, and include both anatomic barriers and behavior modifications. If an infection is established, resistance is aimed at reducing or eliminating pathogens. To defend against the great variety of microbes, the immune system has numerous molecular and cellular functions, collectively called mediators, or **effector mechanisms**, suited to resist different categories of pathogens. Their description is a major aspect of this book. Finally, tolerance involves responses that enhance a tissue's capacity to resist damage induced by microbes. This meaning of the term 'tolerance' has been used extensively in the context of disease susceptibility in plants rather than animal immunity. For example, increasing growth by activating dormant meristems, the undifferentiated cells that generate new parts of the plant, is a common tolerance mechanism in response to damage. This should be distinguished from the term **immunological tolerance**, which refers to mechanisms that prevent an immune response from being mounted against the host's own tissues.

Anatomic and chemical barriers are the initial defenses against infection (Fig. 1.5). The skin and mucosal surfaces represent a kind of avoidance strategy that prevents exposure of internal tissues to microbes. At most anatomic barriers, additional resistance mechanisms further strengthen host defenses. For example, mucosal surfaces produce a variety of **antimicrobial proteins** that act as natural antibiotics to prevent microbes from entering the body.

If these barriers are breached or evaded, other components of the innate immune system can immediately come into play. We mentioned earlier the discovery by Jules Bordet of **complement**, which acts with antibodies to lyse bacteria. Complement is a group of around 30 different plasma proteins that act together and are one of the most important effector mechanisms in serum and interstitial tissues. Complement not only acts in conjunction with antibodies, but can also target foreign organisms in the absence of a specific antibody; thus it contributes to both innate and adaptive responses. We will examine anatomic barriers, the antimicrobial proteins, and complement in greater detail in Chapter 2.

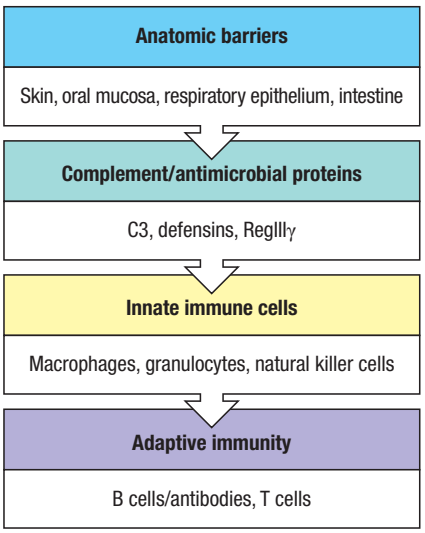


Fig. 1.5 Protection against pathogens relies on several levels of defense. The first is the anatomic barrier provided by the body's epithelial surfaces. Second, various chemical and enzymatic systems, including complement, act as an immediate antimicrobial barrier near these epithelia. If epithelia are breached, nearby various innate lymphoid cells can coordinate a rapid cell-mediated defense. If the pathogen overcomes these barriers, the slower-acting defenses of the adaptive immune system are brought to bear.

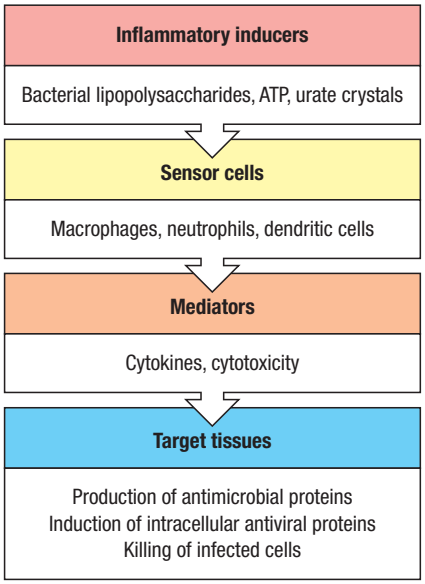


Fig. 1.6 Cell-mediated immunity proceeds in a series of steps. Inflammatory inducers are chemical structures that indicate the presence of invading microbes or the cellular damage produced by them. Sensor cells detect these inducers by expressing various innate recognition receptors, and in response produce a variety of mediators that act directly in defense or that further propagate the immune response. Mediators include many cytokines, and they act on various target tissues, such as epithelial cells, to induce antimicrobial proteins and resist intracellular viral growth; or on other immune cells, such as ILCs that produce other cytokines that amplify the immune response.

1-3 The immune system is activated by inflammatory inducers that indicate the presence of pathogens or tissue damage.

A pathogen that breaches the host's anatomic and chemical barriers will encounter the cellular defenses of innate immunity. Cellular immune responses are initiated when **sensor cells** detect **inflammatory inducers** (Fig. 1.6). Sensor cells include many cell types that detect **inflammatory mediators** through expression of many **innate recognition receptors**, which are encoded by a relatively small number of genes that remain constant over an individual's lifetime. Inflammatory inducers that trigger these receptors include molecular components unique to bacteria or viruses, such as bacterial lipopolysaccharides, or molecules such as ATP, which is not normally found in the extracellular space. Triggering these receptors can activate innate immune cells to produce various mediators that either act directly to destroy invading microbes, or act on other cells to propagate the immune response. For example, macrophages can ingest microbes and produce toxic chemical mediators, such as degradative enzymes or reactive oxygen intermediates, to kill them. Dendritic cells may produce cytokine mediators, including many cytokines that activate target tissues, such as epithelial or other immune cells, to resist or kill invading microbes more efficiently. We will discuss these receptors and mediators briefly below and in much greater detail in Chapter 3.

Innate immune responses occur rapidly on exposure to an infectious organism (Fig. 1.7). In contrast, responses by the adaptive immune system take days rather than hours to develop. However, the adaptive immune system is capable of eliminating infections more efficiently because of exquisite specificity

Phases of the immune response

Response		Typical time after infection to start of response	Duration of response
Innate immune response	Inflammation, complement activation, phagocytosis, and destruction of pathogen	Minutes	Days
Adaptive immune response	Interaction between antigen-presenting dendritic cells and antigen-specific T cells: recognition of antigen, adhesion, co-stimulation, T-cell proliferation and differentiation	Hours	Days
	Activation of antigen-specific B cells	Hours	Days
	Formation of effector and memory T cells	Days	Weeks
	Interaction of T cells with B cells, formation of germinal centers. Formation of effector B cells (plasma cells) and memory B cells. Production of antibody	Days	Weeks
	Emigration of effector lymphocytes from peripheral lymphoid organs	A few days	Weeks
	Elimination of pathogen by effector cells and antibody	A few days	Weeks
Immunological memory	Maintenance of memory B cells and T cells and high serum or mucosal antibody levels. Protection against reinfection	Days to weeks	Can be lifelong

Fig. 1.7 Phases of the immune response.

of antigen recognition by its lymphocytes. In contrast to a limited repertoire of receptors expressed by innate immune cells, lymphocytes express highly specialized **antigen receptors** that collectively possess a vast repertoire of specificity. This enables the adaptive immune system to respond to virtually any pathogen and effectively focus resources to eliminate pathogens that have evaded or overwhelmed innate immunity. But the adaptive immune system interacts with, and relies on, cells of the innate immune system for many of its functions. The next several sections will introduce the major components of the innate immune system and prepare us to consider adaptive immunity later in the chapter.

1-4 The myeloid lineage comprises most of the cells of the innate immune system.

The **common myeloid progenitor (CMP)** is the precursor of the macrophages, granulocytes (the collective term for the white blood cells called neutrophils, eosinophils, and basophils), mast cells, and dendritic cells of the innate immune system. Macrophages, granulocytes, and dendritic cells make up the three types of phagocytes in the immune system. The CMP also generates megakaryocytes and red blood cells, which we will not be concerned with here. The cells of the myeloid lineage are shown in Fig. 1.8.

Macrophages are resident in almost all tissues. Many tissue-resident macrophages arise during embryonic development, but some macrophages that arise in the adult animal from the bone marrow are the mature form of **monocytes**, which circulate in the blood and continually migrate into tissues, where they differentiate. Macrophages are relatively long-lived cells and perform several different functions throughout the innate immune response and the subsequent adaptive immune response. One is to engulf and kill invading microorganisms. This phagocytic function provides a first defense in innate immunity. Macrophages also dispose of pathogens and infected cells targeted by an adaptive immune response. Both monocytes and macrophages are phagocytic, but most infections occur in the tissues, and so it is primarily macrophages that perform this important protective function. An additional and crucial role of macrophages is to orchestrate immune responses: they help induce inflammation, which, as we shall see, is a prerequisite to a successful immune response, and they produce many inflammatory mediators that activate other immune-system cells and recruit them into an immune response.

Local inflammation and the phagocytosis of invading bacteria can also be triggered by the activation of complement. Bacterial surfaces can activate the complement system, inducing a cascade of proteolytic reactions that coat the microbes with fragments of specific proteins of the complement system.

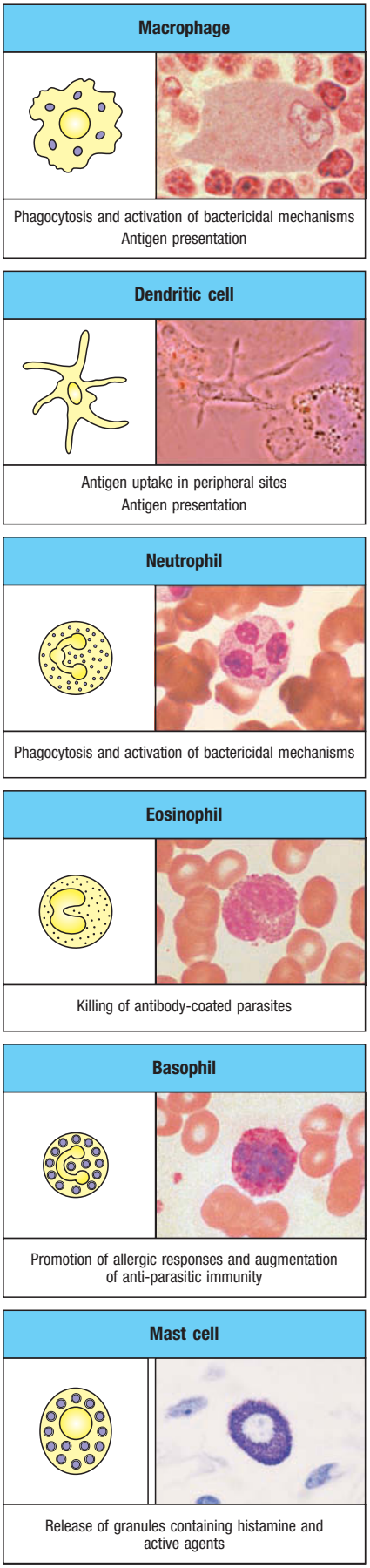


Fig. 1.8 Myeloid cells in innate and adaptive immunity. In the rest of the book, these cells will be represented in the schematic form shown on the left. A photomicrograph of each cell type is shown on the right. Macrophages and neutrophils are primarily phagocytic cells that engulf pathogens and destroy them in intracellular vesicles, a function they perform in both innate and adaptive immune responses. Dendritic cells are phagocytic when they are immature and can take up pathogens; after maturing, they function as specialized cells that present pathogen antigens to T lymphocytes in a form they can recognize, thus activating T lymphocytes and initiating adaptive immune responses. Macrophages can also present antigens to T lymphocytes and can activate them. The other myeloid cells are primarily secretory cells that release the contents of their prominent granules upon activation via antibody during an adaptive immune response. Eosinophils are thought to be involved in attacking large antibody-coated parasites such as worms; basophils are also thought to be involved in anti-parasite immunity. Mast cells are tissue cells that trigger a local inflammatory response to antigen by releasing substances that act on local blood vessels. Mast cells, eosinophils, and basophils are also important in allergic responses. Photographs courtesy of N. Rooney, R. Steinman, and D. Friend.

Microbes coated in this way are recognized by specific **complement receptors** on macrophages and neutrophils, taken up by phagocytosis, and destroyed. In addition to their specialized role in the immune system, macrophages act as general scavenger cells in the body, clearing it of dead cells and cell debris.

The **granulocytes** are named for the densely staining granules in their cytoplasm; they are also called **polymorphonuclear leukocytes** because of their oddly shaped nuclei. The three types of granulocytes—neutrophils, eosinophils, and basophils— are distinguished by the different staining properties of their granules, which serve distinct functions. Granulocytes are all relatively short-lived, surviving for only a few days. They mature in the bone marrow, and their production increases during immune responses, when they migrate to sites of infection or inflammation. The phagocytic **neutrophils** are the most numerous and important cells in innate immune responses: they take up a variety of microorganisms by phagocytosis and efficiently destroy them in intracellular vesicles by using degradative enzymes and other antimicrobial substances stored in their cytoplasmic granules. Hereditary deficiencies in neutrophil function open the way to overwhelming bacterial infection, which is fatal if untreated. Their role is discussed further in Chapter 3.

Eosinophils and **basophils** are less abundant than neutrophils, but like neutrophils, they have granules containing a variety of enzymes and toxic proteins, which are released when these cells are activated. Eosinophils and basophils are thought to be important chiefly in defense against parasites, which are too large to be ingested by macrophages or neutrophils. They can also contribute to allergic inflammatory reactions, in which their effects are damaging rather than protective.

Mast cells begin development in the bone marrow, but migrate as immature precursors that mature in peripheral tissues, especially skin, intestines, and airway mucosa. Their granules contain many inflammatory mediators, such as histamine and various proteases, which play a role in protecting the internal surfaces from pathogens, including parasitic worms. We cover eosinophils, basophils, and mast cells and their role in allergic inflammation further in Chapters 10 and 14.

MOVIE 1.1 

Dendritic cells were discovered in the 1970s by **Ralph Steinman**, for which he received half the 2011 Nobel Prize. These cells form the third class of phagocytic cells of the immune system and include several related lineages whose distinct functions are still being clarified. Most dendritic cells have elaborate membranous processes, like the dendrites of nerve cells. Immature dendritic cells migrate through the bloodstream from the bone marrow to enter tissues. They take up particulate matter by phagocytosis and also continually ingest large amounts of the extracellular fluid and its contents by a process known as **macropinocytosis**. They degrade the pathogens that they take up, but their main role in the immune system is not the clearance of microorganisms. Instead, dendritic cells are a major class of sensor cells whose encounter with pathogens triggers them to produce mediators that activate other immune cells. Dendritic cells were discovered because of their role in activating a particular class of lymphocytes—T lymphocytes—of the adaptive immune system, and we will return to this activity when we discuss T-cell activation in Section 1-15. But dendritic cells and the mediators they produce also play a critical role in controlling responses of cells of the innate immune system.

1-5 Sensor cells express pattern recognition receptors that provide an initial discrimination between self and nonself.

Long before the mechanisms of innate recognition were discovered, it was recognized that purified antigens such as proteins often did not evoke an immune response in an experimental immunization—that is, they were not