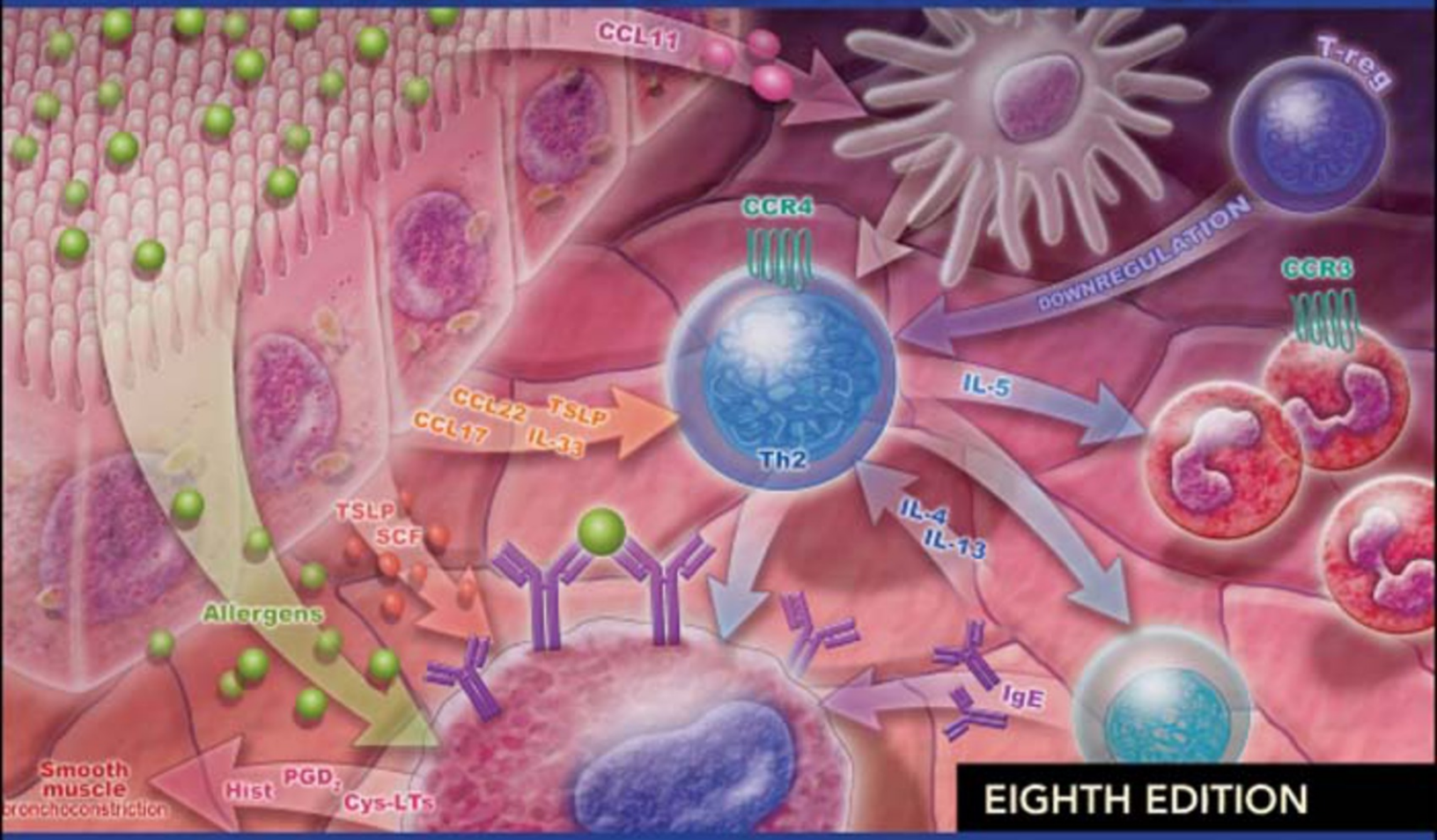
Middleton's ALLERGY

Volume 1

PRINCIPLES & PRACTICE



EIGHTH EDITION

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Middleton's ALLERGY PRINCIPLES AND PRACTICE

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EIGHTH EDITION—VOLUME 1

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PREFACE TO THE EIGHTH EDITION

With the publication of the eighth edition of *Middleton's Allergy: Principles and Practice*, the "beat goes on" for a textbook that was established nearly 40 years ago. Over these years, the book has continued to meet the educational needs of a diverse readership—students, trainees, investigators, and practitioners. Although there are new "verses" to the original "score" to reflect advances and discoveries over the past 4 decades, the basic "melody" to this textbook has been retained and builds on the success of the previous editions. The success over time for this textbook is an ongoing testimony to the insight, design, and wisdom of the founding editors: Elliott Middleton, Jr., Elliot F. Ellis, and Charles E. Reed. In 1978 they were academic leaders with expertise in the science and clinical practice of our specialty. Their visionary approach in the original design of this textbook recognized the need not only for a comprehensive textbook to codify state-of-the-art information on the ever-expanding and evolving science of allergic diseases and inflammation, but also to then translate this hard-won knowledge from research to clinical practice. This singular need and goal remain today the manifest vision of this undertaking.

It was their concept and design—one that has been adhered to in subsequent editions, including this eighth edition—that a comprehensive text should be built around two major informational foci. The first is the need to have a broad and comprehensive review and discussion of the underlying scientific basis that forms a foundation for allergic diseases (i.e., the *principles*). The second major component of the text builds upon and translates these scientific principles into discussions on the diagnosis and treatment of allergic diseases (i.e., the *practice*). It is the fondest hope of their successors, now seven in number, that the current eighth edition maintains the goals and standards so wisely established by Drs. Middleton, Ellis, and Reed.

In planning the eighth edition of *Middleton's Allergy*, a number of organizational changes were implemented. The ever-expanding knowledge of basic immunology fundamentals was applied to common diseases—including asthma, food allergies, and atopic dermatitis, for example—to add greater understanding of the pathogenesis and pathophysiology pathways of these disorders, which in turn would delineate more effectively treatment opportunities, both current and future. Although many examples of this approach are present in the eighth edition text, one of the most striking is the emergence since the last edition of new and lifesaving treatments for hereditary and acquired angioedemas. For years the fundamental defect in hereditary angioedema has been known, but it has taken a decade of exploration of its pathways to devise not just one, but several effective and safe treatments for patients with hereditary and, it is hoped, other forms of kinin-mediated angioedemas.

New technology continues to expand the identification and recognition of new aspects and "players" in the dynamic immune system network. Every attempt has been made to ensure that this advanced knowledge was included in this text, particularly as it may relate to allergic and immunologic diseases. In that spirit, the "overview" to immunity and how it works has been expanded to include chapters on both innate and adaptive immunity. Both of these components of immune responses are applicable to allergic diseases, and a broadened role for innate immune mechanisms is at the forefront of cutting-edge research. Other chapters covering the fundamental aspects of the immune system have been greatly expanded to reflect relevant advances, especially new insights about the roles of regulatory T cells in both sensitization and immunotherapy.

Advances in understanding of the origins and pathways of allergic diseases have accelerated tests of whether biologic therapies can be used to modulate, if not modify, human allergic and immunologic diseases. The rationale for these advances is often new pathways that may have direct and selective applicability to allergic reactions. To amplify more fully the seventh edition, three newly minted chapters were added: Immune Tolerance, Immunobiology of IgE and IgE Receptors, and Resolution of Allergic Inflammation. New findings expounded in these chapters hold promise of identifying novel potential targets for prevention and treatment of allergic disorders.

A separate section on aerobiology and allergens (Section B) has been added to the eighth edition to expand topics that are both unique and fundamental to the origins of a reaction to an environmental allergen: the structure and properties of foreign substances that become allergens, the host-environmental interactions leading to clinical disease, the role of air quality, and the standardization of allergen measurements in the assessment and management of allergic diseases. A new chapter, Particulate and Pollen Interactions, highlights how allergens and environmental particulates can and do interact to promote allergic sensitization.

New chapters have also been added to reflect advances of emerging fundamental and/or clinical importance, including: Respiratory Tract Mucosal Immunology, Ontogeny of Allergic Diseases and Asthma, Mouse Models of Allergic Airways Disease, Lung Imaging, and Gastrointestinal Mucosal Immunology. The topic of allergic bronchopulmonary aspergillosis and hypersensitivity pneumonitis receives new emphasis in this edition, reflecting the clear inclusion of these disorders within the clinical spectrum of allergy and immunology.

Asthma remains the predominant component of the section on the respiratory tract, and 10 chapters have undergone extensive revisions to reflect new information and clinical translation. The major advances in asthma pathogenesis are found in a newly authored chapter with subsequent chapters discussing diagnosis, treatment, and special aspects of asthma—occupational, exercise, and during pregnancy. Asthma is a heterogeneous disease and this is noted in many aspects, including onset, severity, and responsiveness to treatment. Heterogeneity is also reflected in asthma in terms of the ages of the patients affected. To recognize these critical distinctions, new chapters were delineated to deal with the unique aspects in the diagnosis and management of children and adults.

Systemic manifestations of allergic and immunologic disease are covered in Section G. In addition to comprehensive coverage of specific disorders (e.g., eosinophilia and eosinophil-related disorders), mastocytosis, drug allergy, human immunodeficiency virus, and anaphylaxis, chapters are devoted to diagnostic methods relevant for allergy evaluations, including recent advances such as component analysis. In the past 2 decades,

research on food allergies has been unprecedented and has led to a greater recognition and appreciation of the scope of these allergic reactions and, more recently, of how to provide safe definitive prevention and treatments as alternatives to avoidance. Consequently, a new chapter on food allergy management has been added.

Finally, the section on therapeutics for allergic and immunologic diseases remains extensive and includes many new topics. This section has traditionally been a strength of the Middleton text and from our perspective continues to be so in the eighth edition. Control of allergic reactions by pharmacologic and immunologic means remains a main focus. An expanded discussion of immunotherapy includes a new chapter on sublingual immunotherapy to reflect its major advances and interest and its emerging clinical use. Two other chapters are now part of the Therapeutics section: Cytokine-Specific Therapy in Asthma and Complementary and Alternative Medicine. The use of biologics in allergic diseases is of considerable interest and reflects the culmination of applying knowledge from the basic biology of disease pathways to novel therapies for disease processes that may not be responsive to current treatment because of uniquely responsive subpopulations of patients.

The eighth edition continues to expand innovations of the seventh edition that brought widespread endorsement and acclaim. These include full-color coding and accenting, coordinated artwork with consistent format, an insistence on tabular and schematic graphical presentations wherever possible, summaries of important concepts for each chapter, and extensive referencing with an emphasis on recent findings. With this edition we also began the process of encouraging authors to conform their contributions to a common outline format so that there is some consistency in order of presentation within chapters. All of these features, plus other enhancements such as reference links and ability to extract figures as slide copy, are available on the searchable web version available to those who acquire the electronic format.

Along with the major content changes in the science and treatment of allergic diseases, the eighth edition of Middleton has seen changes in our editors. Dr. F. Estelle R. Simons has stepped down as an editor. We greatly miss her scholarship of allergic diseases but we are grateful that she and Dr. Cezmi A. Akdis have continued to author their very comprehensive and tour de force chapter Histamine and H_1-Antihistamines. Drs. Robyn E. O'Hehir and Wesley Burks are new and welcome additions as editors. They have brought special expertise in immunology/asthma and food allergy, respectively, as well as a fresh view to the overall direction of *Middleton's Allergy: Principles and Practice*. In addition, Dr. O'Hehir's acceptance means that we now have editors from three continents, which hopefully allows and encourages a fully global perspective.

The authorship for this text continues to expand in terms of geographic origin. The 215 contributing authors come from 17 countries on 5 continents. The Middleton text continues to evolve over time to become global in perspective, and editorial care has been exercised to ensure clear understanding of differences in practice norms, especially between the United States and Europe. Another continuing editorial policy is the systematic turnover of chapter authorship to ensure that fresh perspectives are aired and new voices can be heard, even when there is nothing fundamentally wrong with the "older" author. This sometimes results in perceived insults when authors are "dropped," but we believe the value of this principle continues to prove itself. Hence, in this edition, you will find new coauthorship in a majority of chapters, and totally new presentations in 43 of 102 chapters! We believe this newness alone is sufficient reason to acquire and engage the eighth edition—even for experienced clinicians and investigators.

In our opinion, the authors who have graciously contributed 102 chapters and two appendixes to the eighth edition have provided readers from all levels with comprehensive, evidence-based information and timely reviews of allergic diseases. They have "told the story" of the principles of our diseases as well as translated this information into practice for the most effective current care and treatment. It is impossible to sufficiently thank all of the authors for their wonderful and informative chapters. It has been our responsibility—and pleasure—to orchestrate their well-written chapters into a book that we hope will continue to effectively serve and meet the needs of our readership, from student to investigator to care provider.

This monumental cooperative effort among authors and editors could not have been undertaken without the superb support of our publishing staff at Elsevier, for whom we are especially grateful. Based in London, Joanne Scott and her associates Devika Ponnambalam and Humayra Rahman Khan arranged international conference calls, organized and documented our efforts and progress, and kept both authors and editors on track for an on-time completion. Belinda Kuhn, senior content strategist, and her predecessor, Sue Hodgson, oversaw the planning and evolution of the project over the past 4 years. Louise King in St. Louis managed the layout and proofing process, and numerous others at Elsevier did great service in artwork and design, publicity, and production. Mike Carcel, Louis Forgione, and Brett MacNaughton in Philadelphia managed the art line and cover and text design. It was a pleasure to work with this excellent multinational staff of professionals.

Lastly, a word about the future. Medical publishing is changing rapidly and we will change with it. The eighth edition will be published in print form and simultaneously issued in electronic format, as was true for the seventh edition. But the traditional 5-year cycle for completely new editions will be replaced by a continuously revised e-edition, which will allow all content to remain current. The details of this new era for the Middleton text are being finalized and should be available by the time of publication.

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May 2013

PREFACE TO THE FIRST EDITION

Allergy, once a confusing subject for clinician and researcher alike, has emerged as a medical science in which immunology, physiology, and pharmacology interface uniquely. Our present state of knowledge is the culmination of the efforts of many workers over many decades of research in the clinic and laboratory. We want to acknowledge our incalculable debt to these investigators, both basic scientists and clinicians, who taught us not only fact but more importantly concepts and scientific method.

Several textbooks on allergy are already in existence. Why another one? We pondered this question for some time before embarking on what turned out to be, expectedly, a rather formidable task. It was our opinion that a truly comprehensive book about allergy should focus strongly not only on the exciting developments of the past decade or two in immunology but also provide in-depth coverage of equally pertinent new information on physiology and pharmacology, two areas of critical importance to the student of allergy. We have made no attempt to cover all of the subject matter considered to fall under the general rubric of clinical immunology and so do not include sections dealing with rheumatology, other connective tissue disorders, immunohematology, or tumor immunology, for example, since these subjects are well covered elsewhere.

The chapters dealing with immunology, pharmacology, and physiology appear at the beginning in the basic science section of the book to provide the necessary conceptual framework for the clinical science section, which deals with the variety of clinical states that fall within the purview of allergy and the allergist. The value of the clinical descriptions is vastly enhanced by a careful reading of the earlier chapters.

We were most fortunate in securing a truly outstanding "star-studded" cast of contributors who managed to find time in their already overcrowded schedules to help us write the book. We thank them all for their efforts and are grateful for the patient indulgence of a few who put up with some predictable editorial fussing meant to achieve proper balance and avoid excessive overlap.

Most of the chapters can be read as free-standing articles or monographs on that particular subject. This has led to a certain irreducible amount of duplication. By and large, there is consistency among chapters in which comparable material has been presented by different authors, but the reader will find occasional areas of controversy, a natural state of affairs in a rapidly growing field.

It is our opinion that some chapters in this book represent the most comprehensive summaries of the subject matter to be found in print. Thus Allergy: Principles and Practice serves not only as a textbook but as a reference book. Indeed, this was our intent, but original estimates for the length of the book were necessarily revised upward as it became clear that much excellent material could not properly be left out. The final product then turns out to be a book we hope will be useful to all students of allergy: practitioners, clinical investigators, other researchers, allergy trainees, and medical students.

The generous and unstinting help of many people in addition to the contributors made this book possible. Without the competent and devoted secretarial assistance of Marci Dame, Evelyn Beimers, Bonnie Barcy, Carol Speery, and Candace Anderson, the task could not have been accomplished. We thank our wives and families for their forbearance, while we were sequestered away from home for day and night weekend sessions during the planning and editing phases. From the beginning their support has been essential to the successful completion of our job. A number of colleagues, too numerous to name, provided help in critical reading of manuscripts. To these and others who were helpful in a variety of ways, we offer thanks.

We are saddened that two contributors died during the preparation of the book. Jane Harnett is the senior author of the chapter dealing with aspirin idiosyncrasy. Dr. Harnett compiled much of the information for the chapter and worked on the manuscript under extremely difficult circumstances up to within only a few days of her untimely death. She is remembered fondly and with respect by all those with whom she worked. Robert P. Orange, one of the most brilliant and creative investigators of his generation, died suddenly during the preparation of the book. No one can guess what additional important discoveries Dr. Orange would have made had he not died so prematurely.

We would like to record here our personal sorrow at the loss of these fine physicians. We hope that their representation in this textbook will help keep memories of them alive.

Elliott Middleton, Jr.
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1978

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SECTION A

Basic Sciences Underlying Allergy and Immunology

1 Innate Immunity

ANDREW H. LIU | RICHARD B. JOHNSTON, JR. | MATTHEW J. FENTON

CONTENTS

SUMMARY OF IMPORTANT CONCEPTS

» The innate immune system distinguishes microbes by their molecular components that are not made by the host. These pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs).
» Antimicrobial peptides and proteins secreted in the skin and mucous membranes protect against microbial pathogens.
» Innate immune activation leads to multifaceted antimicrobial responses by resident cells (e.g., macrophages, dendritic cells, epithelial cells, mast cells) and infiltrating cells (e.g., neutrophils, natural killer cells, dendritic cells, monocytes).
» The innate immune system activates and instructs the adaptive immune system for antigen-specific T and B lymphocyte responses and the development of immunologic memory.
» Innate immune defenses are highly efficient and include homeostatic mechanisms that downregulate inflammation to optimize the health of the host.
» Like antimicrobial immunity, allergen recognition and uptake, allergic sensitization, inflammation, and disease originate in the innate immune system.

Introduction

The innate immune system has a long evolutionary heritage, with elements shared by most vertebrates and even with plants and insects. All of these organisms require an innate immune system to exist in a microbe-laden environment. Evolution has worked elegance into the protective and homeostatic mechanisms provided by innate immunity.

Innate immune responses can be characterized as receptor-guided responses that recognize molecular components of microorganisms that are not made by the host, as well as host molecules that are released by damaged cells or produced by host cells during an inflammatory response. These *pattern recognition receptors* (PRRs) are innate (inborn); they are not adapted, tailored, or expanded by clonal selection, as are the recognition receptors of T and B lymphocytes in acquired immunity. PRRs can bind some allergens.

Early in the life of an organism, innate immunity is ready to respond immediately to and provide host defenses against microorganisms. The innate immune system has sensitive detection mechanisms that rapidly amplify other innate immune components when needed. Innate immune responses bridge the gap to adaptive immune responses, which require days to amplify and become effective. In addition to its sentinel detection and first-responder roles, the innate immune system activates and instructs adaptive immunity, regulates inflammation, and maintains an efficient homeostasis to allow the organism to develop, grow, and thrive in its environment. Unfortunately, allergic sensitization, inflammation, and disease may originate during aberrant innate immune development. The innate roots of allergy are considered in this chapter.

Microbial Pattern Recognition by the Innate Immune System

Microbial recognition by the innate immune system is mediated by germline-encoded receptors with genetically predetermined specificities for microbial constituents. Natural selection has formed and refined the repertoire of innate immune receptors to recognize highly conserved molecular structures that distinguish large groups of microorganisms from the host. These microbe-specific structures are called *pathogen-associated molecular patterns* (PAMPs), and the PRRs of the innate immune system recognize them (Table 1-1). Although PAMP structures are biochemically distinct, they share common features:

- PAMPs are produced only by microbes, not by their hosts.
- PAMP structures recognized by the innate immune system are usually fundamental to the integrity, survival, and pathogenicity of the microorganisms.
- PAMPs are common molecular structures shared by entire classes of pathogens.

For example, bacterial endotoxin is a lipopolysaccharide (LPS) PAMP that makes up most of the outer membrane layer of all gram-negative bacteria. Lipid A is a highly conserved structure of the lipid bilayer of the outer bacterial cell membrane that confers much of endotoxin's biologic activities.[1] Myeloid differentiation factor 2 (MD-2, also called lymphocyte antigen 96 [LY96]) and Toll-like receptor 4 (TLR4) combine to form a PRR–cell-signaling complex that specifically interacts with the lipid A component of endotoxin (Fig. 1-1).[2] Other PAMPs include common microbial cell membrane components

TABLE 1-1 Innate Pattern Recognition Receptors in Humans

Pattern Recognition Receptors	PAMP Structures Recognized	Functions
SECRETED		
Antimicrobial peptides	Microbial membranes (negatively charged)	Opsonization, microbial cell lysis, immune cell chemoattractant
α- and β-Defensins		
Cathelicidin (LL-37)		
Dermcidin		
RegIIIγ		
Collectins		
Mannose-binding lectin	Microbial mannan	Opsonization, complement activation, microbial cell lysis, chemoattraction, phagocytosis
Surfactant proteins A and D	Bacterial cell wall lipids; viral coat proteins	Opsonization, killing, phagocytosis, proinflammatory and antiinflammatory mediator release
Pentraxins		
C-reactive protein	Bacterial phospholipids (phosphorylcholine)	Opsonization, complement activation, microbial cell lysis, chemoattraction, phagocytosis
SECRETED AND MEMBRANE BOUND		
CD14	Endotoxin	TLR4 signaling
LPS binding protein	Endotoxin	TLR4 signaling
MD-2	Endotoxin	TLR4 coreceptor
MEMBRANE BOUND		
Toll-like receptors*	Microbial PAMPs	Immune cell activation
C-type lectin receptors		
Mannose receptor (CD206)	Microbial mannan	Cell activation, phagocytosis, proinflammatory mediator release
DECTIN-1	β-1,3-Glucan	Cell activation, phagocytosis, proinflammatory mediator release
DECTIN-2	Fungal mannose	Cell activation, phagocytosis, proinflammatory mediator release
DC-SIGN	Microbial mannose, fucose	Immunoregulation, IL-10 production
Siglecs	Sialic acid containing glycans	Cell inhibition, endocytosis
CYTOSOLIC		
NOD-like receptors		
NOD-1	Peptidoglycans from gram-negative bacteria	Cell activation
NOD-2	Bacterial muramyl dipeptides	Cell activation
NLRP1	Anthrax lethal toxin	PAMP recognition in Inflammasome
NLRP3 (cryopyrin)	Microbial RNA	PAMP recognition in Inflammasome
NLRC4	Bacterial flagellin	PAMP recognition in Inflammasome
RIG-I and MDA5	Viral double-stranded RNA	Type 1 IFN responses

DC-SIGN, Dendritic cell–specific intracellular adhesion molecule 3 (ICAM-3)–grabbing nonintegrin; *DECTIN*, dendritic cell–specific receptor; *IFN*, interferon; *IL*, interleukin; *LPS*, lipopolysaccharide; *MD-2*, myeloid differentiation factor 2 (also called lymphocyte antigen 96 [LY98]); *MDA5*, melanoma differentiation–associated 5 (also called interferon induced with helicase domain 1 [IFIH1]); *NLR*, NOD-like receptor; *NOD*, nucleotide-binding oligomerization domain protein; *PAMP*, pathogen-associated molecular pattern; *RegIIIγ*, regenerating islet-derived 3 γ (REG3G); *RIG-I*, retinoic acid–inducible 1 (also called DDX58); *Siglecs*, sialic acid–binding immunoglobulin-like lectins; *TLR*, Toll-like receptor.
*See Table 1-2.

and nucleic acids with molecular features distinct from those of animals or humans.

This approach to microbial recognition by PRRs in innate immunity is fundamentally different from the development of microbial recognition in the adaptive immune system by T and B lymphocytes. Each T and B lymphocyte acquires a structurally unique receptor during developmental processes of somatic recombination. This process generates a very diverse, almost limitless repertoire of antigen specificities (approximately 10^{14} different immunoglobulin receptors and 10^{18} different T cell receptors), from which the useful receptors (e.g., those specific for microbial pathogens rather than self) are selected for clonal expansion. Clonal expansion of antibody recognition includes greater diversification, specificity, and affinity. Useful receptors of adaptive immunity are identified and learned in the individual organism over time and cannot be passed onto progeny. The innate immune system relies on PRRs, each distinguishing large classes of microbes from self by shared, conserved PAMPs. Their usefulness has been determined through eons of natural selection. The germline-encoded PRRs are passed on to progeny. In comparison, the adaptive immune system generates great antigen receptor diversity through instructive, selective processes that are individualized for each host.

Pattern Recognition Receptors

PRRs of the innate immune system can be divided into two groups: secreted receptors and transmembrane signal-transducing receptors (see Table 1-1). *Secreted PRRs* typically have multiple effects in innate immunity and host defense, including direct microbial killing, serving as helper proteins for transmembrane receptors, opsonization for phagocytosis, and chemoattraction of innate and adaptive immune effector cells. *Transmembrane PRRs* are expressed on many innate immune

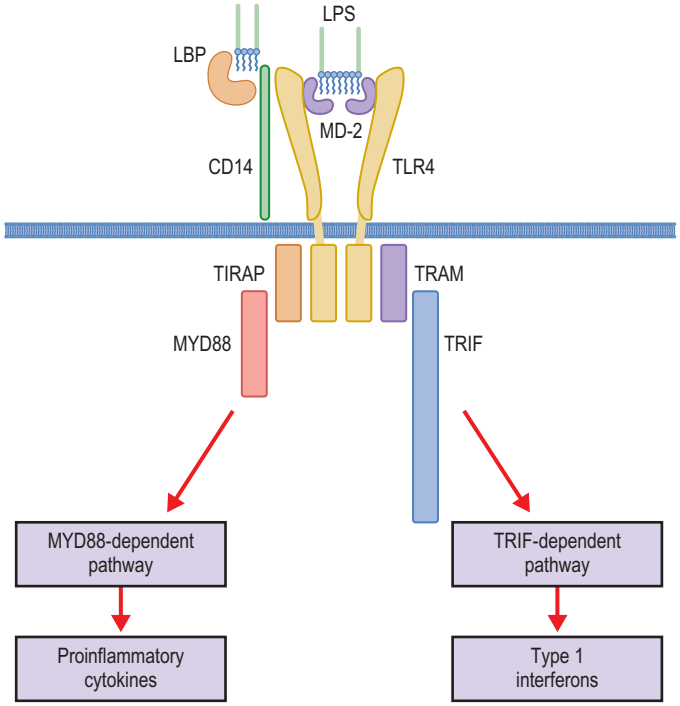

Figure 1-1 Endotoxin recognition and cell activation through Toll-like receptor 4 (TLR4). Lipopolysaccharide (LPS) (i.e., endotoxin) from the outer cell wall of gram-negative bacteria is a prototypical microbial pathogen-associated molecular pattern (PAMP) that is bound by soluble LPS-binding protein (LBP) and CD14 and transferred to myeloid differentiation factor 2 (MD-2). MD-2 specifically binds LPS and forms signal-transducing multimers with TLR4. Four signal-transducing adaptor proteins are recruited to the LPS–MD-2–TLR multimers: MYD88 and TIRAP of the MYD88-dependent pathway, and TRIF and TRAM of the TRIF-dependent pathway. The MYD88-dependent pathway induces the expression of inflammatory cytokines (e.g., TNF-α, IL-1, IL-6, IL-8) and costimulatory molecules (e.g., CD80). The TRIF-dependent pathway mediates the induction of type 1 interferons and interferon-inducible genes. *IL*, Interleukin; *MD-2*, myeloid differentiation factor 2 (also called lymphocyte antigen 96 [LY98]); *MYD88*, myeloid differentiation primary response gene 88; *TIRAP*, Toll–interleukin-1 receptor (TIR) domain-containing adaptor protein; *TNF*, tumor necrosis factor; *TRAM*, TRIF-related adaptor molecule; *TRIF*, TIR domain–containing adaptor protein inducing interferon-β (also called Toll-like receptor adaptor protein 1 [TICAM1]). *(Adapted from Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. Cytokine 2008;42:145-51.)*

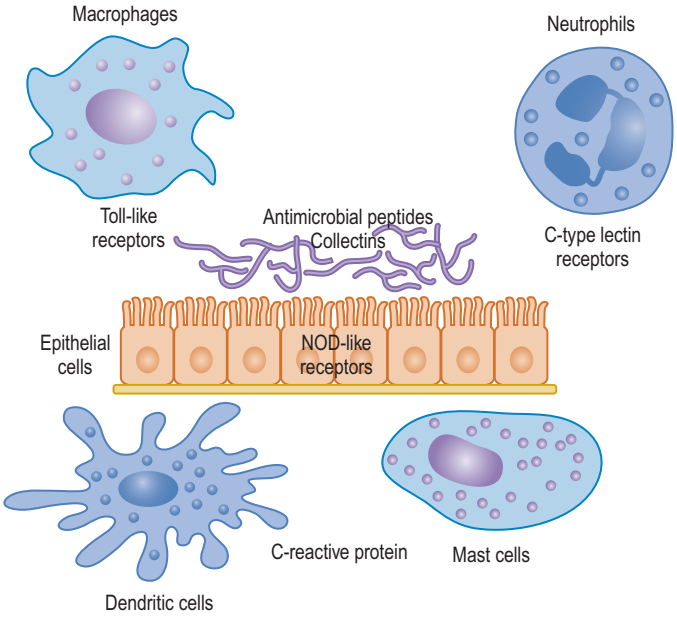

Figure 1-2 Main categories of pattern recognition receptors and the innate immune cell types that express them. *NOD*, Nucleotide-binding oligomerization domain protein. *(Adapted from Liu AH. Innate microbial sensors and their relevance to allergy. J Allergy Clin Immunol 2008;122:846-58.)*

cell types, including macrophages, dendritic cells (DCs), monocytes, and B lymphocytes—the professional antigen-presenting cells (Fig. 1-2). These PRRs are exemplified by the Toll-like receptors and their associated recognition, enhancing, and signal transduction proteins (Table 1-2, and see Fig. 1-2). Innate immune efficiency is achieved in part by the constitutive expression of some of these receptors as sentinels, with rapid upregulation of other PRRs occurring with innate immune activation.

ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (AMPs) are secreted PRRs that are microbicidal and rapidly acting. When secreted onto epithelial surfaces, they create a microbicidal shield against microbial attachment and invasion. As components of the antimicrobial repertoire of phagocytic cells, they complement oxidative microbicidal activities within phagolysosomes. AMPs have antimicrobial activity against a broad range of bacteria, fungi, chlamydiae, and enveloped viruses.[3,4]

AMPs target the membranes of microorganisms. Although there is a great diversity of AMPs between and within species, they share a fundamental feature in their molecular structures of clustering hydrophobic, cationic amino acids (Fig. 1-3).[4,5] This molecular feature of AMPs exploits a distinct vulnerability in the structure of microbial membranes—the outer bilayer of microbial membranes is largely populated by negatively charged phospholipids, an attractive surface for the cationic and hydrophobic domains of AMPs to bind. In contrast, the outer cell walls of plants and animals are composed of lipids with no net charge. AMPs integrate into the microbial outer membrane and form pores and cracks, thereby disrupting cell membrane integrity and function.

In humans, the two main categories of AMPs are defensins (α and β classes) and the cathelicidin LL-37 (see Table 1-1). The human α-defensins HD1 and HD2 are granule proteins of neutrophils; HD5 and HD6 are synthesized by Paneth cells at the base of small intestinal crypts.[6] The HD6 lacks direct bactericidal activity but has the special capacity to link to bacterial surfaces and self-assemble into nanonets that entangle the bacteria, thereby protecting the intestine from invasion.[7,8] Human β-defensins (HBDs) are expressed on all epithelial surfaces, including those of the airways, urinary and gastrointestinal tracts, and skin. Their production by epithelial cells can be constitutive (e.g., HBD1) or inducible (e.g., HBD2, HBD3, HBD4). Expression of HBD2 is induced in epithelial cells by bacterial PAMPs through TLR2 or TLR4.[9,10] Stimulation of epithelium by innate inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), also induces defensin production.[11]

Human cathelicidin LL-37 is released from neutrophils and epithelial cells, and it exhibits a broad range of antimicrobial

TABLE 1-2 Toll-like Receptors in Humans

Toll-like Receptors	Cell Location	Ligands	Microbial Sources
TLR1	Surface	Lipoproteins, lipoteichoic acid	Gram-positive bacteria, mycoplasma
TLR2	Surface	Lipoproteins, alarmins Peptidoglycan, lipoteichoic acid Zymosan Lipoarabinomannan	Bacterial cell walls and membranes Gram-positive bacteria cell walls Fungi and mycobacteria cell walls
TLR3	Cytosol	Double-stranded RNA	Viral RNA
TLR4	Surface	Endotoxin, alarmins, viral coat proteins	Gram-negative bacteria cell walls Respiratory syncytial virus
TLR5	Surface	Flagellin	Bacteria
TLR6	Surface	Lipoproteins, lipoteichoic acid	Gram-positive bacteria cell walls and membranes
TLR7	Cytosol	Single-stranded RNA	Viral RNA
TLR8	Cytosol	Single-stranded RNA	Viral RNA
TLR9	Cytosol	Unmethylated CpG DNA	Bacterial and viral DNA
TLR10	Surface	Lipoproteins	Bacterial cell walls and membranes

CpG, Cytosine-phosphate-guanine oligonucleotide.

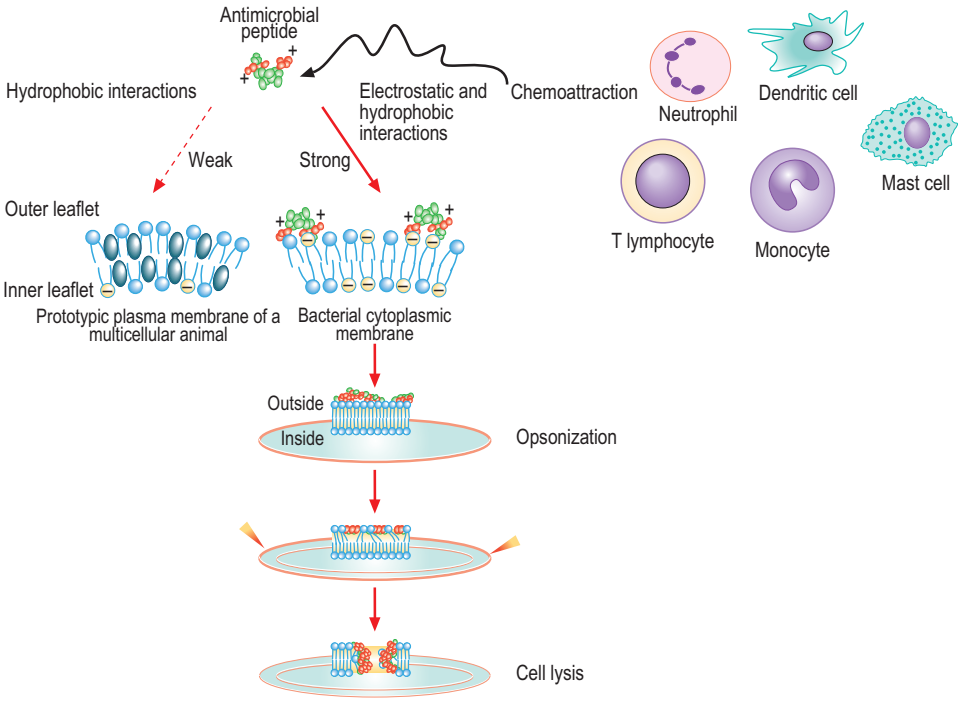

Figure 1-3 Antimicrobial peptides (AMPs) are cationic and contain a large proportion of hydrophobic amino acid residues. They target the exposed outer membrane of bacteria that is dense with negatively charged phospholipid head groups. This is different from the cell membranes of plants and animals that are spared AMP binding because their outer cell membrane lipids have no net charge. AMPs integrate into bacterial membranes and form holes that physically disrupt membrane integrity and lyse target cells. AMPs are chemoattractive for a variety of immune cells, while also carpeting and opsonizing bacterial targets for recognition and uptake by phagocytes bearing AMP receptors. *(Adapted from Zasloff M. Antimicrobial peptides of multicellular organisms. Nature 2002;415:389-95.)*

activities.[12] LL-37 is induced by vitamin D; the gene encoding LL-37 has a vitamin D receptor binding site.[13,14] In keratinocytes and macrophages, stimulation of TLR2 results in the induction of CYP27B1, the cytochrome P-450 enzyme that converts 25-hydroxyvitamin D_3 (25-OH-D) to the active form of 1,25-dihydroxyvitamin D_3 (1,25-OH-D), which induces LL-37 expression. By this route, vitamin D can influence microbicidal defenses of the skin and circulating phagocytic cells.[15,16] It has been proposed that certain human infections, such as by *Mycobacterium tuberculosis*, might be more prevalent among populations with inadequate plasma levels of vitamin D.[17]

A genomic search for defensin sequence homology in humans revealed five β-defensin gene clusters and as many as 25 additional defensins.[18] Other types of AMPs include dermcidin in sweat[19] and the lectin protein RegIIIγ (REG3G) in the gut. The colon is protected by an attached mucus layer that acts as a physical barrier. The counterpart to this protective barrier in the small intestine is a less dense layer of mucus that allows

nutrient absorption while protecting the gut with REG3G.[20,21] This suggests that what is currently known about human AMPs may be only a sampling of what is available.

AMPs typically work in concert with larger secreted antibacterial proteins such as lysozyme, bacterial permeability increasing protein, lactoferrin, and lipocalin, and are often synthesized by the same cells. Lysozyme, for example, is produced by epithelial cells, such as Paneth cells, and is found in neutrophil granules; lysozyme degrades the bacterial peptidoglycan cell wall of bacteria killed by AMPs.[22]

AMPs also serve as chemoattractants for innate and adaptive immune cells. Human α-defensin attracts immature DCs and peripheral blood T cells, enhancing antigen-specific adaptive immune responses.[23] For chemoattraction, some AMPs bind to receptors that also bind PAMPs or chemokines. For example, LL-37 attracts neutrophils, monocytes, mast cells, and T lymphocytes through formyl peptide-like receptor 1 (FPRL1), which is a PRR that also binds bacterial formyl peptides.[24] The β-defensins HBD2 and HBD3 are inducible and chemoattractive for immature DCs and memory T lymphocytes through the chemokine receptor CCR6.[23] Recruitment of DCs by AMPs induces their maturation. The β-defensins and LL-37 are also chemoattractive for mast cells and can induce their degranulation.[25,26]

To summarize, when AMPs are induced at a site of injury, they act directly to destroy microbial invaders and to attract an array of defensive cells that provide backup support to defend the breached barrier. AMPs probably control commensal relationships to maintain health in the gut and maybe elsewhere. Inflammation results when the AMP-based defenses have proved inadequate and robust secondary defensive responses are mobilized.

COLLECTINS

Collectins are secreted C-type lectin receptors (CLRs) that are structurally similar to the transmembrane CLRs (discussed later) and contain a collagenous domain.[27] Mannose-binding lectin (MBL) is an acute phase reactant that recognizes terminal mannose residues of carbohydrates on gram-positive and gram-negative bacteria, fungi, yeast, and some viruses and parasites.[28] MBL is structurally similar to the complement component C1q, and like C1q, it activates the classic complement cascade through MBL-associated serine proteases that are related to C1r and C1s and cleave C4, C2, and C3, leading to amplified opsonization, membrane pore formation, cell lysis, and neutrophil chemoattraction.

Two of the four pulmonary surfactant proteins, SP-A and SP-D, are collectins with similar structures and multiple innate immune functions. Structurally, they share carbohydrate domains that bind oligosaccharides specific for a variety of microbes (e.g., gram-positive and gram-negative bacteria, viruses, fungi). They recognize a wide variety of PAMPs, such as bacterial LPS, mycobacterial lipoarabinomannan, other bacterial lipids, and common viral proteins, such as influenza hemagglutinin and neuraminidase envelope glycoproteins and respiratory syncytial virus (RSV) G and F fusion proteins.[29] SP-A and SP-D mediate multiple antimicrobial functions. They aggregate and opsonize microbes for phagocytosis by alveolar macrophages, monocytes, neutrophils, and DCs. They also trigger nuclear factor-κB (NF-κB) activation and cytokine production trough TLR4 and TLR2. SP-A induces the expression of scavenger and mannose receptors on phagocytes, thereby improving phagocytosis. SP-A and SP-D have direct bactericidal[30] and fungicidal[31] properties, and they help to dampen inflammatory responses by enhancing the clearance of proinflammatory apoptotic cells by macrophages.[32]

PENTRAXINS

Pentraxins are acute phase reactant PRRs that are secreted in response to TLR activation or proinflammatory cytokines.[33] C-reactive protein (CRP) was the first PRR and the first pentraxin to be described. CRP specifically binds bacterial phospholipids (e.g., phosphorylcholine) and the complement factor C1q, thereby opsonizing bacteria and activating the classic complement cascade. CRP also directly binds Fcγ receptors on phagocytes, further promoting phagocytosis.

TOLL-LIKE RECEPTORS (see Table 1-2)

The immediate cellular responders of the innate immune system (e.g., monocytes, macrophages, DCs, epithelial cells, neutrophils) and many other cell types express a family of transmembrane PRRs with functional roots found in the Toll receptor of *Drosophila*.[34] These Toll-like receptors (TLRs) are structurally similar, with large, leucine-rich extracellular domains and cytoplasmic domains that are similar to those of the mammalian IL-1 receptor (see Table 1-2).[35] The IL-1 receptor and TLRs share an MYD88-dependent signaling pathway that leads to NF-κB activation.

TLR4 was the first human TLR identified, and it is specific for bacterial endotoxin. Endotoxin, a prototypical PAMP, is a gram-negative bacterial cell wall LPS with a highly conserved lipid A moiety.[1] Very small amounts of endotoxin (i.e., picogram amounts, estimated to equal about 10 LPS molecules/cell) are immunostimulatory.[36] This very high sensitivity for endotoxin-mediated cell activation can be attributed to the endotoxin receptor complex (see Fig. 1-1). Lipopolysaccharide binding protein (LBP) and CD14 are soluble proteins that capture and transfer LPS to the MD-2/TLR4 complex.[37,38] MD-2 specifically binds LPS and forms signal-transducing multimers with TLR4.[2] Although LBP and CD14 are not classic PRRs in that their binding specificity is not limited to PAMPs, they improve cellular detection of and sensitivity to endotoxin.[38] Other factors that heighten immune cellular sensitivity to endotoxin include priming of TLR4-mediated activation by innate immune cytokines (e.g., interferons), low-level endotoxin exposure, and other PAMP exposures.[36,39-41] Conversely, repeated, prolonged, or high-level endotoxin exposure induces cellular unresponsiveness or tolerance.[41]

Ligand-induced oligomerization of TLR4 induces the recruitment of four intracellular signal-transducing adaptor proteins through their Toll/IL-1 receptor (TIR) domains: myeloid differentiation primary response protein 88 (MYD88) and TIR domain-containing adaptor protein (TIRAP, previously called MAL) of the MYD88-dependent pathway and TIR domain–containing adaptor protein–inducing interferon-β (TRIF, also called Toll-like receptor adaptor protein 1 [TICAM1]) and TRIF-related adaptor molecule (TRAM) of the MYD88-independent or TRIF-dependent pathway (see Fig. 1-1).[42] Different TLRs use different combinations of adaptor proteins for downstream signaling; TLR4 is the only known TLR that uses all four of these adaptor proteins. The MyD88-dependent

pathway induces the expression of costimulatory molecules (e.g., CD80) and inflammatory cytokines (e.g., TNF-α, IL-1, IL-6, IL-8) through a series of signal-transducing intermediates that lead to the nuclear translocation of transcription factors NF-κB and activator protein 1 (AP-1). The TRIF-dependent pathway mediates the induction of type 1 interferons and interferon-inducible genes through activation of the transcription factor interferon regulatory factor 3 (IRF3).

Ten human TLRs have been identified (see Table 1-2). They collectively recognize a diverse range of microbial cell wall components, proteins, and nucleic acids, the classic PAMPs. Unlike gram-negative bacteria, the cell walls or membranes of other bacteria (e.g., gram-positive bacteria, mycoplasma) do not contain endotoxin, but they contain peptidoglycan and lipoproteins that are recognized by TLR2, TLR1, TLR6, and possibly TLR10.[43,44] TLR5 recognizes bacterial flagellin.[45] The cytosine-phosphate-guanine (CpG) sequences of bacterial and viral DNA are unmethylated, distinguishing microbial DNA from mammalian DNA; microbial unmethylated CpG is recognized by TLR9.[46] TLR7 and TLR8 are closely related to TLR9 and recognize virus-derived, single-stranded RNA.[47] Double-stranded RNA, unique to certain viruses, is recognized by TLR3.[48] TLR2 and TLR4 also bind members of the family of alarmins, proteins that are passively released from necrotic cells during infection or tissue injury, thereby reducing inflammation.[49]

C-TYPE LECTIN RECEPTORS

CLRs are structurally similar PRRs.[50] Some CLRs are microbial sensors that seem especially relevant to fungal recognition and immunity: mannose receptor, dendritic cell–specific ICAM-3–grabbing nonintegrin (DC-SIGN), DECTIN-1 (C-type lectin domain family 7 member A [CLEC7A]), DECTIN-2 (C-type lectin domain family 6 member A [CLEC6A]), and the collectins.

The mannose receptor (CD206) recognizes carbohydrates with terminal mannan that are characteristic of a variety of microbes, especially fungi. It is widely expressed on tissue macrophages, mediating microbial phagocytosis and NF-κB activation with proinflammatory cytokine production.[51,52] DECTIN-1 binds β-1,3-glucan, a major cell wall component of a wide variety of fungi.[53,54] DECTIN-1 induces a variety of cellular responses through its intracellular immunoreceptor tyrosine-based activating motif (ITAM)–like motif, including the activation of phospholipase A_2, cyclooxygenase 2, endocytosis or phagocytosis, and the production of proinflammatory cytokines and chemokines. DECTIN-2 recognizes high-mannose structures such as the hyphal forms of fungi.[55] Its cytoplasmic tail associates with the Fc receptor γ chain for intracellular signaling.[56] DC-SIGN (CD209) is primarily expressed on the cell surface of immature DCs and similarly recognizes mannose and fucose structures on a wide variety of microbes.[57] DC-SIGN may have an immunoregulatory role; activation induces an IL-10–biased cytokine response and reduces proinflammatory cytokine production induced through other PRRs.[58]

SIALIC ACID–BINDING IMMUNOGLOBULIN-LIKE LECTINS

Sialic acid–binding immunoglobulin-like lectins (Siglecs) are a family of receptors that bind sialic acid–containing glycans expressed on cell surfaces. Siglecs promote cell-cell interactions, regulate cell functions, and mediate microbial endoctyosis.[59] Different Siglecs are expressed by different immune cell types. For example, Siglec-1 (CD169 or sialoadhesin) is macrophage specific, Siglec-2 (CD22) is B lymphocyte specific, and the CD33-related Siglecs are specific for innate immune cells. Siglecs typically are inhibitory receptors. Some (e.g., sialoadhesin, CD33-related Siglecs) recognize sialic acid–expressing microbes, mediate their endocytosis, and dampen inflammatory and immune responses to these pathogens.

NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN–LIKE RECEPTORS

Nucleotide-binding oligomerization domain (NOD)–like receptors (NLRs) are cytosolic PRRs that are structurally similar and recognize microbial PAMPs that find their way into cellular cytoplasm.[60] The human NLR family has 23 members that can be conceptually organized in two groups. The best characterized, NOD1 and NOD2, recognize different core motifs of bacterial peptidoglycans.[61] NOD1 is specific for a core motif of peptidoglycans of primarily gram-negative bacteria.[62,63] NOD2 detects the peptidoglycan muramyl dipeptide in all gram-positive and gram-negative bacteria.[64,65] NOD2 has been of particular interest because mutations in the human *NOD2* gene are associated with an increased risk of Crohn disease.[66,67]

A different set of NLRs (including NLRP1, NLRP3, and NLRC4) form a protein scaffold for the cytosolic inflammasome signaling platform for caspase 1 (CASP1) activation and the processing and maturation of proinflammatory IL-1β and IL-18.[60] These NLRs recognize a diverse range of microbial PAMPs that find their way into cellular cytoplasm, including anthrax lethal toxin (NLRP1),[68] bacterial flagellin (NLRC4),[69] bacterial and viral RNA (NLRP3),[70,71] and bacterial pore-forming toxins such as nigericin and maitotoxin (NLRP3).[72] The RNA helicases retinoic acid–inducible 1 (RIG-I, also called DDX58) and melanoma differentiation–associated 5 (MDA5, now called interferon induced with helicase domain 1 [IFIH1]) are PRRs that recognize double-stranded RNA viruses and mediate type 1 interferon antiviral responses.[73]

Resident Cellular Responses of Innate Immunity

Microbial detection by PRRs activates the cells that express or bind them. Those in frontline positions for detection are the first responders of the innate immune system: macrophages, DCs, epithelial cells, and mast cells (Fig. 1-4).

DCs are key sentinels of the innate immune system. They exemplify its immediate cellular response, and they direct lymphocyte responses. DCs can be subdivided into classic myeloid (mDC) and plasmacytoid (pDC) types, which are thought to originate from a common DC precursor in the bone marrow.[74] The mDCs are recruited from the blood to histologic sites with high levels of antigen exposure (e.g., skin, mucosal surfaces, lymph nodes, spleen).[75] With their long dendrites and their PRR-rich cell surfaces, mDCs form a subepithelial web that is sensitive to microbes, inflammation, and cellular stress. In the airways, antigens are immediately captured by mucosal mDCs across epithelial tight junctions.[76] In the gastrointestinal tract, mucosal mDCs extend dendrites between epithelial cells into the gut lumen for antigen sampling.[77] After activation, mDCs quickly alert and instruct the immune system by secreting

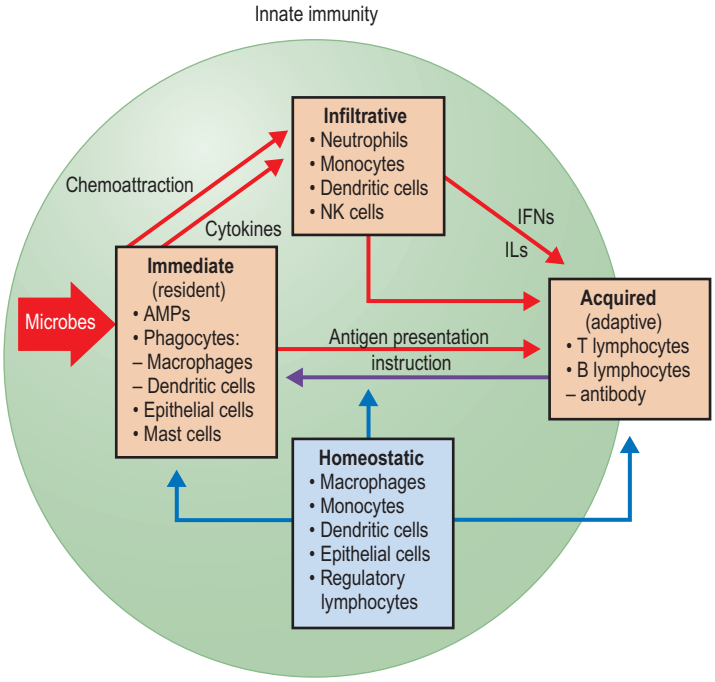

Figure 1-4 Innate immune responses to microbes can be broadly characterized as antimicrobial or homeostatic. Antimicrobial responses begin with protective layers of antimicrobial peptides and detection by immune cells residing at the epithelial interface. Often, these immediate responses sufficiently protect the host. If this first layer of host defense is inadequate, the frontline responders attract infiltrative innate immune cells that are activated as they approach the source of inflammation. Immediate and infiltrating immune cells stimulate adaptive immune responses and educate lymphocytes through antigen presentation and costimulation. Homeostatic responses by innate immune cells downregulate inflammatory and antimicrobial immune responses when they are no longer needed to optimize the use of resources and well-being of the host. *AMP*, Antimicrobial peptide; *IFN*, interferon; *IL*, interleukin; *NK*, natural killer.

activating cytokines such as interferons and migrating to draining lymph nodes for T lymphocyte instruction.

The functions of mDCs are developmentally related.[78,79] They migrate from the bone marrow to peripheral tissues in an immature form, at which stage their role is primarily sentinel detection. They readily sense, sample, and process incoming antigen through dense PRR expression (i.e., TLR1 through TLR6),[80] but they have a poor ability to stimulate T lymphocytes. After sensing environmental microbial PAMPs or inflammatory stress, mDCs become activated scavengers of antigen, and they subsequently return to draining lymph nodes. They mature during this migration. As mature mDCs, their antigen uptake and processing functions are shut down, and large amounts of processed antigen are displayed in cell surface major histocompatibility complex (MHC) molecules with a battery of costimulatory factors for T lymphocyte education. The central role of DCs in directing T lymphocyte development in health (see "Innate Instruction of Adaptive Immune Responses") and in allergic and asthmatic disease (see "Innate Immunity and Allergy") is addressed later in this chapter. The mDCs also can be superior stimulators of natural killer (NK) and natural killer T (NKT) cells by virtue of their robust IL-12 production.[79]

Compared with mDCs, pDCs are sentinel antiviral responders, expressing TLR7 and TLR9 for recognizing viral infections[80] and, on stimulation, releasing large amounts of interferon-α (IFN-α) to limit viral replication.[81] They can also act as antigen-presenting cells and control T lymphocyte responses.[82] Langerhans cells, although similar to DCs in their function, seem to originate from an embryonic precursor that populates the epidermis before birth, differentiates and self-renews in situ, and proliferates during inflammation.[83]

Macrophages are similar to DCs in their histologic location in areas of environmental antigen exposure, cell surface expression of PRRs, capacity to be immediate cellular responders, and ability to phagocytose organisms, digest them, and present antigens to lymphocytes. Macrophages are distributed throughout all central organs, where they protect tissues through phagocytic killing, remove dead tissue and apoptotic cells, and secrete more than 100 proteins that mediate host defense and inflammation. Tissue macrophages are derived from blood monocytes, which leave the circulation and migrate into organs and tissues, where they differentiate into the macrophages characteristic of that tissue (e.g., Kupffer cells of the liver). Functionally, macrophages are central keepers of immune homeostasis and well-being (see "Homeostasis in the Innate Immune System").

In addition to the traditional antigen-presenting cells of innate immunity, epithelial cells and mast cells are resident sentinel cells of innate immune responses. These cells are in anatomic positions of high levels of antigenic exposure, express PRRs that allow them to recognize and immediately respond to PAMPs, and direct innate immune responses. Human airway epithelial cells express multiple TLRs and, when PAMP-stimulated, produce proinflammatory cytokines.[84] Human keratinocytes express a mannose-binding receptor that mediates killing of *Candida* organisms.[85] In the gastrointestinal tract, TLR-mediated epithelial responses to commensal bacterial PAMPs (i.e., TLR4 and TLR2 ligands) mediate epithelial integrity and resilience to injury.[86]

Large numbers of mast cells reside in the interstitium of peripheral tissues. They express TLR1, TLR2, TLR4, and TLR6[87]; complement receptors for C3a and C5a[88]; and MBL receptors. On PRR activation, mast cells synthesize numerous cytokines and mediators that characterize innate immune responses. They are key sources of immediate release of TNF-α and IL-8, which are uniquely preformed in mast cells, and their immediate TNF-α release may have a central role in effective antimicrobial responses to infections.[89,90] Mast cells also make classic inflammatory mediators (e.g., histamine, heparin, leukotrienes, platelet-activating factor), proteases (e.g., tryptase, chymase), and AMPs (e.g., cathelicidin LL-37,[91] defensins[92]).

Infiltrative Cellular Responses of Innate Immunity

Infiltrative cellular responses are potent antimicrobial effectors that usually are recruited by an innate immune intermediary to induce the full weight of their response, but they can respond directly to microbial stimuli through their own surface-expressed PRRs (see Fig. 1.4).

Neutrophils, the most abundant circulating phagocytes in the human host, are recruited into sites of infection and inflammation by a variety of chemotactic signals. Circulating neutrophils are short-lived (≈24 hours), and about 10^{11} cells die each day.[93] This constant stream of neutrophil death would be potently inflammatory without the extraordinarily efficient uptake and processing of apoptotic neutrophils by macrophages and DCs to prevent release of toxic constituents, a process called *efferocytosis*.[94]

In response to infection, circulating neutrophils adhere to adjacent vascular endothelium, migrate to the site of infection, and ingest and kill the invaders. Neutrophils have PRRs for different types of chemoattractants, including *N*-formyl bacterial oligopeptide, complement-derived C5a, and leukotriene B_4 secreted by numerous immune cells on activation. Activated innate immune cells and epithelial cells secrete the neutrophil chemokine IL-8. These neutrophil chemoattractants diffuse from the site of infection to provide a chemotactic gradient for neutrophil migration and to further activate neutrophils as they transmigrate.[95,96]

On reaching the infected site, neutrophils phagocytose invading microorganisms that are opsonized by complement C3 fragments (e.g., C3b, iC3b[97]) and immunoglobulin G (IgG).[98] After phagocytosis, microbicidal mechanisms kill the ingested microbes almost immediately by microbicidal products such as α-defensins (e.g., human neutrophil peptides [HNPs] 1 through 4) released into the microbe-containing phagosome from intracellular granules and highly reactive oxidizing agents generated by membrane NADPH oxidase and myeloperoxidase (e.g., O_2^-, H_2O_2, hypochlorous acid).[99] In humans, phagocyte NADPH oxidase has an essential role in killing and preventing infection with certain common organisms (e.g., *Staphylococcus aureus, Serratia,* enteric bacteria, *Aspergillus*).[100] An increased role for neutrophil granule proteases (i.e., neutrophil elastase and cathepsin G) has been recognized. These cationic proteases are released and activated with alkalinization and K^+ ion fluxes into phagocytic vacuoles.[101] These pH and potassium requirements for protease solubilization and activity restrict their toxicity to phagocytic vacuoles and limit damage to host tissues.[99]

NK cells are an innate immune cell type with unique features. They are lymphoid cells that do not express antigen-specific receptors derived from recombination and clonal selection, such as T cell receptors or surface immunoglobulin. Although NK cells express PRRs such as TLR2, TLR3, TLR4, TLR5, TLR7, and TLR8 and recognize and respond to the respective TLR ligands directly,[102,103] they are best known for responding in an antigen-independent manner to help contain viral infections (especially herpesvirus infections) and malignant tumors by recognizing aberrant host cells for elimination. NK cells distinguish healthy host cells through inhibitory receptors such as the killer cell immunoglobulin-like receptor (KIR) and CD94/NKG2A receptors that recognize MHC class I molecules expressed on healthy cells (Fig. 1-5).[104,105] Binding of these receptors inhibits NK cell–mediated lysis and cytokine secretion. Virus-infected and malignant cells often downregulate MHC class I molecules, rendering them susceptible to attack by NK cells.[106] These inhibitory receptors on NK cells are counterbalanced by activating receptors, such as the NKG2D receptor that recognizes stress ligands expressed on cell surfaces in response to intracellular DNA damage.[107]

Recruited and activated NK cells mediate antimicrobial activities by induction of apoptosis of cell targets and cytokine secretion that is thought to promote innate immune functions and contribute to adaptive immune responses. Target cell apoptosis results from granule exocytosis and death-receptor engagement. NK cells have granules with perforins and granzymes that are released on activation into the synapse between target and effector cell, disrupting target cell membranes and inducing apoptosis (see Fig. 1-5).[108] NK cells also mediate apoptosis by expressing FAS ligand (FASLG) and TNF-related apoptosis-inducing ligand (TRAIL, now called tumor necrosis factor superfamily member 10 [TNFSF10]), which bind the FAS and TNFRSF10 receptors, respectively, on target cells.[109]

Activated NK cells are known for their secretion of interferon-γ (IFN-γ) in particular, but they also secrete TNF-α, growth factors, IL-5, IL-10, IL-13, and chemokines.[110] DCs recruit, interact with, and activate NK cells through cytokines (e.g., type I interferons, IL-12, IL-18) and cell-to-cell surface interactions.[110] NK cells can activate bystander immature DCs by producing TNF-α and IFN-γ along with cell-cell contact.[111] Reciprocal NK-DC interactions occur in secondary lymphoid organs, where NK cells respond to IL-12 produced by mature DCs by producing IFN-γ and promoting the development of helper T cell type 1 (Th1) and cytotoxic T lymphocytes.[112-114]

Innate Instruction of Adaptive Immune Responses

The immediate and infiltrative responses of innate immunity set the stage for their instruction of adaptive immunity and the maintenance of immunologic memory. Because the adaptive immune system essentially has a limitless antigen receptor repertoire, instruction is necessary to guide adaptive antimicrobial immune responses toward pathogens and not self-antigens or harmless environmental antigens. Microbial pattern recognition by innate immune cells controls the activation of adaptive immune responses by directing microbial antigens linked to TLRs through the cellular processes leading to antigen presentation[115] and the expression of costimulatory molecules (e.g., CD80 with CD86).

A legacy of research on the prototypical PAMP endotoxin is helpful in understanding PAMP control of adaptive immunity. Endotoxin can be used as an essential adjuvant in the induction