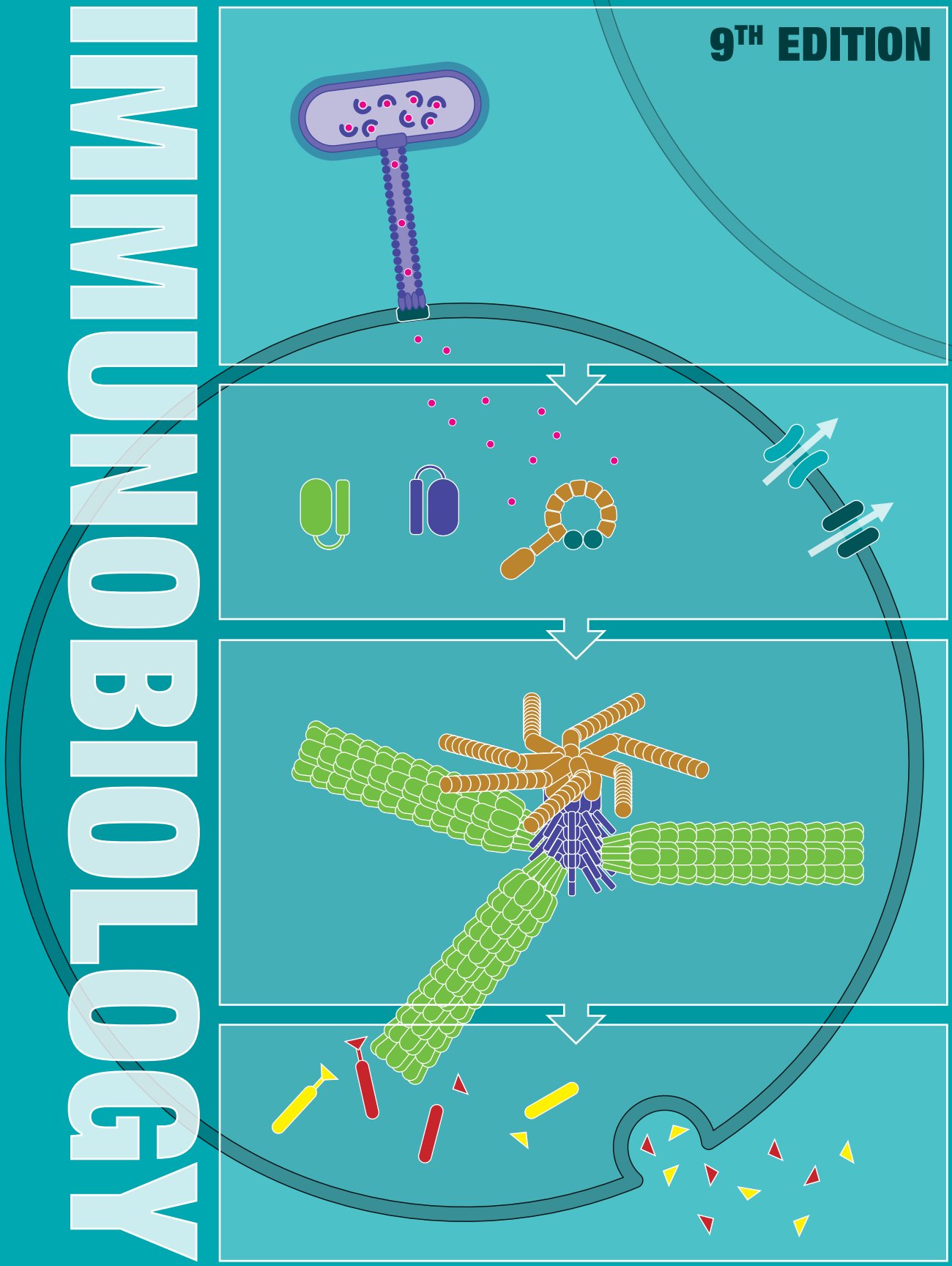
JANEWAY'S

IMMUNOBIOLOGY

9TH EDITION



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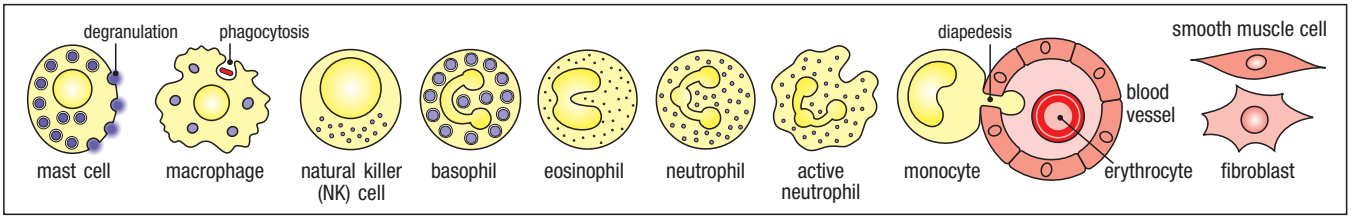

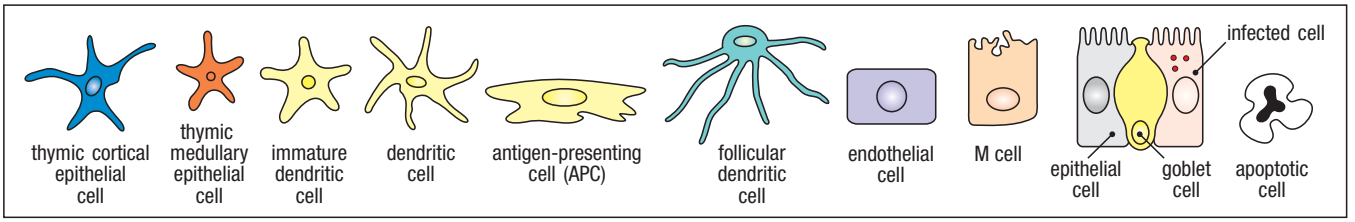

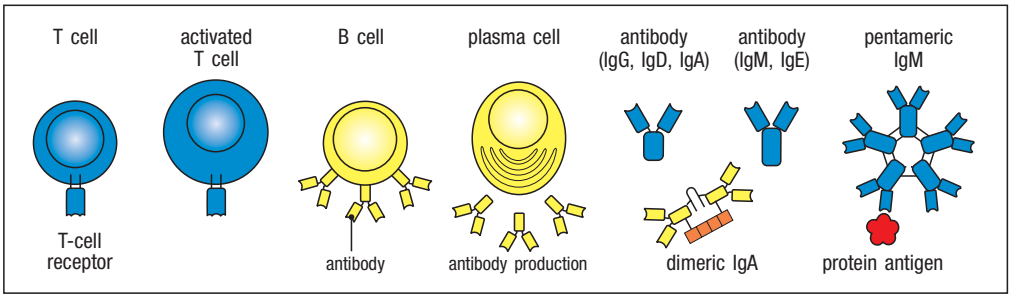

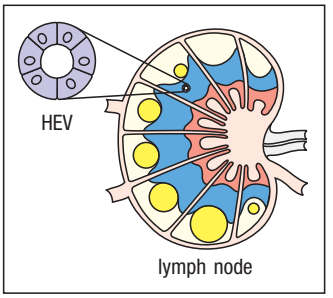

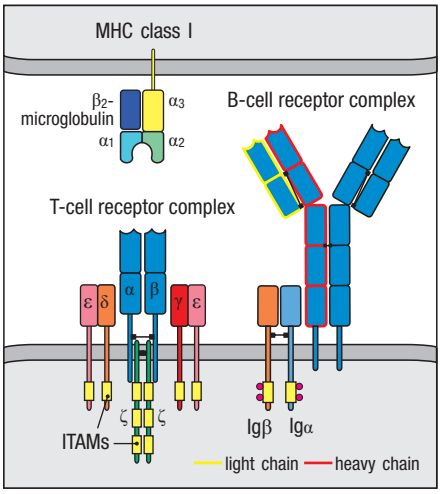

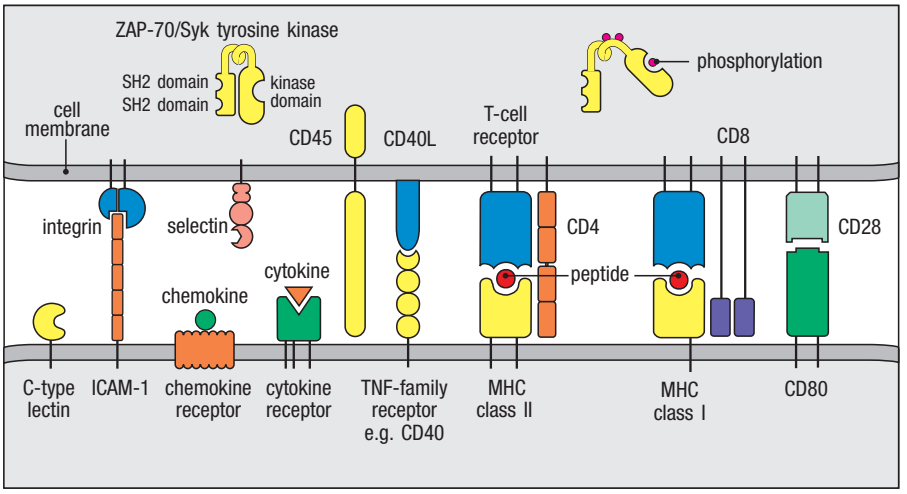

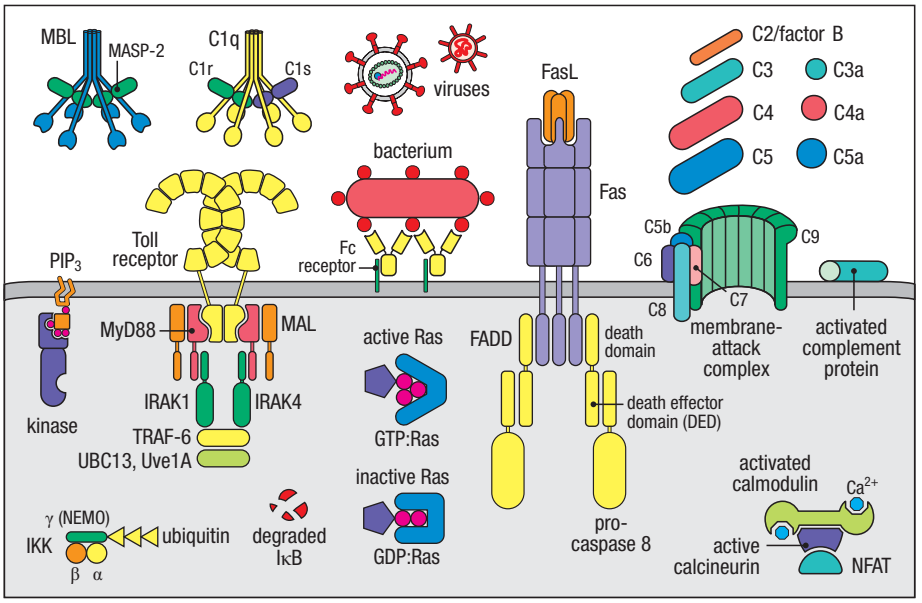

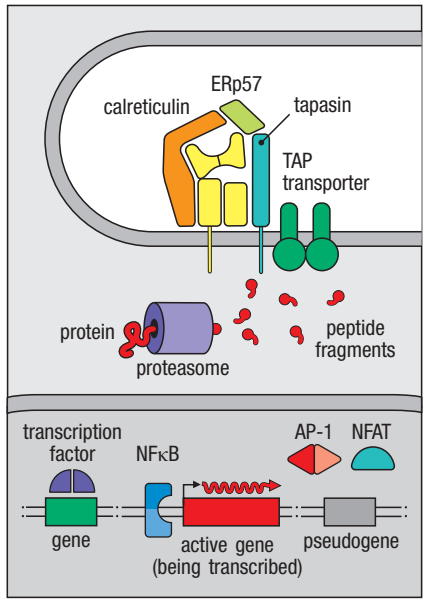

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JANEWAY'S IMMUNO BIOLOGY

9TH EDITION

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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

dendritic cells). This results in heightened susceptibility to intracellular bacteria, particularly atypical *Mycobacterium* spp., without the myeloproliferative syndrome seen in patients with the autosomal recessive variant.

13-14 Defects in complement components and complement-regulatory proteins cause defective humoral immune function and tissue damage.

The diseases discussed so far are mainly due to disturbances of the adaptive immune system. In the next few sections we look at some immunodeficiency diseases that affect cells and molecules of the innate immune system. We start with the complement system, which can be activated by any of three pathways that converge on the cleavage and activation of complement component C3, allowing it to bind covalently to pathogen surfaces, where it acts as an opsonin (discussed in Chapter 2). Not surprisingly, the spectrum of infections associated with complement deficiencies overlaps substantially with that seen in patients with deficiencies in antibody production. In particular, there is increased susceptibility to extracellular bacteria that require opsonization by antibody and/or complement for efficient clearance by phagocytes (Fig. 13.11). Defects in the activation of C3 by any of the three pathways, as well as defects in C3 itself, are associated with increased susceptibility to infection by a range of pyogenic bacteria, including *S. pneumoniae*, emphasizing the role of C3 as a central effector that promotes the phagocytosis and clearance of capsulated bacteria.

In contrast, defects in the membrane-attack components of complement (C5-C9) downstream of C3 activation have more limited effects, and result almost exclusively in susceptibility to *Neisseria* species. A similar susceptibility to *Neisseria* species is found in patients with defects in the alternative complement pathway components factor D and properdin, indicating that defense against these bacteria, which can survive intracellularly, is largely mediated via antibody-independent extracellular lysis by the membrane-attack complex. Data from large-population studies in Japan, where endemic *N. meningitidis* infection is rare, show that the risk each year of infection with this organism

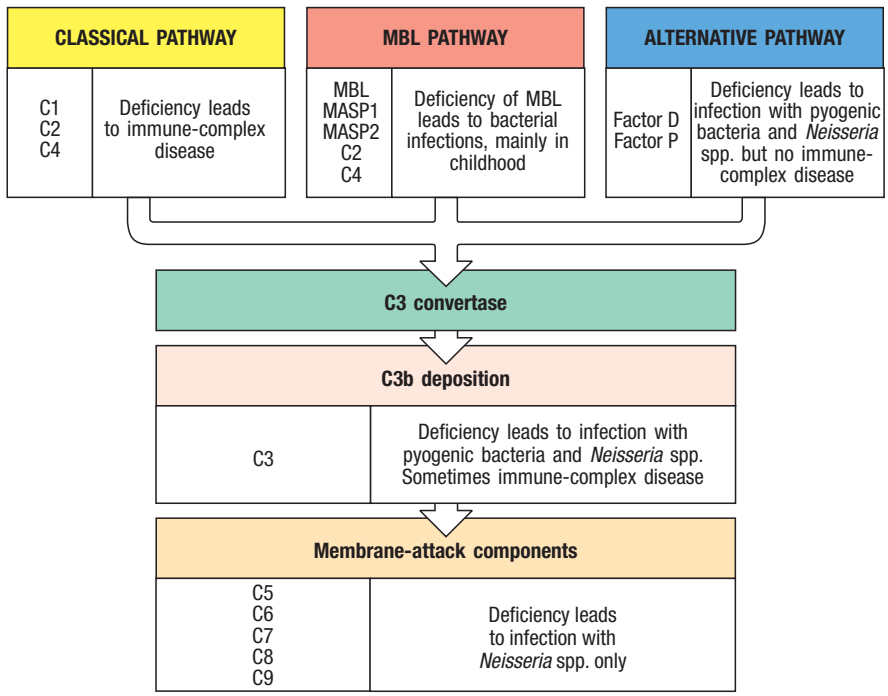

Fig. 13.11 Defects in complement components are associated with susceptibility to certain infections and the accumulation of immune complexes. Defects in the early components of the alternative pathway and in C3 lead to susceptibility to extracellular pathogens, particularly pyogenic bacteria. Defects in the early components of the classical pathway predominantly affect the processing of immune complexes (see Section 10-20) and the clearance of apoptotic cells, leading to immune-complex disease. Deficiency of mannose-binding lectin (MBL), the recognition molecule of the mannose-binding lectin pathway, is associated with bacterial infections, mainly in early childhood. Defects in the membrane-attack components are associated only with susceptibility to strains of *Neisseria* species, the causative agents of meningitis and gonorrhea, implying that the effector pathway is important chiefly in defense against these organisms.

is approximately 1 in 2,000,000 to a normal person. This compares with a risk of 1 in 200 to a person in the same population with an inherited deficiency of one of the membrane-attack complex proteins—a 10,000-fold increase in risk.

The early components of the classical complement pathway are particularly important for the elimination of immune complexes (discussed in Section 10-20) and apoptotic cells, which can cause significant pathology in autoimmune diseases such as systemic lupus erythematosus. This aspect of inherited complement deficiency is discussed in Chapter 15. Deficiencies in mannose-binding lectin (MBL), which initiates complement activation independently of antibody (see Section 2-6), are relatively common (found in 5% of the population). MBL deficiency may be associated with a mild immunodeficiency that results in an increased incidence of bacterial infection in early childhood. A similar phenotype is found in patients with defects in the gene that encodes the MBL-associated serine protease-2 (*MASP2*).

Another set of complement-related diseases is caused by defects in complement-control proteins (Fig. 13.12). Deficiencies in decay-accelerating factor (DAF) or protectin (CD59), membrane-associated control proteins that protect the surfaces of the body's cells from complement activation, lead to destruction of red blood cells, resulting in the disease **paroxysmal nocturnal hemoglobinuria**, as discussed in Section 2-16. Deficiencies in soluble complement-regulatory proteins such as factor I and factor H have various outcomes. Homozygous **factor I deficiency** is a rare defect that results in uncontrolled activity of the alternative pathway C3 convertase, leading to a *de facto* C3 deficiency (see Section 2-16). Deficiencies in MCP, factor I, or factor H can also cause a condition known as **atypical hemolytic–uremic syndrome**, so called because it leads to lysis of red blood cells (hemolysis) and impaired kidney function (uremia).

A striking consequence of the loss of a complement-regulatory protein is seen in patients with C1-inhibitor defects, which cause the syndrome known as **hereditary angioedema** (**HAE**) (see Section 2-16). Deficiency of C1 inhibitor results in a failure to regulate both the blood clotting and complement activation pathways, leading to excessive production of vasoactive mediators that cause fluid accumulation in the tissues (edema) and local laryngeal swelling that can result in suffocation.

Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to encapsulated bacteria
C5–C9	Susceptibility to *Neisseria*
Factor D, prosperdin (factor P)	Susceptibility to encapsulated bacteria and *Neisseria* but no immune-complex disease
Factor I	Similar effects to deficency of C3
MCP, factor I or factor H	Atypical hemolytic-uremic syndrome
Polymorphisms in factor H	Age-related macular degeneration
DAF, CD59	Autoimmune-like conditions, including paroxysmal nocturnal hemoglobinuria
C1INH	Herditary angiodema (HAE)

Fig. 13.12 Defects in complement-control proteins are associated with a range of diseases.

13-15 Defects in phagocytic cells permit widespread bacterial infections.

Deficiencies in phagocyte numbers or function can be associated with severe immunodeficiency; indeed, a total absence of neutrophils is incompatible with survival in a normal environment. Phagocyte immunodeficiencies can be grouped into four general types: deficiencies in phagocyte production, phagocyte adhesion, phagocyte activation, and phagocyte killing of microorganisms (Fig. 13.13). We consider each in turn.

Inherited deficiencies of neutrophil production (**neutropenias**) are classified either as **severe congenital neutropenia** (**SCN**) or **cyclic neutropenia**. In severe congenital neutropenia, which can be inherited as a dominant or recessive trait, the neutrophil count is persistently less than 0.5×10^9 per liter of blood (normal numbers are 3×10^9 to 5.5×10^9 per liter). Cyclic neutropenia is characterized by fluctuation in neutrophil numbers from near normal to very low or undetectable with an approximate cycle time of 21 days, resulting in periodicity of infectious risk. The most common causes of SCN are sporadic or autosomal dominant mutations of the gene that encodes neutrophil elastase (*ELA2*), a component of the azurophilic, or primary, granules involved in the degradation of phagocytosed microbes. Altered targeting of defective elastase 2 to granules causes apoptosis of developing myelocytes and a developmental block at the promyelocyte–myelocyte stage. Some mutations of *ELA2* cause

Type of defect/name of syndrome	Associated infections or other diseases
Congenital neutropenias (e.g., elastase 2 deficiency)	Widespread pyogenic bacterial infections
Leukocyte adhesion deficiency	Widespread pyogenic bacterial infections
TLR signaling defects (e.g., MyD88 or IRAK4)	Severe cold pyogenic bacterial infections
Chronic granulomatous disease	Intracellular and extracellular infection, granulomas
G6PD deficiency	Defective respiratory burst, chronic infection
Myeloperoxidase deficiency	Defective intracellular killing, chronic infection
Chediak–Higashi syndrome	Intracellular and extracellular infection, granulomas

Fig. 13.13 Defects in phagocytic cells are associated with persistence of bacterial infection. Defects in neutrophil development caused by congenital neutropenias result in profound defects in antibacterial defense. Impairment of the leukocyte integrins with a common β_2 subunit (CD18) or defects in the selectin ligand sialyl-Lewis^X, prevent phagocytic cell adhesion and migration to sites of infection (leukocyte adhesion deficiency). Inability to transmit signals through Toll-like receptors (TLRs), due to defects in MyD88 or IRAK4, for example, impairs the proximal sensing of many infectious agents by innate immune cells. The respiratory burst is defective in chronic granulomatous disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and myeloperoxidase deficiency. In chronic granulomatous disease, infections persist because macrophage activation is defective, leading to chronic stimulation of CD4 T cells and hence to granulomas. Vesicle fusion in phagocytes is defective in Chediak–Higashi syndrome. These diseases illustrate the critical role of phagocytes in removing and killing pathogenic bacteria.

cyclic neutropenia; how the mutant elastase causes a 21-day cycle in neutropenia is still a mystery. A rare autosomal dominant form of SCN is caused by mutations in the oncogene *GFI1*, which encodes a transcriptional repressor that acts on *ELA2*. This finding arose from the unexpected observation that mice lacking the protein Gfi1 are neutropenic due to overexpression of *Ela2*.

Autosomal recessive forms of SCN have also been identified. Deficiency of the mitochondrial protein HAX1 leads to increased apoptosis in developing myeloid cells, resulting in a severe neutropenia referred to as **Kostmann's disease**. The heightened sensitivity of developing neutrophils to apoptosis is highlighted by SCN associated with genetic defects in glucose metabolism. Patients with recessive mutations in the genes encoding the glucose-6-phosphatase catalytic subunit 3 (*G6PC3*) or the glucose-6-phosphate translocase 1 (*SLC37A4*) also demonstrate increased apoptosis during granulocyte development that results in neutropenia. Acquired neutropenia associated with chemotherapy, malignancy, or aplastic anemia is also associated with a similar spectrum of severe pyogenic bacterial infections. Finally, neutropenia can also be a feature of other primary immunodeficiency diseases, including CD40 ligand deficiency, CVID, XLA, Wiskott–Aldrich syndrome, and GATA2 deficiency. Some patients exhibit formation of autoantibodies that lead to accelerated destruction of neutrophils.

Defects in the migration of phagocytic cells to extravascular sites of infection can cause serious immunodeficiency. Leukocytes reach such sites by emigrating from blood vessels in a tightly regulated process (see Fig. 3.31). Deficiencies in the molecules involved in each stage of this process can prevent neutrophils and macrophages from penetrating infected tissues, and are referred to as **leukocyte adhesion deficiencies** (**LADs**). Deficiency in the leukocyte integrin common β_2 subunit CD18, which is a component of LFA-1, MAC-1, and p150:95, prevents the migration of leukocytes into an infected site by abolishing the cells' ability to adhere tightly to the endothelium. Because it was the first LAD to be characterized, it is now referred to as type 1 LAD, or LAD-1, and is the most common LAD variant. Reduced rolling of leukocytes on the endothelium has been described in rare patients who lack the sialyl-Lewis^X antigen owing to a deficiency in the GDP-fucose-specific transporter that is involved in the biosynthesis of sialyl-Lewis^X and other fucosylated ligands for the selectins. This is referred to as type 2 LAD or LAD-2. LAD-3 results from deficiency of Kindlin-3, a protein involved in the induction of the high-affinity binding state of β integrins required for firm adhesion. Each variant of LAD has an autosomal recessive pattern of inheritance and causes severe, life-threatening bacterial or fungal infections early in life that are characterized by impaired wound healing and, in pyogenic bacterial infections, the absence of