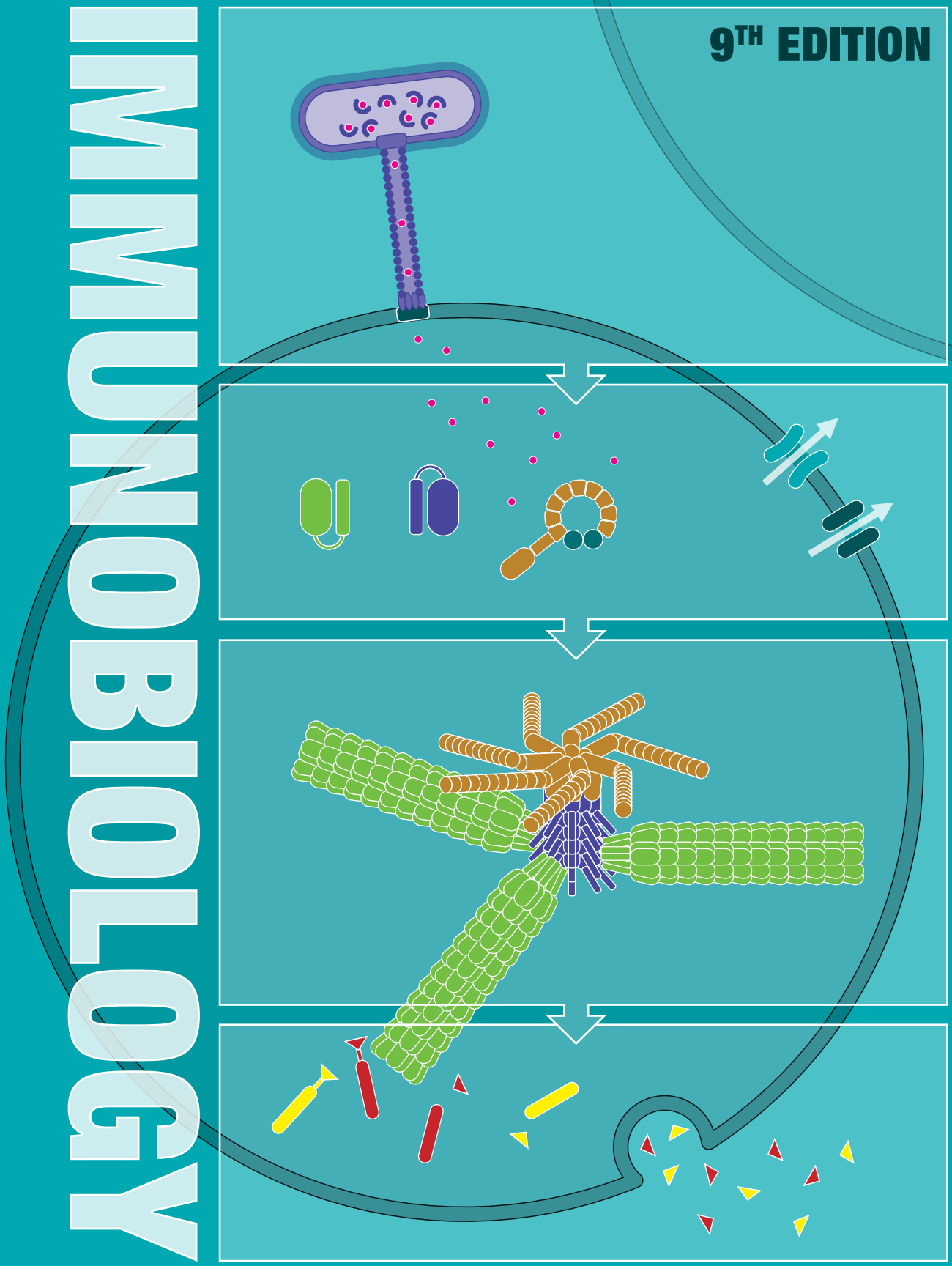
JANEWAY'S

IMMUNOBIOLOGY

9TH EDITION



KENNETH MURPHY & CASEY WEAVER

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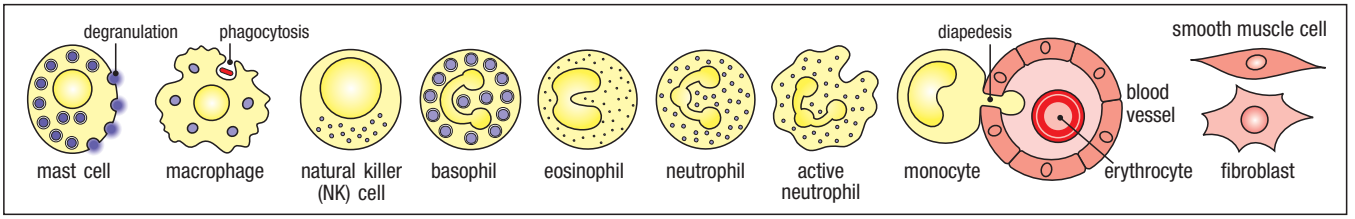

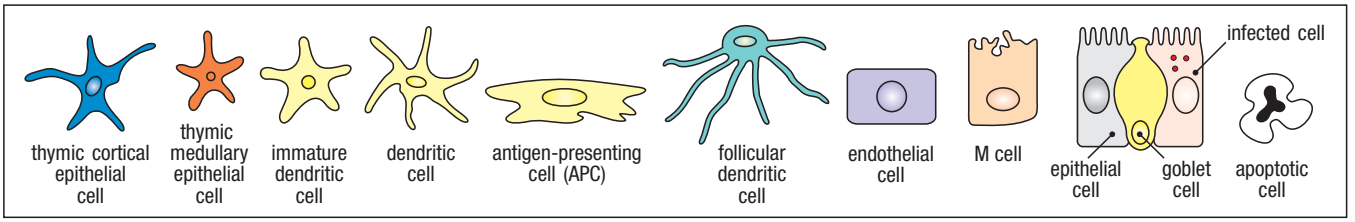

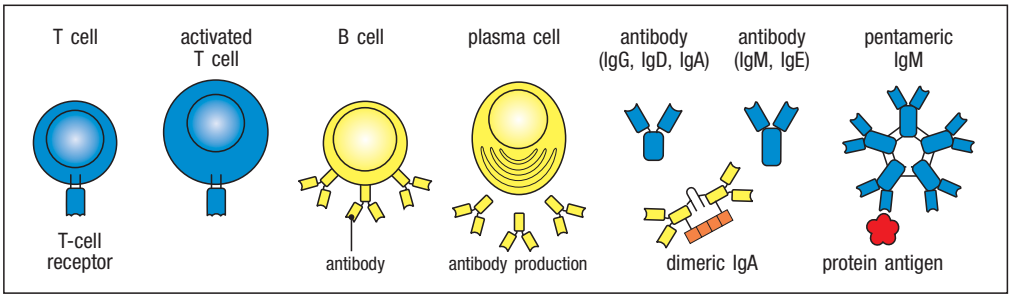

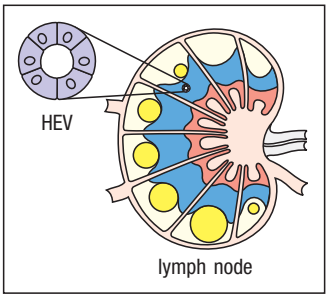

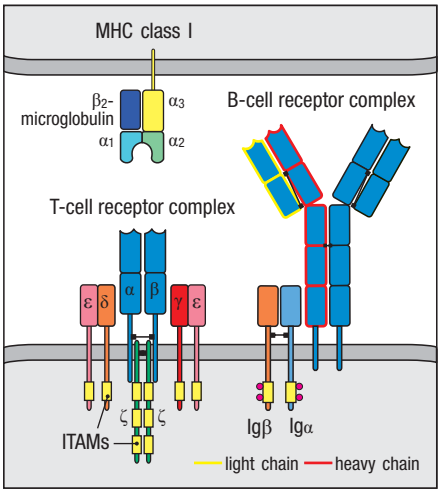

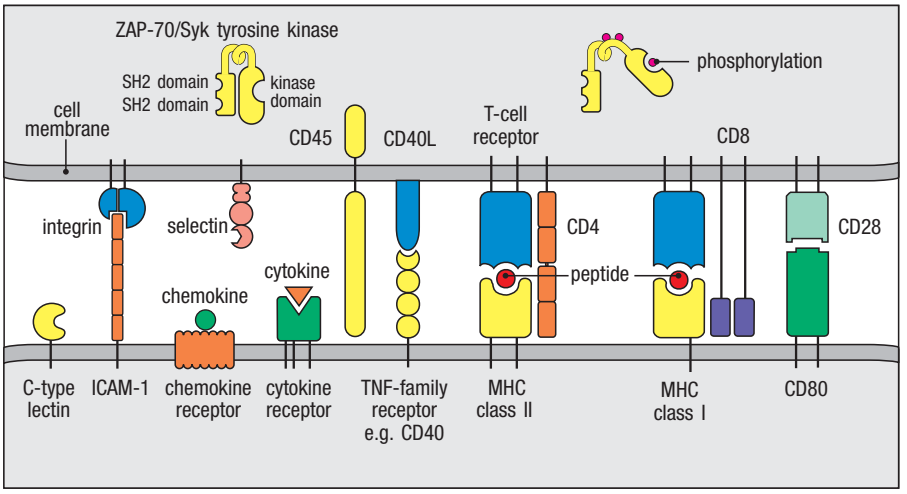

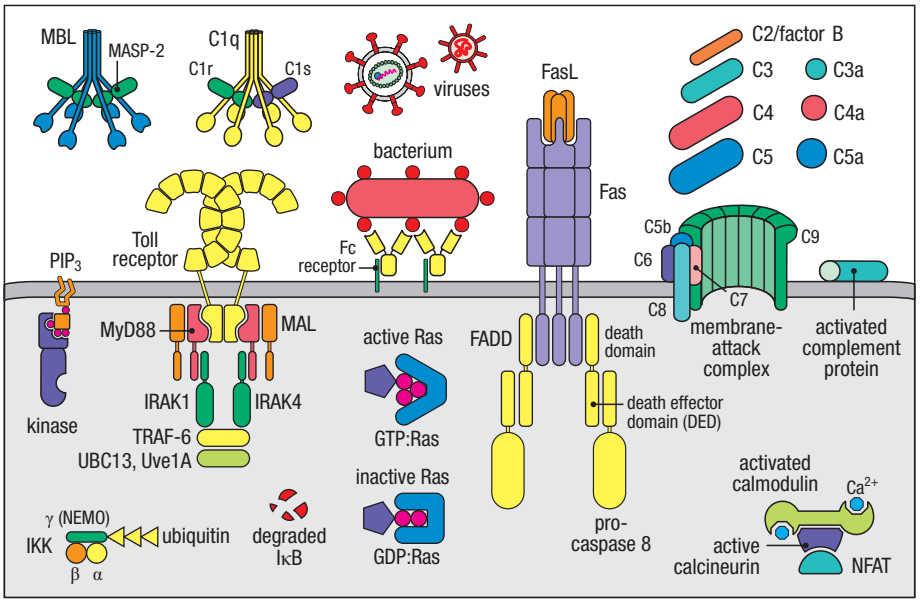

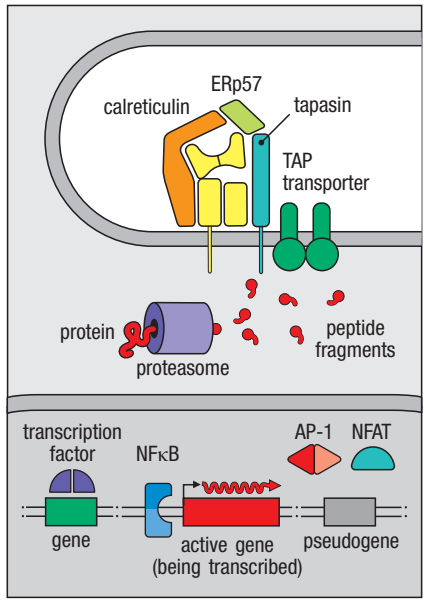

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Kenneth Murphy
Washington University School of Medicine, St. Louis

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

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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.

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Detailed Contents

APPENDICES

Fig. 13.1 Human immunodeficiency syndromes. The specific gene defect, the consequence for the immune system, and the resulting disease susceptibilities are listed for some common and some rare human immunodeficiency syndromes. Severe combined immunodeficiency (SCID) can be due to many different defects, as summarized in Fig. 13.2 and described in the text. AID, activation-induced cytidine deaminase; ATM, ataxia telangiectasia-mutated protein; EBV, Epstein–Barr virus; IKK, inhibitor of κ B kinase; STAT3, signal transducer and activator of transcription 3; TAP, transporters associated with antigen processing; UNG, uracil-DNA glycosylase.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	See text and Fig. 13.2		General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T cells	General
MHC class I deficiency	Mutations in TAP1, TAP2, and tapasin	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott–Aldrich syndrome	X-linked; defective WASp gene	Defective anti-polysaccharide antibody, impaired T-cell activation responses, and T_{reg} dysfunction	Encapsulated extracellular bacteria Herpesvirus infections (e.g., HSV, EBV)
X-linked agamma-globulinemia	Loss of BTK tyrosine kinase	No B cells	Extracellular bacteria, enteroviruses
Hyper-IgM syndrome	CD40 ligand deficiency CD40 deficiency NEMO (IKK) deficiency	No isotype switching and/or no somatic hypermutation plus T-cell defects	Extracellular bacteria *Pneumocystis jirovecii* *Cryptosporidium parvum*
Hyper-IgM syndrome—B-cell intrinsic	AID deficiency UNG deficiency	No isotype switching +/– normal somatic hypermutation	Extracellular bacteria
Hyper-IgE syndrome (Job's syndrome)	Defective STAT3	Block in T_H17 cell differentiation Elevated IgE	Extracellular bacteria and fungi
Common variable immunodeficiency	Mutations in TACI, ICOS, CD19, etc.	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
X-linked lympho-proliferative syndrome	Mutations in SAP or XIAP	Inability to control B-cell growth	EBV-driven B-cell tumors Fatal infectious mononucleosis
Ataxia telangiectasia	Mutations in ATM	T cells reduced	Respiratory infections
Bloom's syndrome	Defective DNA helicase	T cells reduced Reduced antibody levels	Respiratory infections

a role for the cytokine in T-cell maturation and trafficking. Mice with targeted mutations in IL-15 itself or the α chain of its receptor also have no NK cells and relatively normal T-cell development, but they show a more specific T-cell defect, primarily limited to impaired maintenance of memory CD8 T cells.

Humans with a deficiency of the IL-7 receptor α chain have no T cells but normal levels of NK cells, illustrating that IL-7 signaling, while essential for T-cell development, is not essential for the development of NK cells (see Fig. 13.2). Interestingly, mice with a gene-targeted deficiency of the IL-7R

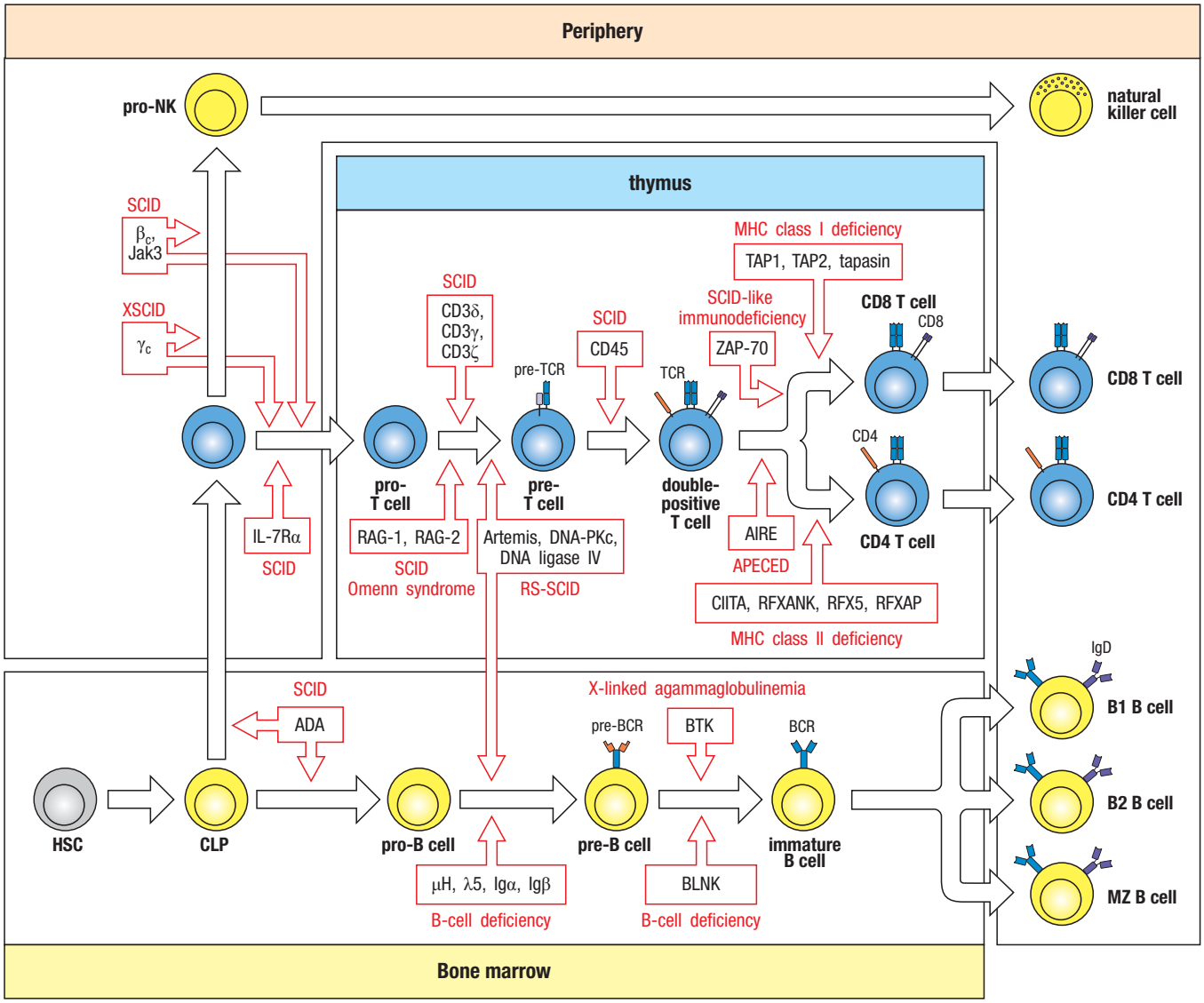

Fig. 13.2 Defects in T-cell and B-cell development that cause immunodeficiency. The pathways leading to circulating naive T cells and B cells are shown here. Mutations in genes that encode the proteins (indicated in red boxes) are known to cause human immunodeficiency diseases. BCR, B-cell receptor; CLP, common lymphoid progenitor; HSC, hematopoietic stem cell; MZ B cell, marginal zone B cell; pre-BCR, pre-B-cell receptor; pre-TCR, pre-T-cell receptor; RS-SCID, radiation-sensitive SCID; SCID, severe combined immunodeficiency; TCR, T-cell receptor; XSCID, X-linked SCID. Immunodeficiency can also be caused by mutations in genes in the thymic epithelium that impair thymic development, and thus T-cell development.

share with humans a deficiency of T cells, but also lack B cells, which is not the case in humans. This illustrates the species-specific role of certain cytokines, and provides a cautionary note against extrapolating findings from mice to humans. In humans and mice whose T cells show defective production of IL-2 after receptor stimulation, most T-cell development itself is normal, although there is impaired development of FoxP3$^+$ T_{reg} cells that predisposes to immune-regulatory abnormalities and autoimmunity (see Chapter 15). The more limited effects of individual cytokine signaling defects are in contrast to the global defects in T- and NK-cell development in patients with XSCID.

As in all serious T-cell deficiencies, patients with XSCID do not make effective antibody responses to most antigens, although their B cells seem normal. Most, but not all, naive IgM-positive B cells from female carriers of XSCID have inactivated the defective X chromosome rather than the normal one (see Section 13-3), showing that B-cell development is affected by, but is not wholly