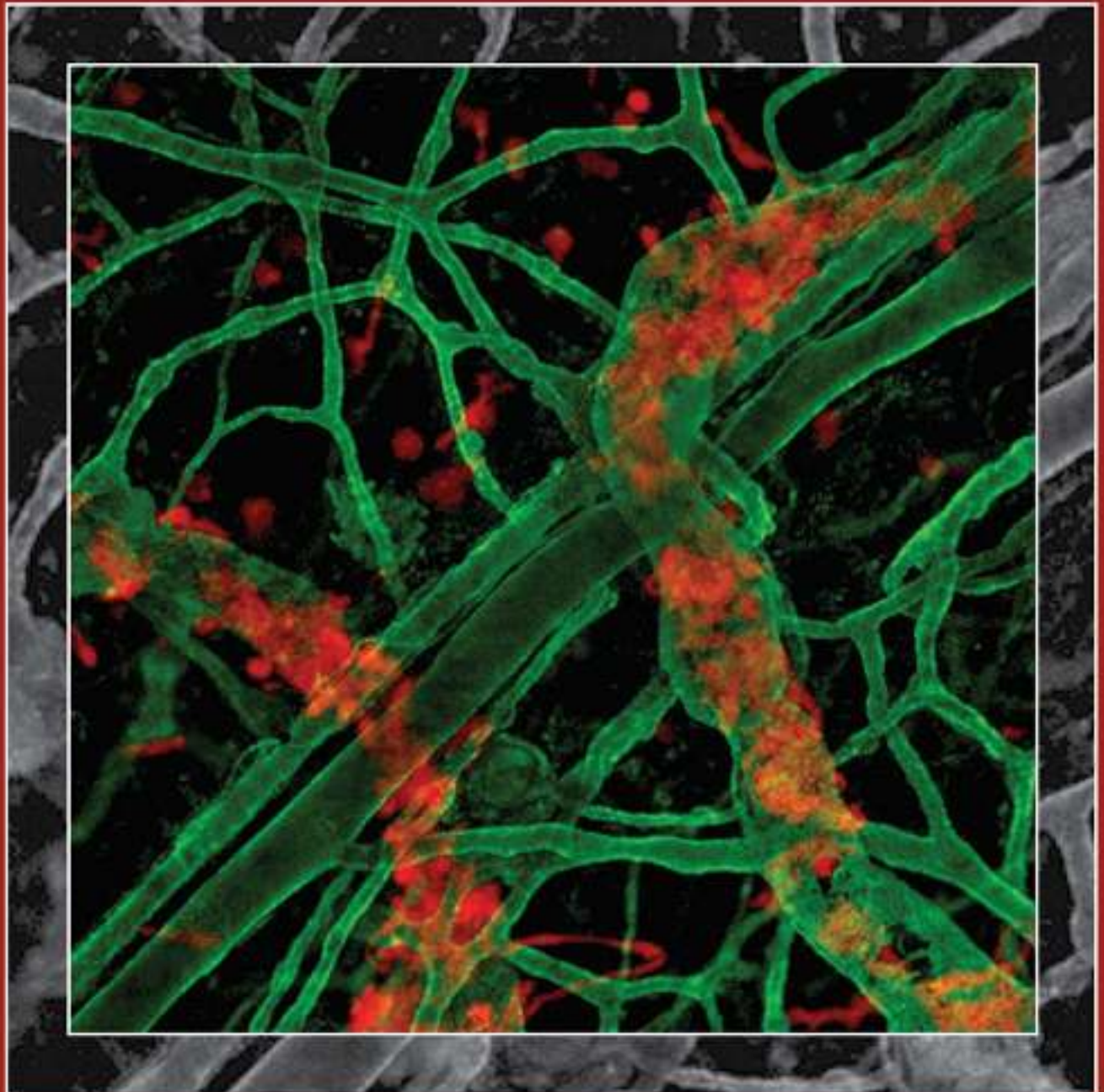


Kuby

IMMUNOLOGY

SEVENTH EDITION

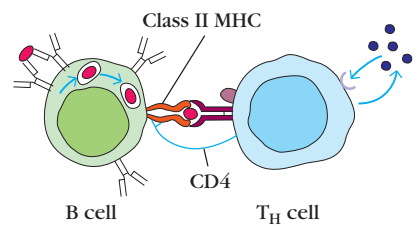
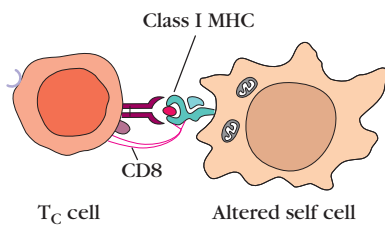
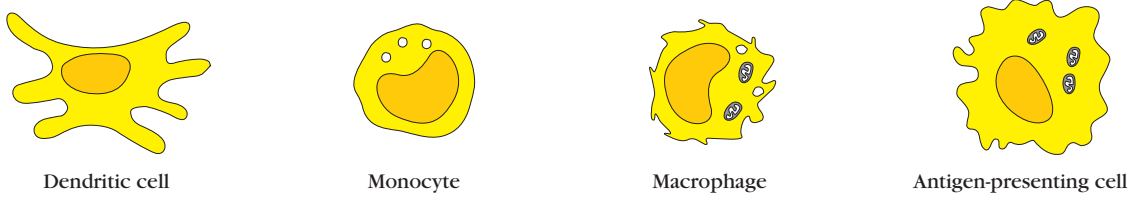
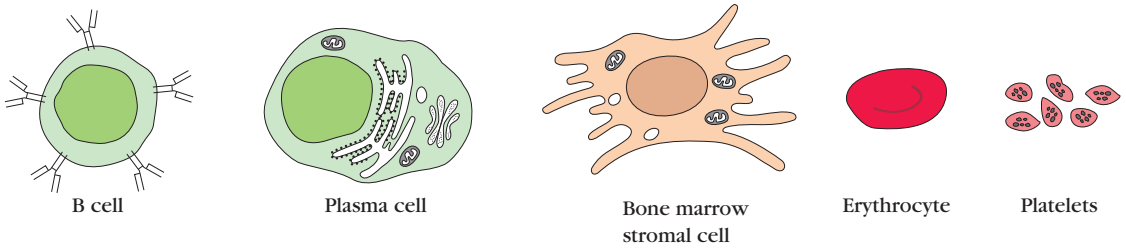
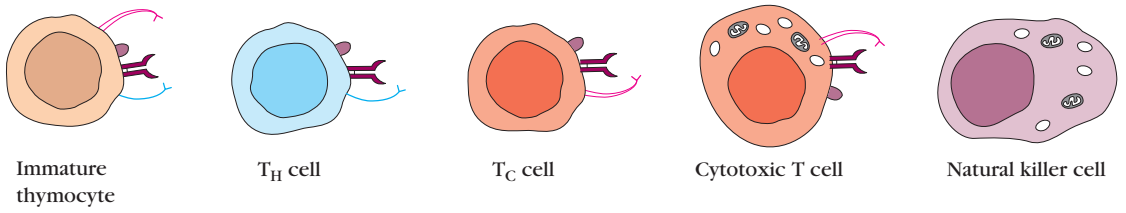
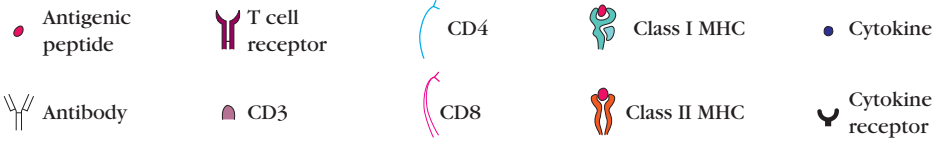


OWEN ■ PUNT ■ STRANFORD

KUBY

Immunology

Icons Used in This Book



KUBY

Immunology

Judith A. Owen

Haverford College

Jenni Punt

Haverford College

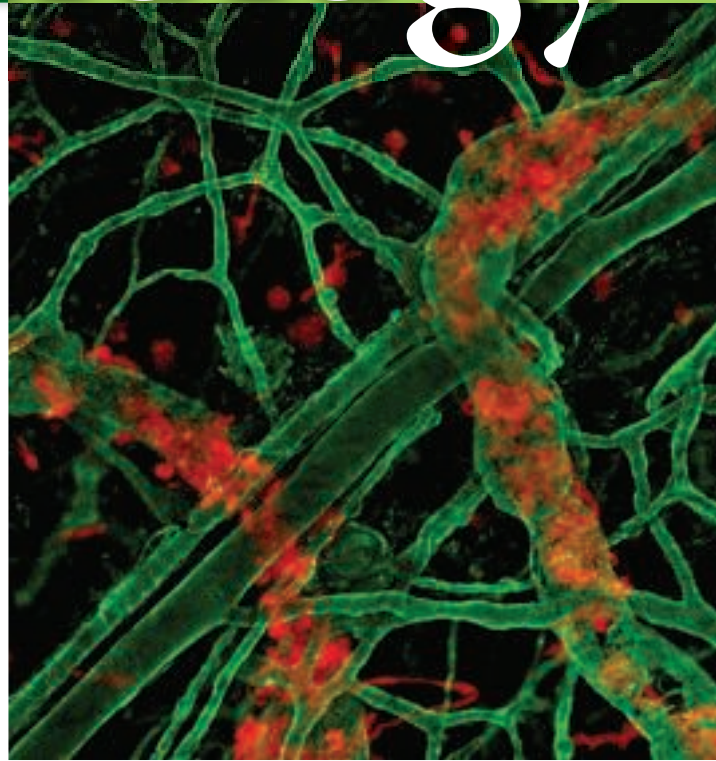
Sharon A. Stranford

Mount Holyoke College

with contributions by

Patricia P. Jones

Stanford University



Seventh Edition



W. H. Freeman and Company • New York

Publisher: Susan Winslow
Senior Acquisitions Editor: Lauren Schultz
Associate Director of Marketing: Debbie Clare
Marketing Assistant: Lindsay Neff
Developmental Editor: Erica Champion
Developmental Editor: Irene Pech
Developmental Coordinator: Sara Ruth Blake
Associate Media Editor: Allison Michael
Supplements Editor: Yasmine Ebadat
Senior Project Manager at Aptara: Sherrill Redd
Photo Editor: Christine Buese
Photo Researcher: Elyse Reider
Art Director: Diana Blume
Text Designer: Marsha Cohen
Illustrations: Imagineering
Illustration Coordinator: Janice Donnola
Production Coordinator: Lawrence Guerra
Composition: Aptara®, Inc.
Printing and Binding: RR Donnelley

Library of Congress Control Number: 2012950797

North American Edition

Cover image:

©2009 Pflücke and Sixt. Originally published in
The Journal of Experimental Medicine. 206:2925-2935.
doi:10.1084/jem.20091739.

Image provided by Holger Pflücke and Michael Sixt.

International Edition

Cover design: Dirk Kaufman

Cover image: Nastco/iStockphoto.com

North American Edition

ISBN-13: 978-14292-1919-8

ISBN-10: 1-4292-1919-X

International Edition

ISBN-13: 978-14641-3784-6

ISBN-10: 1-4641-3784-6

© 1992, 1994, 1997, 2000, 2003, 2007, 2013

by W. H. Freeman and Company

All rights reserved

Printed in the United States of America

First printing

North American Edition

W. H. Freeman and Company

41 Madison Avenue

New York, NY 10010

www.whfreeman.com

International Edition

Macmillan Higher Education

Houndmills, Basingstoke

RG21 6XS, England

www.macmillanhighered.com/international

To all our students, fellows, and colleagues who have made our careers in immunology a source of joy and excitement, and to our families who made these careers possible. We hope that future generations of immunology students will find this subject as fascinating and rewarding as we have.

About the Authors

All four authors are active scholars and teachers who have been/are recipients of research grants from the NIH and the NSF. We have all served in various capacities as grant proposal reviewers for NSF, NIH, HHMI, and other funding bodies as well as evaluating manuscripts submitted for publication in immunological journals. In addition, we are all active members of the American Association of Immunologists and have served our national organization in a variety of ways.



Judy Owen holds B.A. and M.A. (Hons) degrees from Cambridge University. She pursued her Ph.D. at the University of Pennsylvania with the late Dr. Norman Klinman and her post-doctoral fellowship with Dr. Peter Doherty in viral immunology. She was appointed to the faculty of Haverford College, one of the first undergraduate colleges to offer a course in immunology, in 1981. She teaches numerous laboratory and lecture courses in biochemistry and immunology and has received several teaching and mentorship awards. She is a participant in the First Year Writing Program and has been involved in curriculum development across the College.



Jenni Punt received her A.B. from Bryn Mawr College (*magna cum laude*) majoring in Biology at Haverford College. She received her VMD (*summa cum laude*) and Ph.D. in immunology from the University of Pennsylvania and was a Damon Runyon-Walter Winchell Physician-Scientist fellow with Dr. Alfred Singer at the National Institutes of Health. She was appointed to the faculty of Haverford College in 1996 where she teaches cell biology and immunology and performs research in T cell development and hematopoiesis. She has received several teaching awards and has contributed to the development of college-wide curricular initiatives.

Together, Jenni Punt and Judy Owen developed and ran the first AAI Introductory Immunology course, which is now offered on an annual basis.



Sharon Stranford obtained her B.A. with Honors in Biology from Arcadia University and her Ph.D. in Microbiology and Immunology from Hahnemann (now Drexel) University, where she studied autoimmunity with funding from the Multiple Sclerosis Foundation. She pursued postdoctoral studies in transplantation immunology at Oxford University in England, followed by a fellowship at the University of California, San Francisco, working on HIV/AIDS with Dr. Jay Levy. From 1999 to 2001, Sharon was a Visiting Assistant Professor of Biology at Amherst College, and in 2001 joined the faculty of Mount Holyoke College as a Clare Boothe Luce Assistant Professor. She teaches courses in introductory biology, cell biology, immunology, and infectious disease, as well as a new interdisciplinary course called Controversies in Public Health.



Pat Jones graduated from Oberlin College in Ohio with Highest Honors in Biology and obtained her Ph.D. in Biology with Distinction from the Johns Hopkins University. She was a postdoctoral fellow of the Arthritis Foundation for two years in the Department of Biochemistry and Biophysics at the University of California, San Francisco, Medical School, followed by two years as an NSF postdoctoral fellow in the Departments of Genetics and Medicine/Immunology at Stanford University School of Medicine. In 1978 she was appointed Assistant Professor of Biology at Stanford and is now a full professor. Pat has received several undergraduate teaching awards, was the founding Director of the Ph.D. Program in Immunology, and in July, 2011, she assumed the position of Director of Stanford Immunology, a position that coordinates activities in immunology across the university.

Chapter 1

Overview of the Immune System 1

A Historical Perspective of Immunology 2

Early vaccination studies led the way to immunology 2

Vaccination is an ongoing, worldwide enterprise 3

Immunology is about more than just vaccines and infectious disease 4

Immunity involves both humoral and cellular components 6

How are foreign substances recognized by the immune system? 9

Important Concepts for Understanding the Mammalian Immune Response 11

Pathogens come in many forms and must first breach natural barriers 12

The immune response quickly becomes tailored to suit the assault 12

Pathogen recognition molecules can be encoded in the germline or randomly generated 14

Tolerance ensures that the immune system avoids destroying the host 15

The immune response is composed of two interconnected arms: innate immunity and adaptive immunity 16

Adaptive immune responses typically generate memory 17

The Good, Bad, and Ugly of the Immune System 19

Inappropriate or dysfunctional immune responses can result in a range of disorders 19

The immune response renders tissue transplantation challenging 22

Cancer presents a unique challenge to the immune response 22

SUMMARY 23

REFERENCES 23

USEFUL WEB SITES 23

STUDY QUESTIONS 24

Chapter 2

Cells, Organs, and Micro-environments of the Immune System 27

Cells of the Immune System 27

Hematopoietic stem cells have the ability to differentiate into many types of blood cells 28

Hematopoiesis is the process by which hematopoietic stem cells develop into mature blood cells 32

Cells of the myeloid lineage are the first responders to infection 32

Cells of the lymphoid lineage regulate the adaptive immune response 37

Primary Lymphoid Organs—Where Immune Cells Develop 41

The bone marrow provides niches for hematopoietic stem cells to self-renew and differentiate into myeloid cells and B lymphocytes 41

The thymus is a primary lymphoid organ where T cells mature 41

Secondary Lymphoid Organs—Where the Immune Response Is Initiated 48

Secondary lymphoid organs are distributed throughout the body and share some anatomical features 48

Lymphoid organs are connected to each other and to infected tissue by two different circulatory systems: blood and lymphatics 48

The lymph node is a highly specialized secondary lymphoid organ 50

The spleen organizes the immune response against blood-borne pathogens	53	Signal-induced PIP ₂ breakdown by PLC causes an increase in cytoplasmic calcium ion concentration	75
MALT organizes the response to antigen that enters mucosal tissues	53	Ubiquitination may inhibit or enhance signal transduction	76
The skin is an innate immune barrier and also includes lymphoid tissue	56	Frequently Encountered Signaling Pathways	77
Tertiary lymphoid tissues also organize and maintain an immune response	57	The PLC pathway induces calcium release and PKC activation	77
SUMMARY	60	The Ras/Map kinase cascade activates transcription through AP-1	78
REFERENCES	60	PKC activates the NF- κ B transcription factor	79
USEFUL WEB SITES	61	The Structure of Antibodies	80
STUDY QUESTIONS	61	Antibodies are made up of multiple immunoglobulin domains	80
		Antibodies share a common structure of two light chains and two heavy chains	81
Chapter 3		There are two major classes of antibody light chains	85
Receptors and Signaling: B and T-Cell Receptors	65	There are five major classes of antibody heavy chains	85
Receptor-Ligand Interactions	66	Antibodies and antibody fragments can serve as antigens	86
Receptor-ligand binding occurs via multiple noncovalent bonds	66	Each of the domains of the antibody heavy and light chains mediate specific functions	88
How do we quantitate the strength of receptor-ligand interactions?	66	X-ray crystallography has been used to define the structural basis of antigen-antibody binding	90
Interactions between receptors and ligands can be multivalent	67	Signal Transduction in B Cells	91
Receptor and ligand expression can vary during the course of an immune response	68	Antigen binding results in docking of adapter molecules and enzymes into the BCR-Ig α /Ig β membrane complex	91
Local concentrations of cytokines and other ligands may be extremely high	68	B cells use many of the downstream signaling pathways described above	92
Common Strategies Used in Many Signaling Pathways	69	B cells also receive signals through co-receptors	94
Ligand binding can induce conformational changes in, and/or clustering of, the receptor	71	T-Cell Receptors and Signaling	95
Some receptors require receptor-associated molecules to signal cell activation	71	The T-cell receptor is a heterodimer with variable and constant regions	95
Ligand-induced receptor clustering can alter receptor location	71	The T-cell signal transduction complex includes CD3	98
Tyrosine phosphorylation is an early step in many signaling pathways	73	The T cell co-receptors CD4 and CD8 also bind the MHC	99
Adapter proteins gather members of signaling pathways	74	Lck is the first tyrosine kinase activated in T cell signaling	100
Phosphorylation on serine and threonine residues is also a common step in signaling pathways	74	T cells use downstream signaling strategies similar to those of B cells	100
Phosphorylation of membrane phospholipids recruits PH domain-containing proteins to the cell membrane	75	SUMMARY	101
		REFERENCES	102
		USEFUL WEB SITES	102
		STUDY QUESTIONS	103

Chapter 4

Receptors and Signaling: Cytokines and Chemokines 105

General Properties of Cytokines and Chemokines 106

- Cytokines mediate the activation, proliferation, and differentiation of target cells 107
- Cytokines have numerous biological functions 107
- Cytokines can elicit and support the activation of specific T-cell subpopulations 107
- Cell activation may alter the expression of receptors and adhesion molecules 109
- Cytokines are concentrated between secreting and target cells 110
- Signaling through multiple receptors can fine tune a cellular response 110

Six Families of Cytokines and Associated Receptor Molecules 111

- Cytokines of the IL-1 family promote proinflammatory signals 113
- Hematopoietin (Class I) family cytokines share three-dimensional structural motifs, but induce a diversity of functions in target cells 116
- The Interferon (Class II) cytokine family was the first to be discovered 119
- Members of the TNF cytokine family can signal development, activation, or death 123
- The IL-17 family is a recently discovered, proinflammatory cytokine cluster 127
- Chemokines direct the migration of leukocytes through the body 129

Cytokine Antagonists 133

- The IL-1 receptor antagonist blocks the IL-1 cytokine receptor 133
- Cytokine antagonists can be derived from cleavage of the cytokine receptor 134
- Some viruses have developed strategies to exploit cytokine activity 134

Cytokine-Related Diseases 134

- Septic shock is relatively common and potentially lethal 135
- Bacterial toxic shock is caused by superantigen induction of T-cell cytokine secretion 135
- Cytokine activity is implicated in lymphoid and myeloid cancers 137

- Cytokine storms may have caused many deaths in the 1918 Spanish influenza 137

Cytokine-Based Therapies 137

- SUMMARY 138
- REFERENCES 138
- USEFUL WEB SITES 139
- STUDY QUESTIONS 140

Chapter 5

Innate Immunity 141

Anatomical Barriers to Infection 143

- Epithelial barriers prevent pathogen entry into the body's interior 143
- Antimicrobial proteins and peptides kill would-be invaders 145

Phagocytosis 147

- Microbes are recognized by receptors on phagocytic cells 147
- Phagocytosed microbes are killed by multiple mechanisms 151
- Phagocytosis contributes to cell turnover and the clearance of dead cells 152

Induced Cellular Innate Responses 152

- Cellular pattern recognition receptors activate responses to microbes and cell damage 153
- Toll-like receptors recognize many types of pathogen molecules 153
- C-type lectin receptors bind carbohydrates on the surfaces of extracellular pathogens 158
- Retinoic acid-inducible gene-I-like receptors bind viral RNA in the cytosol of infected cells 160
- Nod-like receptors are activated by a variety of PAMPs, DAMPs, and other harmful substances 160
- Expression of innate immunity proteins is induced by PRR signaling 160

Inflammatory Responses 166

- Inflammation results from innate responses triggered by infection, tissue damage, or harmful substances 167
- Proteins of the acute phase response contribute to innate immunity and inflammation 168

Natural Killer Cells 168

Regulation and Evasion of Innate and Inflammatory Responses 169

Innate and inflammatory responses can be harmful	169	The Regulation of Complement Activity	210
Innate and inflammatory responses are regulated both positively and negatively	172	Complement activity is passively regulated by protein stability and cell surface composition	210
Pathogens have evolved mechanisms to evade innate and inflammatory responses	173	The C1 inhibitor, C1INH, promotes dissociation of C1 components	211
Interactions Between the Innate and Adaptive Immune Systems	173	Decay Accelerating Factors promote decay of C3 convertases	211
The innate immune system activates and regulates adaptive immune responses	174	Factor I degrades C3b and C4b	212
Adjuvants activate innate immune responses to increase the effectiveness of immunizations	175	Protectin inhibits the MAC attack	213
Some pathogen clearance mechanisms are common to both innate and adaptive immune responses	176	Carboxypeptidases can inactivate the anaphylatoxins, C3a and C5a	213
Ubiquity of Innate Immunity	176	Complement Deficiencies	213
Plants rely on innate immune responses to combat infections	177	Microbial Complement Evasion Strategies	214
Invertebrate and vertebrate innate immune responses show both similarities and differences	177	Some pathogens interfere with the first step of immunoglobulin-mediated complement activation	215
SUMMARY	180	Microbial proteins bind and inactivate complement proteins	215
REFERENCES	181	Microbial proteases destroy complement proteins	215
USEFUL WEB SITES	182	Some microbes mimic or bind complement regulatory proteins	215
STUDY QUESTIONS	182	The Evolutionary Origins of the Complement System	215
Chapter 6		SUMMARY	219
The Complement System	187	REFERENCES	220
The Major Pathways of Complement Activation	189	USEFUL WEB SITES	220
The classical pathway is initiated by antibody binding	190	STUDY QUESTIONS	221
The lectin pathway is initiated when soluble proteins recognize microbial antigens	195		
The alternative pathway is initiated in three distinct ways	196	Chapter 7	
The three complement pathways converge at the formation of the C5 convertase	200	The Organization and Expression of Lymphocyte Receptor Genes	225
C5 initiates the generation of the MAC	200	The Puzzle of Immunoglobulin Gene Structure	226
The Diverse Functions of Complement	201	Investigators proposed two early theoretical models of antibody genetics	226
Complement receptors connect complement-tagged pathogens to effector cells	201	Breakthrough experiments revealed that multiple gene segments encode the light chain	227
Complement enhances host defense against infection	204	Multigene Organization of Ig Genes	231
Complement mediates the interface between innate and adaptive immunities	207	Kappa light-chain genes include V, J, and C segments	231
Complement aids in the contraction phase of the immune response	207	Lambda light-chain genes pair each J segment with a particular C segment	231
Complement mediates CNS synapse elimination	210	Heavy-chain gene organization includes V _H , D, J _H , and C _H segments	232

The Mechanism of V(D)J Recombination **232**

Recombination is directed by signal sequences 233

Gene segments are joined by the RAG1/2 recombinase combination 234

V(D)J recombination results in a functional Ig variable region gene 235

V(D)J recombination can occur between segments transcribed in either the same or opposite directions 239

Five mechanisms generate antibody diversity in naïve B cells 239

B-Cell Receptor Expression **242**

Allelic exclusion ensures that each B cell synthesizes only one heavy chain and one light chain 242

Receptor editing of potentially autoreactive receptors occurs in light chains 243

Ig gene transcription is tightly regulated 244

Mature B cells express both IgM and IgD antibodies by a process that involves mRNA splicing 246

T-Cell Receptor Genes and Expression **247**

Understanding the protein structure of the TCR was critical to the process of discovering the genes 247

The β -chain gene was discovered simultaneously in two different laboratories 249

A search for the α -chain gene led to the γ -chain gene instead 250

TCR genes undergo a process of rearrangement very similar to that of Ig genes 251

TCR expression is controlled by allelic exclusion 253

TCR gene expression is tightly regulated 253

SUMMARY **255**

REFERENCES **256**

USEFUL WEB SITES **257**

STUDY QUESTIONS **258**

Chapter 8

The Major Histocompatibility Complex and Antigen Presentation **261**

The Structure and Function of MHC Molecules **262**

Class I molecules have a glycoprotein heavy chain and a small protein light chain 262

Class II molecules have two non-identical glycoprotein chains 262

Class I and II molecules exhibit polymorphism in the region that binds to peptides 263

General Organization and Inheritance of the MHC **267**

The MHC locus encodes three major classes of molecules 268

The exon/intron arrangement of class I and II genes reflects their domain structure 270

Allelic forms of MHC genes are inherited in linked groups called haplotypes 270

MHC molecules are codominantly expressed 271

Class I and class II molecules exhibit diversity at both the individual and species levels 273

MHC polymorphism has functional relevance 276

The Role of the MHC and Expression Patterns **277**

MHC molecules present both intracellular and extracellular antigens 278

MHC class I expression is found throughout the body 278

Expression of MHC class II molecules is primarily restricted to antigen-presenting cells 279

MHC expression can change with changing conditions 279

T cells are restricted to recognizing peptides presented in the context of self-MHC alleles 281

Evidence suggests different antigen processing and presentation pathways 284

The Endogenous Pathway of Antigen Processing and Presentation **285**

Peptides are generated by protease complexes called proteasomes 285

Peptides are transported from the cytosol to the RER 285

Chaperones aid peptide assembly with MHC class I molecules 286

The Exogenous Pathway of Antigen Processing and Presentation **288**

Peptides are generated from internalized molecules in endocytic vesicles 288

The invariant chain guides transport of class II MHC molecules to endocytic vesicles 289

Peptides assemble with class II MHC molecules by displacing CLIP 289

Cross-Presentation of Exogenous Antigens **291**

Dendritic cells appear to be the primary cross-presenting cell type	292	Apoptosis allows cells to die without triggering an inflammatory response	318
Mechanisms and Functions of Cross-Presentation	292	Different stimuli initiate apoptosis, but all activate caspases	318
Presentation of Nonpeptide Antigens	293	Apoptosis of peripheral T cells is mediated by the extrinsic (Fas) pathway	320
SUMMARY	295	TCR-mediated negative selection in the thymus induces the intrinsic (mitochondria-mediated) apoptotic pathway	321
REFERENCES	295	Bcl-2 family members can inhibit or induce apoptosis	321
USEFUL WEB SITES	296	SUMMARY	324
STUDY QUESTIONS	296	REFERENCES	325
		USEFUL WEB SITES	326
		STUDY QUESTIONS	327
Chapter 9			
T-Cell Development	299	Chapter 10	
Early Thymocyte Development	301	B-Cell Development	329
Thymocytes progress through four double-negative stages	301	The Site of Hematopoiesis	330
Thymocytes can express either TCR $\alpha\beta$ or TCR $\gamma\delta$ receptors	302	The site of B-cell generation changes during gestation	330
DN thymocytes undergo β -selection, which results in proliferation and differentiation	303	Hematopoiesis in the fetal liver differs from that in the adult bone marrow	332
Positive and Negative Selection	304	B-Cell Development in the Bone Marrow	332
Thymocytes “learn” MHC restriction in the thymus	305	The stages of hematopoiesis are defined by cell-surface markers, transcription-factor expression, and immunoglobulin gene rearrangements	334
T cells undergo positive and negative selection	305	The earliest steps in lymphocyte differentiation culminate in the generation of a common lymphoid progenitor	337
Positive selection ensures MHC restriction	307	The later steps of B-cell development result in commitment to the B-cell phenotype	339
Negative selection (central tolerance) ensures self-tolerance	310	Immature B cells in the bone marrow are exquisitely sensitive to tolerance induction	344
The selection paradox: Why don’t we delete all cells we positively select?	312	Many, but not all, self-reactive B cells are deleted within the bone marrow	345
An alternative model can explain the thymic selection paradox	313	B cells exported from the bone marrow are still functionally immature	345
Do positive and negative selection occur at the same stage of development, or in sequence?	314	Mature, primary B-2 B cells migrate to the lymphoid follicles	349
Lineage Commitment	314	The Development of B-1 and Marginal-Zone B Cells	351
Several models have been proposed to explain lineage commitment	314	B-1 B cells are derived from a separate developmental lineage	351
Double-positive thymocytes may commit to other types of lymphocytes	316	Marginal-zone cells share phenotypic and functional characteristics with B-1 B cells and arise at the T2 stage	352
Exit from the Thymus and Final Maturation	316	Comparison of B- and T-Cell Development	352
Other Mechanisms That Maintain Self-Tolerance	316		
T _{REG} cells negatively regulate immune responses	317		
Peripheral mechanisms of tolerance also protect against autoreactive thymocytes	318		
Apoptosis	318		

SUMMARY	354
REFERENCES	355
USEFUL WEB SITES	355
STUDY QUESTIONS	356

Chapter 11

T-Cell Activation, Differentiation, and Memory 357

T-Cell Activation and the Two-Signal Hypothesis 358

Costimulatory signals are required for optimal T-cell activation and proliferation	359
Clonal anergy results if a costimulatory signal is absent	363
Cytokines provide Signal 3	364
Antigen-presenting cells have characteristic costimulatory properties	365
Superantigens are a special class of T-cell activators	366

T-Cell Differentiation 368

Helper T cells can be divided into distinct subsets	370
The differentiation of T helper cell subsets is regulated by polarizing cytokines	371
Effector T helper cell subsets are distinguished by three properties	372
Helper T cells may not be irrevocably committed to a lineage	378
Helper T-cell subsets play critical roles in immune health and disease	378

T-Cell Memory 379

Naïve, effector, and memory T cells display broad differences in surface protein expression	379
T_{CM} and T_{EM} are distinguished by their locale and commitment to effector function	380
How and when do memory cells arise?	380
What signals induce memory cell commitment?	381
Do memory cells reflect the heterogeneity of effector cells generated during a primary response?	381
Are there differences between $CD4^+$ and $CD8^+$ memory T cells?	381
How are memory cells maintained over many years?	381

SUMMARY	381
REFERENCES	382
USEFUL WEB SITES	383
STUDY QUESTIONS	383

Chapter 12

B-Cell Activation, Differentiation, and Memory Generation 385

T-Dependent B-Cell Responses 388

T-dependent antigens require T-cell help to generate an antibody response	388
Antigen recognition by mature B cells provides a survival signal	389
B cells encounter antigen in the lymph nodes and spleen	390
B-cell recognition of cell-bound antigen results in membrane spreading	391
What causes the clustering of the B-cell receptors upon antigen binding?	392
Antigen receptor clustering induces internalization and antigen presentation by the B cell	393
Activated B cells migrate to find antigen-specific T cells	393
Activated B cells move either into the extra-follicular space or into the follicles to form germinal centers	395
Plasma cells form within the primary focus	395
Other activated B cells move into the follicles and initiate a germinal center response	396
Somatic hypermutation and affinity selection occur within the germinal center	398
Class switch recombination occurs within the germinal center after antigen contact	401
Most newly generated B cells are lost at the end of the primary immune response	403
Some germinal center cells complete their maturation as plasma cells	403
B-cell memory provides a rapid and strong response to secondary infection	404

T-Independent B-Cell Responses 406

T-independent antigens stimulate antibody production without the need for T-cell help	406
Two novel subclasses of B cells mediate the response to T-independent antigens	407

Negative Regulation of B Cells 411

Negative signaling through CD22 shuts down unnecessary BCR signaling	411
Negative signaling through the $Fc\gamma RIIIb$ receptor inhibits B-cell activation	411
B-10 B cells act as negative regulators by secreting IL-10	411

SUMMARY	412
REFERENCES	413
USEFUL WEB SITES	414
STUDY QUESTIONS	414

Chapter 13

Effector Responses: Cell- and Antibody-Mediated Immunity 415

Antibody-Mediated Effector Functions 416

Antibodies mediate the clearance and destruction of pathogen in a variety of ways	416
Antibody isotypes mediate different effector functions	419
Fc receptors mediate many effector functions of antibodies	423

Cell-Mediated Effector Responses 427

Cytotoxic T lymphocytes recognize and kill infected or tumor cells via T-cell receptor activation	428
Natural killer cells recognize and kill infected cells and tumor cells by their absence of MHC class I	435
NKT cells bridge the innate and adaptive immune systems	441

Experimental Assessment of Cell-Mediated Cytotoxicity 444

Co-culturing T cells with foreign cells stimulates the mixed-lymphocyte reaction	444
CTL activity can be demonstrated by cell-mediated lympholysis	445
The graft-versus-host reaction is an in vivo indication of cell-mediated cytotoxicity	446

SUMMARY	446
REFERENCES	447
USEFUL WEB SITES	448
STUDY QUESTIONS	448

Chapter 14

The Immune Response in Space and Time 451

Immune Cell Behavior before Antigen Is Introduced 455

Naïve lymphocytes circulate between secondary and tertiary lymphoid tissues	455
---	-----

Naïve lymphocytes sample stromal cells in the lymph nodes	461
Naïve lymphocytes browse for antigen along reticular networks in the lymph node	461

Immune Cell Behavior during the Innate Immune Response 464

Antigen-presenting cells travel to lymph nodes and present processed antigen to T cells	465
Unprocessed antigen also gains access to lymph-node B cells	465

Immune Cell Behavior during the Adaptive Immune Response 467

Naïve CD4 ⁺ T cells arrest their movements after engaging antigens	468
B cells seek help from CD4 ⁺ T cells at the border between the follicle and paracortex of the Lymph Node	468
Dynamic imaging approaches have been used to address a controversy about B-cell behavior in germinal centers	470
CD8 ⁺ T cells are activated in the lymph node via a multicellular interaction	471
Activated lymphocytes exit the lymph node and recirculate	472
A summary of our current understanding	472
The immune response contracts within 10 to 14 days	474

Immune Cell Behavior in Peripheral Tissues 474

Chemokine receptors and integrins regulate homing of effector lymphocytes to peripheral tissues	474
Effector lymphocytes respond to antigen in multiple tissues	475

SUMMARY	480
REFERENCES	481
USEFUL WEB SITES	482
STUDY QUESTIONS	482

Chapter 15

Allergy, Hypersensitivities, and Chronic Inflammation 485

Allergy: A Type I Hypersensitivity Reaction 486

IgE antibodies are responsible for type I hypersensitivity	487
Many allergens can elicit a type I response	487
IgE antibodies act by cross-linking Fcε receptors on the surfaces of innate immune cells	487

IgE receptor signaling is tightly regulated	491		
Innate immune cells produce molecules responsible for type I hypersensitivity symptoms	491		
Type I hypersensitivities are characterized by both early and late responses	494		
There are several categories of type I hypersensitivity reactions	494		
There is a genetic basis for type I hypersensitivity	497		
Diagnostic tests and treatments are available for type I hypersensitivity reactions	498		
The hygiene hypothesis has been advanced to explain increases in allergy incidence	501		
Antibody-Mediated (Type II) Hypersensitivity Reactions	501		
Transfusion reactions are an example of type II hypersensitivity	501		
Hemolytic disease of the newborn is caused by type II reactions	503		
Hemolytic anemia can be drug induced	504		
Immune Complex-Mediated (Type III) Hypersensitivity	505		
Immune complexes can damage various tissues	505		
Immune complex-mediated hypersensitivity can resolve spontaneously	505		
Autoantigens can be involved in immune complex-mediated reactions	506		
Arthus reactions are localized type III hypersensitivity reactions	506		
Delayed-Type (Type IV) Hypersensitivity (DTH)	506		
The initiation of a type IV DTH response involves sensitization by antigen	507		
The effector phase of a classical DTH response is induced by second exposure to a sensitizing antigen	507		
The DTH reaction can be detected by a skin test	508		
Contact dermatitis is a type IV hypersensitivity response	508		
Chronic Inflammation	509		
Infections can cause chronic inflammation	509		
There are noninfectious causes of chronic inflammation	510		
Obesity is associated with chronic inflammation	510		
Chronic inflammation can cause systemic disease	510		
SUMMARY	513		
REFERENCES	515		
USEFUL WEB SITES	515		
STUDY QUESTIONS	516		
		Chapter 16	
		Tolerance, Autoimmunity, and Transplantation	517
		Establishment and Maintenance of Tolerance	518
		Antigen sequestration is one means to protect self antigens from attack	519
		Central tolerance limits development of autoreactive T cells and B cells	520
		Peripheral tolerance regulates autoreactive cells in the circulation	520
		Autoimmunity	525
		Some autoimmune diseases target specific organs	526
		Some autoimmune diseases are systemic	529
		Both intrinsic and extrinsic factors can favor susceptibility to autoimmune disease	531
		Several possible mechanisms have been proposed for the induction of autoimmunity	533
		Autoimmune diseases can be treated by general or pathway-specific immunosuppression	534
		Transplantation Immunology	536
		Graft rejection occurs based on immunologic principles	536
		Graft rejection follows a predictable clinical course	541
		Immunosuppressive therapy can be either general or target-specific	543
		Immune tolerance to allografts is favored in certain instances	545
		Some organs are more amenable to clinical transplantation than others	546
		SUMMARY	549
		REFERENCES	550
		USEFUL WEB SITES	551
		STUDY QUESTIONS	551
		Chapter 17	
		Infectious Diseases and Vaccines	553
		The Importance of Barriers to Infection and the Innate Response	554
		Viral Infections	555
		Many viruses are neutralized by antibodies	556
		Cell-mediated immunity is important for viral control and clearance	556

Viruses employ several different strategies to evade host defense mechanisms	556	B-cell immunodeficiencies exhibit depressed production of one or more antibody isotypes	601
Influenza has been responsible for some of the worst pandemics in history	557	Disruptions to innate components may also impact adaptive responses	601
Bacterial Infections	560	Complement deficiencies are relatively common	603
Immune responses to extracellular and intracellular bacteria can differ	560	Immunodeficiency that disrupts immune regulation can manifest as autoimmunity	603
Bacteria can evade host defense mechanisms at several different stages	563	Immunodeficiency disorders are treated by replacement therapy	604
Tuberculosis is primarily controlled by CD4 ⁺ T cells	564	Animal models of immunodeficiency have been used to study basic immune function	604
Diphtheria can be controlled by immunization with inactivated toxoid	565	Secondary Immunodeficiencies	606
Parasitic Infections	565	HIV/AIDS has claimed millions of lives worldwide	607
Protozoan parasites account for huge worldwide disease burdens	565	The retrovirus HIV-1 is the causative agent of AIDS	608
A variety of diseases are caused by parasitic worms (helminths)	567	HIV-1 is spread by intimate contact with infected body fluids	610
Fungal Infections	569	In vitro studies have revealed the structure and life cycle of HIV-1	612
Innate immunity controls most fungal infections	569	Infection with HIV-1 leads to gradual impairment of immune function	615
Immunity against fungal pathogens can be acquired	571	Active research investigates the mechanism of progression to AIDS	616
Emerging and Re-emerging Infectious Diseases	571	Therapeutic agents inhibit retrovirus replication	619
Some noteworthy new infectious diseases have appeared recently	572	A vaccine may be the only way to stop the HIV/AIDS epidemic	621
Diseases may re-emerge for various reasons	573	SUMMARY	623
Vaccines	574	REFERENCES	623
Protective immunity can be achieved by active or passive immunization	574	USEFUL WEB SITES	624
There are several vaccine strategies, each with unique advantages and challenges	578	STUDY QUESTIONS	624
Conjugate or multivalent vaccines can improve immunogenicity and outcome	583	Chapter 19	
Adjuvants are included to enhance the immune response to a vaccine	585	Cancer and the Immune System	627
SUMMARY	586	Terminology and Common Types of Cancer	627
REFERENCES	587	Malignant Transformation of Cells	628
USEFUL WEB SITES	588	DNA alterations can induce malignant transformation	629
STUDY QUESTIONS	588	The discovery of oncogenes paved the way for our understanding of cancer induction	629
Chapter 18		Genes associated with cancer control cell proliferation and survival	630
Immunodeficiency Disorders	593	Malignant transformation involves multiple steps	633
Primary Immunodeficiencies	593	Tumor Antigens	634
Combined immunodeficiencies disrupt adaptive immunity	597	Tumor-specific antigens are unique to tumor cells	636
		Tumor-associated antigens are normal cellular proteins with unique expression patterns	636

The Immune Response to Cancer 638

- Immunoediting both protects against and promotes tumor growth 639
- Key immunologic pathways mediating tumor eradication have been identified 639
- Some inflammatory responses can promote cancer 642
- Some tumor cells evade immune recognition and activation 643

Cancer Immunotherapy 644

- Monoclonal antibodies can be targeted to tumor cells 644
- Cytokines can be used to augment the immune response to tumors 646
- Tumor-specific T cells can be expanded and reintroduced into patients 647
- New therapeutic vaccines may enhance the anti-tumor immune response 647
- Manipulation of costimulatory signals can improve cancer immunity 647
- Combination cancer therapies are yielding surprising results 648
- SUMMARY 649**
- REFERENCES 650**
- USEFUL WEB SITES 650**
- STUDY QUESTIONS 651**

Chapter 20

Experimental Systems and Methods 653

Antibody Generation 654

- Polyclonal antibodies are secreted by multiple clones of antigen-specific B cells 654
- A monoclonal antibody is the product of a single stimulated B cell 654
- Monoclonal antibodies can be modified for use in the laboratory or the clinic 655

Immunoprecipitation- Based Techniques 656

- Immunoprecipitation can be performed in solution 656
- Immunoprecipitation of soluble antigens can be performed in gel matrices 656
- Immunoprecipitation allows characterization of cell-bound molecules 657

Agglutination Reactions 658

- Hemagglutination reactions can be used to detect antigen conjugated to the surface of red blood cells 658

- Hemagglutination inhibition reactions are used to detect the presence of viruses and of antiviral antibodies 658

- Bacterial agglutination can be used to detect antibodies to bacteria 659

Antibody Assays Based on Antigen Binding to Solid-Phase Supports 659

- Radioimmunoassays are used to measure the concentrations of biologically relevant proteins and hormones in bodily fluids 659

- ELISA assays use antibodies or antigens covalently bound to enzymes 660

- The design of an ELISA assay must consider various methodological options 662

- ELISPOT assays measure molecules secreted by individual cells 663

- Western blotting can identify a specific protein in a complex protein mixture 664

Methods to Determine the Affinity of Antigen-Antibody Interactions 664

- Equilibrium dialysis can be used to measure antibody affinity for antigen 665

- Surface plasmon resonance is commonly used for measurements of antibody affinity 667

Microscopic Visualization of Cells and Subcellular Structures 668

- Immunocytochemistry and immunohistochemistry use enzyme-conjugated antibodies to create images of fixed tissues 668

- Immunoelectron microscopy uses gold beads to visualize antibody-bound antigens 669

Immunofluorescence-Based Imaging Techniques 669

- Fluorescence can be used to visualize cells and molecules 669

- Immunofluorescence microscopy uses antibodies conjugated with fluorescent dyes 669

- Confocal fluorescence microscopy provides three-dimensional images of extraordinary clarity 670

- Multiphoton fluorescence microscopy is a variation of confocal microscopy 670

- Intravital imaging allows observation of immune responses in vivo 671

Flow Cytometry 672

Magnetic Activated Cell Sorting 677

Cell Cycle Analysis 678

- Tritiated (³H) thymidine uptake was one of the first methods used to assess cell division 678

Colorimetric assays for cell division are rapid and eliminate the use of radioactive isotopes	678	Transgenic animals carry genes that have been artificially introduced	684
Bromodeoxyuridine-based assays for cell division use antibodies to detect newly synthesized DNA	678	Knock-in and knockout technologies replace an endogenous with a nonfunctional or engineered gene copy	685
Propidium iodide enables analysis of the cell cycle status of cell populations	678	The <i>cre/lox</i> system enables inducible gene deletion in selected tissues	687
Carboxyfluorescein succinimidyl ester can be used to follow cell division	679	SUMMARY	689
Assays of Cell Death	679	REFERENCES	690
The ⁵¹ Cr release assay was the first assay used to measure cell death	679	USEFUL WEB SITES	690
Fluorescently labeled annexin V measures phosphatidyl serine in the outer lipid envelope of apoptotic cells	680	STUDY QUESTIONS	691
The TUNEL assay measures apoptotically generated DNA fragmentation	680	Appendix I	
Caspase assays measure the activity of enzymes involved in apoptosis	681	CD Antigens	A-1
Biochemical Approaches Used to Elucidate Signal Transduction Pathways	681	Appendix II	
Biochemical inhibitors are often used to identify intermediates in signaling pathways	681	Cytokines	B-1
Many methods are used to identify proteins that interact with molecules of interest	682	Appendix III	
Whole Animal Experimental Systems	682	Chemokines and Chemokine Receptors	C-1
Animal research is subject to federal guidelines that protect nonhuman research subjects	682	Glossary	G-1
Inbred strains can reduce experimental variation	683	Answers to Study Questions	AN-1
Congenic resistant strains are used to study the effects of particular gene loci on immune responses	684	Index	I-1
Adoptive transfer experiments allow in vivo examination of isolated cell populations	684		

Feature Boxes in Kuby 7e

Clinical Focus

- Box 1.1 Vaccine Controversy: What's Truth and What's Myth? p. 5
- Box 1.2 Passive Antibodies and the Iditarod p. 8
- Box 1.3 The Hygiene Hypothesis p. 20
- Box 2.2 Stem Cells—Clinical Uses and Potential p. 42
- Box 3.2 Defects in the B-Cell Signaling Protein Btk Lead to X-Linked Agammaglobulinemia p. 93
- Box 4.2 Therapy with Interferons p. 120
- Box 4.4 Cytokines and Obesity p. 136
- Box 5.2 Genetic Defects in Components of Innate and Inflammatory Responses Associated with Disease p. 170
- Box 6.2 The Complement System as a Therapeutic Target p. 208
- Box 7.3 Some Immunodeficiencies Result from Impaired Receptor Gene Recombination p. 255
- Box 8.2 MHC Alleles and Susceptibility to Certain Diseases p. 277
- Box 8.4 Deficiencies in TAP Can Lead to Bare Lymphocyte Syndrome p. 287
- Box 9.2 How Do T Cells That Cause Type 1 Diabetes Escape Negative Selection? p. 311
- Box 9.3 Failure of Apoptosis Causes Defective Lymphocyte Homeostasis p. 322
- Box 10.1 B-Cell Development in the Aging Individual p. 333
- Box 11.2 Costimulatory Blockade p. 364
- Box 11.4 What a Disease Reveals about the Physiological Role of T_H17 Cells p. 376
- Box 13.1 Monoclonal Antibodies in the Treatment of Cancer p. 420
- Box 15.2 The Genetics of Asthma and Allergy p. 498
- Box 15.3 Type 2 Diabetes, Obesity, and Inflammation p. 511
- Box 16.1 It Takes Guts to Be Tolerant p. 523
- Box 16.2 Why Are Women More Susceptible Than Men to Autoimmunity? Gender Differences in Autoimmune Disease p. 528
- Box 16.4 Is There a Clinical Future for Xenotransplantation? p. 548
- Box 17.1 The 1918 Pandemic Influenza Virus: Should It Publish or Perish? p. 557
- Box 18.1 Prevention of Infant HIV Infection by Anti-Retroviral Treatment p. 610
- Box 19.1 A Vaccine to Prevent Cervical Cancer, and More p. 637

Evolution

- Box 2.4 Variations on Anatomical Themes p. 57
- Box 5.3 Plant Innate Immune Responses p. 178
- Box 7.2 Evolution of Recombined Lymphocyte Receptors p. 240
- Box 8.1 The Sweet Smell of Diversity p. 275

Classic Experiment

- Box 2.1 Isolating Hematopoietic Stem Cells p. 29
- Box 2.3 The Discovery of a Thymus—and Two p. 46
- Box 3.1 The Elucidation of Antibody Structure p. 82
- Box 3.3 The Discovery of the T-Cell Receptor p. 96
- Box 6.1 The Discovery of Properdin p. 198
- Box 7.1 Hozumi and Tonegawa's Experiment: DNA Recombination Occurs in immunoglobulin Genes in Somatic Cells p. 227
- Box 8.3 Demonstration of the Self-MHC Restriction of CD8⁺ T Cells p. 282
- Box 9.1 Insights about Thymic Selection from the First TCR Transgenic Mouse Have Stood the Test of Time p. 308
- Box 10.3 The Stages of B-Cell Development: Characterization of the Hardy Fractions p. 342
- Box 11.1 Discovery of the First Costimulatory Receptor: CD28 p. 362
- Box 12.1 Experimental Proof That Somatic Hypermutation and Antigen- Induced Selection Occurred Within the Germinal Centers p. 399
- Box 13.2 Rethinking Immunological Memory: NK Cells Join Lymphocytes as Memory-Capable Cells p. 442
- Box 15.1 The Discovery and Identification of IgE as the Carrier of Allergic Hypersensitivity p. 488
- Box 16.3 Early Life Exposure to Antigens Favors Tolerance Induction p. 546

Advances

- Box 4.1 Methods Used to Map the Secretome p. 111
- Box 4.3 How Does Chemokine Binding to a Cell-Surface Receptor Result in Cellular Movement Along the Chemokine Gradient? p. 130
- Box 5.1 Inflammasomes p. 162
- Box 6.3 *Staphylococcus aureus* Employs Diverse Methods to Evade Destruction by the Complement System p. 216
- Box 10.2 The Role of miRNAs in the Control of B-Cell Development p. 336
- Box 11.3 How Many TCR Complexes Must Be Engaged to Trigger T-Cell Activation? p. 368
- Box 12.2 New Ideas on B-Cell Help: Not All Cells That Help B Cells Make Antibodies Are T Cells p. 408
- Box 14.1 Dynamic Imaging Techniques p. 452
- Box 14.2 Molecular Regulation of Cell Migration Between and Within Tissues p. 456
- Box 17.2 A Prime and Pull Vaccine Strategy for Preventing Sexually Transmitted Diseases p. 586
- Box 20.1 Flow Cytometry Under the Hood p. 674

Preface

Like all of the previous authors of this book, we are dedicated to the concept that immunology is best taught and learned in an experimentally-based manner, and we have retained that emphasis with this edition. It is our goal that students should complete an immunology course not only with a firm grasp of content, but also with a clear sense of *how* key discoveries were made, what interesting questions remain, and how they might best be answered. We believe that this approach ensures that students both master fundamental immunological concepts and internalize a vision of immunology as an active and ongoing process. Guided by this vision, the new edition has been extensively updated to reflect the recent advances in all aspects of our discipline.

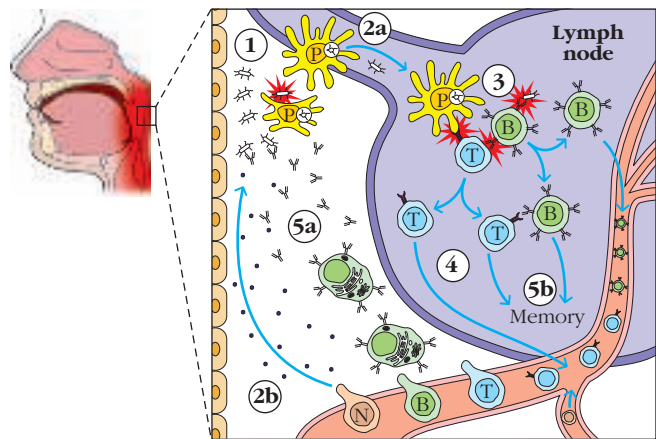
New Authorship

As a brand-new team of authors, we bring experience in both research and undergraduate teaching to the development of this new edition, which continues to reflect a dedication to pedagogical excellence originally modeled by Janis Kuby. We remain deeply respectful of Kuby's unique contribution to the teaching of immunology and hope and trust that this new manifestation of her creation will simply add to her considerable legacy.

Understanding Immunology As a Whole

We recognize that the immune system is an integrated network of cells, molecules, and organs, and that each component relies on the rest to function properly. This presents a pedagogical challenge because to understand the whole, we must attain working knowledge of many related pieces of information, and these do not always build upon each other in simple linear fashion. In acknowledgment of this challenge, this edition presents the “big picture” twice; first as an introductory overview to immunity, then, thirteen chapters later, as an integration of the details students have learned in the intervening text.

Specifically, Chapter 1 has been revised to make it more approachable for students who are new to immunology. The chapter provides a short historical background to the field and an introduction to some of the key players and their roles in the immune response, keeping an eye on fundamental concepts (Overview Figure 1-9). A new section directly addresses some of the biggest conceptual hurdles, but leaves the cellular and molecular details for later chapters.



OVERVIEW FIGURE 1-9 Collaboration between innate and adaptive immunity in resolving an infection.

A new capstone chapter (Chapter 14) integrates the events of an immune response into a complete story, with particular reference to the advanced imaging techniques that have become available since the writing of the previous edition. In this way, the molecular and cellular details presented in Chapters 2-13 are portrayed in context, a moving landscape of immune response events in time and space (Figure 14-5).

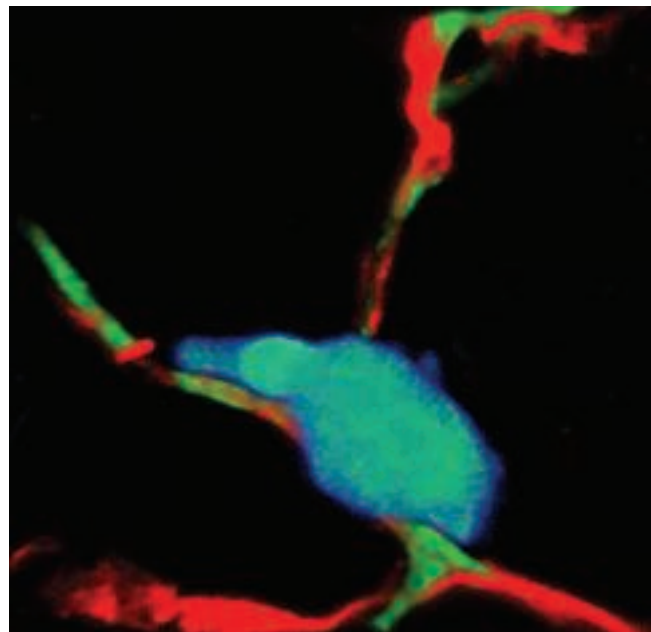


FIGURE 14-5 A T cell (blue) on a fibroblastic reticular network (red and green) in the lymph node.

Focus on the Fundamentals

The order of chapters in the seventh edition has been revised to better reflect the sequence of events that occurs naturally during an immune response *in vivo*. This offers instructors the opportunity to lead their students through the steps of an immune response in a logical sequence, once they have learned the essential features of the tissues, cells, molecular structures, ligand-receptor binding interactions, and signaling pathways necessary for the functioning of the immune system. The placement of innate immunity at the forefront of the immune response enables it to take its rightful place as the first, and often the only, aspect of immunity that an organism needs to counter an immune insult. Similarly, the chapter on complement is located within the sequence in a place that highlights its function as a bridge between innate and adaptive immune processes. However, we recognize that a course in immunology is approached differently by each instructor. Therefore, as much as possible, we have designed each of the chapters so that it can stand alone and be offered in an alternative order.

Challenging All Levels

While this book is written as a text for students new to immunology, it is also our intent to challenge students to reach deeply into the field and to appreciate the connections with other aspects of biology. Instead of reducing difficult topics to vague and simplistic forms, we instead present them with the level of detail and clarity necessary to allow the beginning student to find and understand information they may need in the future. This offers the upper level student a foundation from which they can progress to the investigation of advances and controversies within the current immunological literature. Supplementary focus boxes have been used to add nuance or detail to discussions of particular experiments or ideas without detracting from the flow of information. These boxes, which address experimental approaches, evolutionary connections, clinical aspects, or advanced material, also allow instructors to tailor their use appropriately for individual courses. They provide excellent launching points for more intensive in class discussions relevant to the material.

Some of the most visible changes and improvements include:

- A rewritten chapter on the cells and organs of the immune system (Chapter 2) that includes up to date images reflecting our new understanding of the microenvironments where the host immune system develops and responds.
- The consolidation of signaling pathways into two chapters: Chapter 3 includes a basic introduction to ligand:receptor interactions and principles of receptor

signaling, as well as to specific molecules and pathways involved in signaling through antigen receptors. Chapter 4 includes a more thorough introduction to the roles of cytokines and chemokines in the immune response.

- An expanded and updated treatment of innate immunity (Chapter 5), which now includes comprehensive coverage of the many physical, chemical, and cellular defenses that constitute the innate immune system, as well as the ways in which it activates and regulates adaptive immunity.
- Substantial rewriting of chapters concerned with complement (Chapter 6) and antigen receptor gene rearrangement (Chapter 7). These chapters have been extensively revised for clarity in both text and figures. The description of the complement system has been updated to include the involvement of complement proteins in both innate and adaptive aspects of immunity.
- A restructured presentation of the MHC, with the addition of new information relevant to cross-presentation pathways (Chapter 8) (Figure 8-22b).

(b) DC cross-presentation and activation of CTL

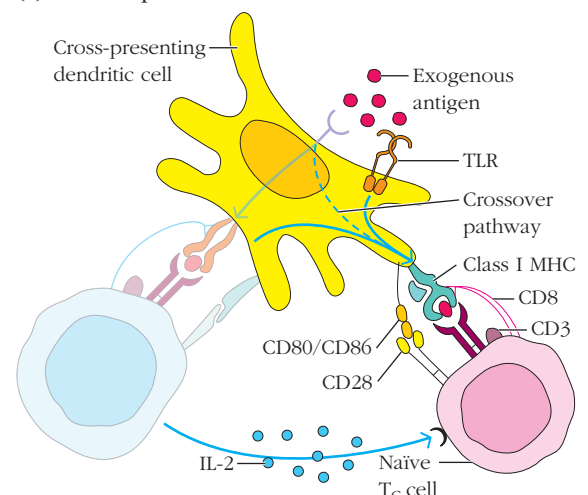


FIGURE 8-22b Exogenous antigen activation of naïve T_c cells requires DC licensing and cross-presentation

- The dedication of specialized chapters concerned with T cell development and T cell activation (Chapters 9 and Chapter 11, respectively). Chapter 11 now includes current descriptions of the multiple helper T cell subsets that regulate the adaptive immune response.
- Substantially rewritten chapters on B cell development and B cell activation (Chapters 10 and 12, respectively) that address the physiological locations as well as the nature of the interacting cells implicated in these processes.
- An updated discussion of the role of effector cells and molecules in clearing infection (Chapter 13), including a more thorough treatment of NK and NKT cells.

- A new chapter that describes advances in understanding and visualizing the dynamic behavior and activities of immune cells in secondary and tertiary tissue (Chapter 14).
- Substantial revision and updating of the clinical chapters (Chapters 15-19) including the addition of several new clinically relevant focus boxes.
- Revised and updated versions of the final methods chapter (Chapter 20), and the appendices of CD antigens, chemokines, and cytokines and their receptors.

Throughout the book, we attempt to provide a “big picture” context for necessary details in a way that facilitates greater student understanding.

Recent Advances and Other Additions

Immunology is a rapidly growing field, with new discoveries, advances in techniques, and previously unappreciated connections coming to light every day. The 7th edition has been thoroughly updated throughout, and now integrates the following new material and concepts:

- New immune cell types and subtypes, as well as the phenotypic plasticity that is possible between certain subtypes of immune cells.
- A greater appreciation for the wide range of mechanisms responsible for innate immunity and the nature and roles of innate responses in sensing danger, inducing inflammation, and shaping the adaptive response (Figure 5-18).

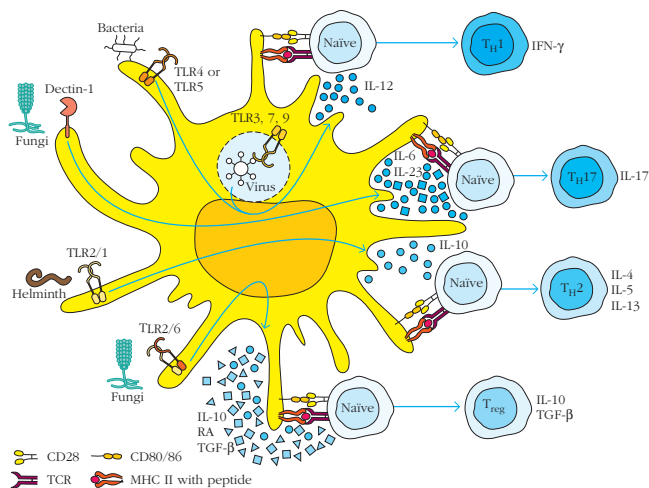


FIGURE 5-18 Differential signaling through dendritic cell PRRs influences helper T cell functions.

- Regulation of immunity, including new regulatory cell types, immunosuppressive chemical messengers and the roles these play, for example, in tolerance and in the nature of responses to different types of antigens (Figure 9-10).

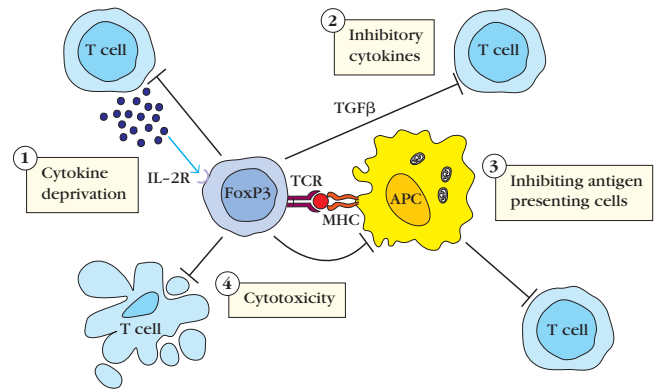


FIGURE 9-10 How regulatory T cells inactivate traditional T cells.

- The roles of the microbiome and commensal organisms in the development and function of immunity, as well as the connections between these and many chronic diseases.
- A new appreciation for the micro environmental substructures that guide immune cell interactions with antigen and with one another (Figure 14-11a).

Antigen delivery to T cells

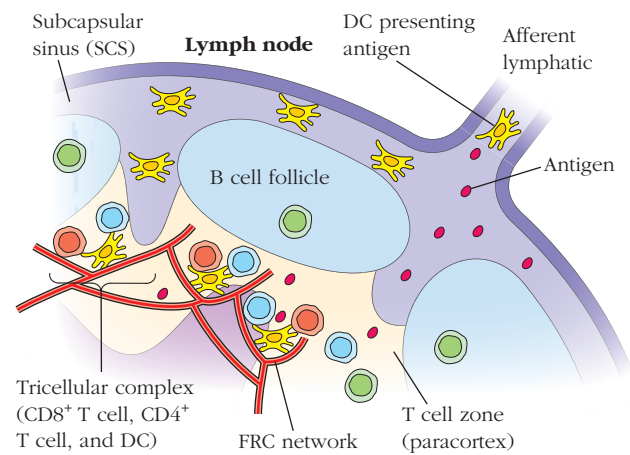


FIGURE 14-11a How antigen travels into a lymph node.

- Many technical advances, especially in the areas of imaging and sequencing, which have collectively enhanced our understanding of immune function and cellular interactions, allowing us to view the immune response in its natural anatomical context, and in real time (see Figure 14-5).

Connections to the Bench, the Clinic, and Beyond

We have made a concerted effort in the 7th edition to integrate experimental and clinical aspects of immunology into the text. In Chapter 2, illustrations of immune cells and tissues are shown alongside histological sections or, where possible, electron

- [read online The Messiah of Stockholm](#)
- [read **Les Jours de l'Éclipse** online](#)
- [download online Michael Symon's Live to Cook: Recipes and Techniques to Rock Your Kitchen](#)
- [read The Sailing Frigate: A History in Ship Models](#)
- [download *Eel \(Animal\)*](#)

- <http://bestarthritiscare.com/library/The-Messiah-of-Stockholm.pdf>
- <http://weddingcellist.com/lib/Les-Jours-de-l---clipse.pdf>
- <http://aseasonedman.com/ebooks/Michael-Symon-s-Live-to-Cook--Recipes-and-Techniques-to-Rock-Your-Kitchen.pdf>
- <http://paulczajak.com/?library/The-Sailing-Frigate--A-History-in-Ship-Models.pdf>
- <http://betsy.wesleychapelcomputerrepair.com/library/Lonely-Planet-Hawaii--9th-Edition-.pdf>