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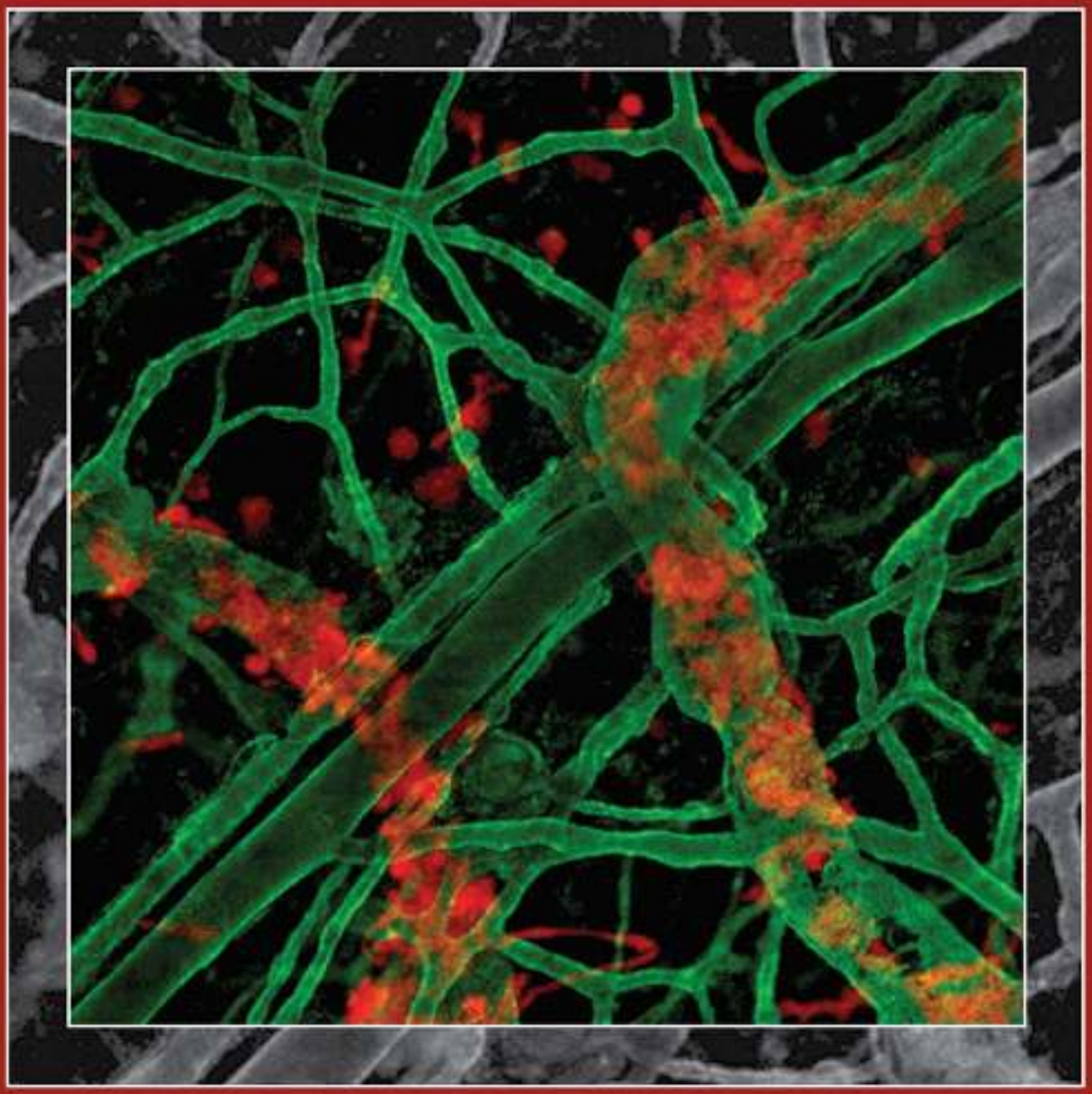
IMMUNOLOGY

SEVENTH EDITION



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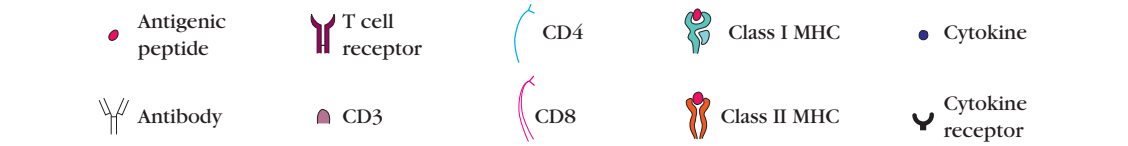
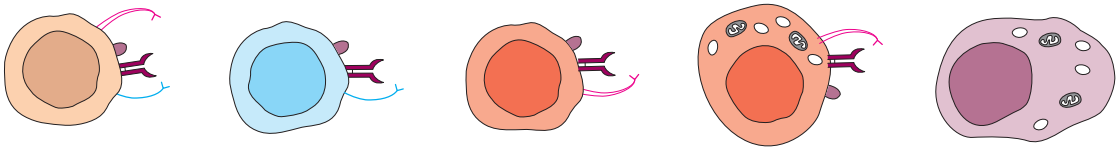




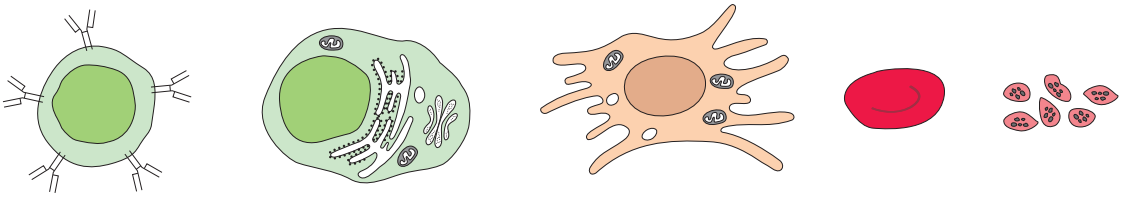
Immature thymocyte

T_H cell

T_C cell

Cytotoxic T cell

Natural killer cell



B cell

Plasma cell

Bone marrow stromal cell

Erythrocyte

Platelets

Neutrophil

Basophil

Eosinophil

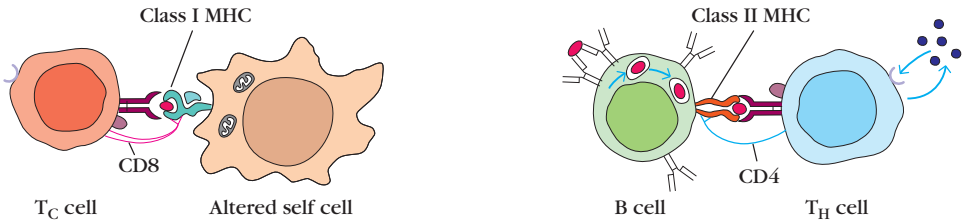
Mast cell

Dendritic cell

Monocyte

Macrophage

Antigen-presenting cell



T_C cell

Altered self cell

B cell

T_H cell

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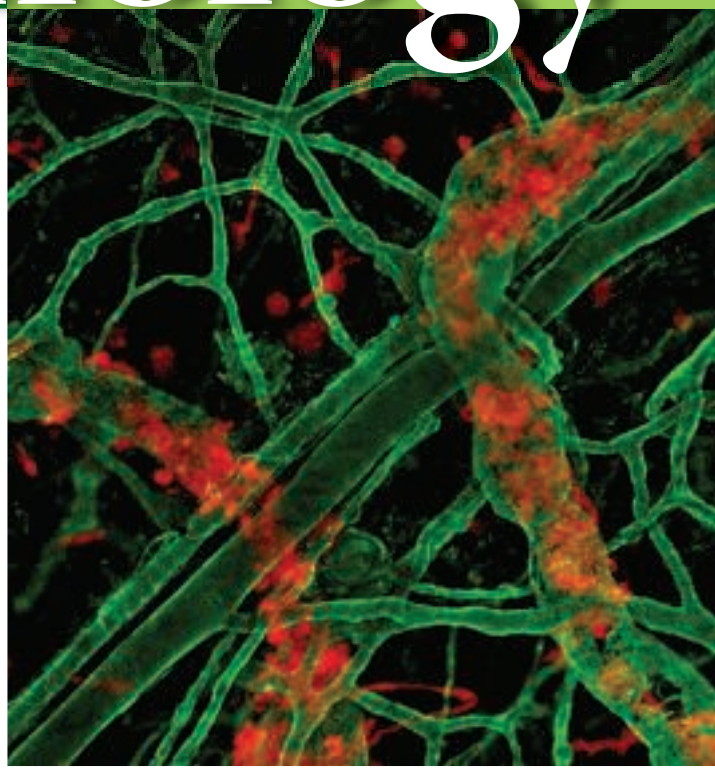

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To all our students, fellows, and colleagues who have made our careers in immunology a source of joy and excitement, and to our families who made these careers possible. We hope that future generations of immunology students will find this subject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

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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.

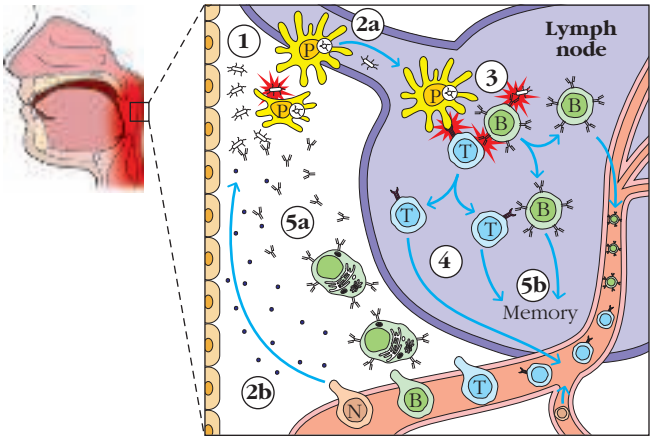
New Authorship

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).

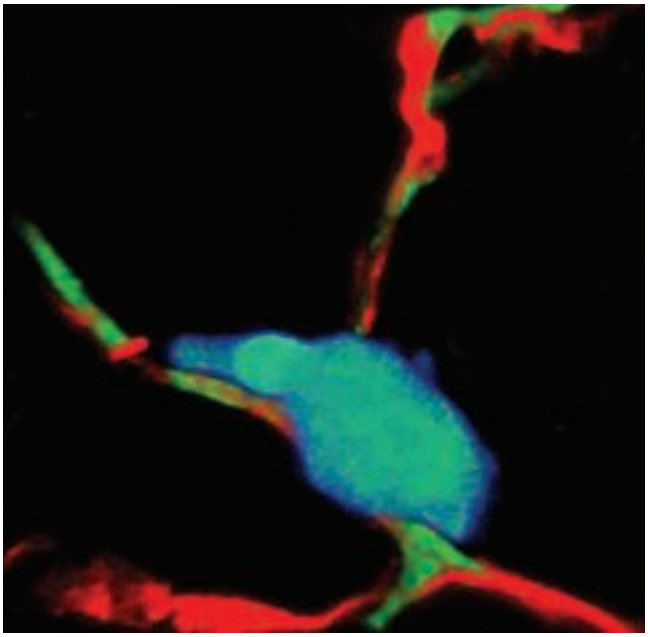


FIGURE 14-5 A T cell (blue) on a fibroblastic reticular network (red and green) in the lymph node.

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).

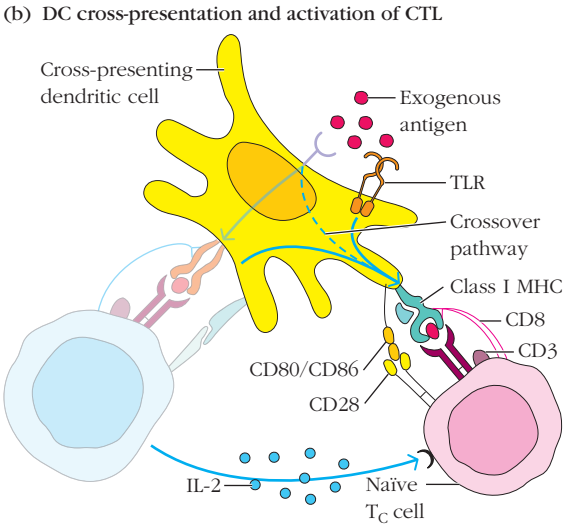


FIGURE 8-22b Exogenous antigen activation of naïve T_C cells requires DC licensing and cross-presentation

- 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).

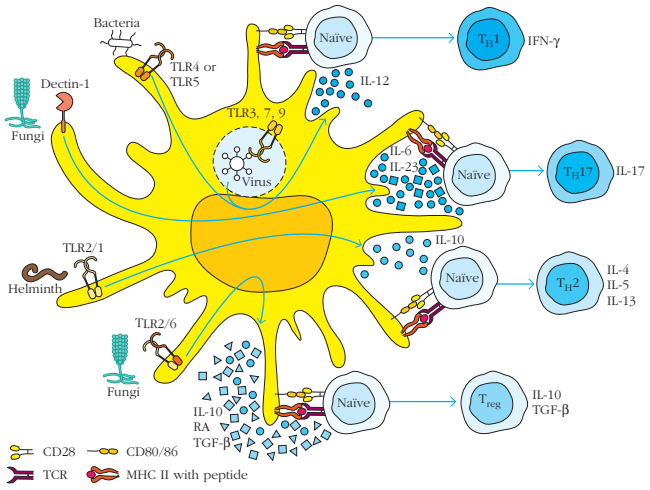


FIGURE 5-18 Differential signaling through dendritic cell PRRs influences helper T cell functions.

- 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).

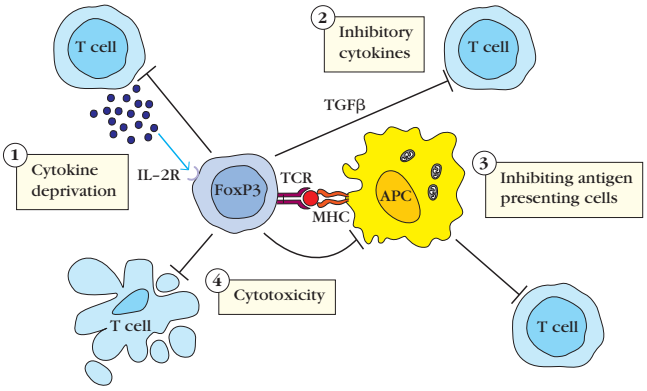


FIGURE 9-10 How regulatory T cells inactivate traditional T cells.

- 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).

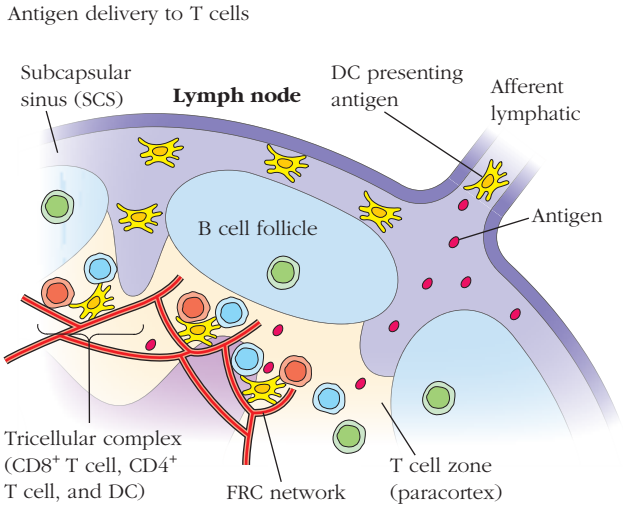


FIGURE 14-11a How antigen travels into a lymph node.

- 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