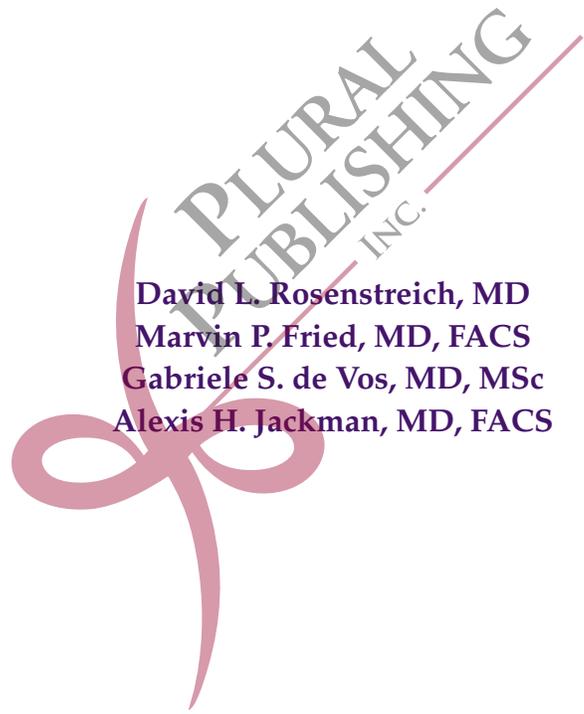


Manual of Allergy and Clinical Immunology for Otolaryngologists



David L. Rosenstreich, MD
Marvin P. Fried, MD, FACS
Gabriele S. de Vos, MD, MSc
Alexis H. Jackman, MD, FACS



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Foreword

The fields of allergy, immunology, and otolaryngology are inextricably linked. Immunologic dysregulation is recognized to be the underpinning of a wide variety of diseases of the head and neck, and on a daily basis the practicing otolaryngologist must draw upon principles of allergy and immunology in the diagnosis and treatment of patients. For example, it is a rare patient presenting with a sinonasal complaint in whom consideration of allergic etiologies is not relevant. The otolaryngologist must also have a strong understanding of autoimmune illnesses to recognize the unique array of potential head and neck manifestations associated with autoimmune disease. Equally important, a deeper understanding of immunopathology may be the key to unlocking the mechanisms of major diseases ranging from chronic rhinosinusitis to head and neck cancer. Thus, it is imperative for the otolaryngologist to master principles of allergy and immunology in order to provide optimal patient care.

The body of knowledge encompassed by allergy and immunology is rapidly evolving and expanding, posing a great challenge for otolaryngologists

seeking to keep up with diagnostic and treatment advances in the field. This splendid textbook offers a comprehensive, multidisciplinary encapsulation of contemporary allergy and immunology for the otolaryngologist. Drs. Rosenstreich, Fried, de Vos, and Jackman have assembled an illustrious group of authors who have managed to distill the essentials of allergy and immunology for the otolaryngologist without sacrificing scientific content or detail. The reader will appreciate clear elucidation of basic science concepts and the practical translation of basic science principles to the clinical management of otolaryngologic illnesses. Diagnostic and treatment guidelines are presented with a comprehensive and pragmatic approach. This book is essential reading for all otolaryngologists, from trainees looking to grasp the breadth of overlap between otolaryngology and allergy/immunology, to seasoned otolaryngologists seeking to update their fund of knowledge with the latest developments in immunophysiology and clinical treatment. The knowledge gained from this expertly edited volume will benefit our patients tremendously.

—Peter H. Hwang, MD
Professor and Chief
Division of Rhinology and Endoscopic
Skull Base Surgery
Department of Otolaryngology-Head &
Neck Surgery
Stanford University School of Medicine

1

Fundamentals of Immunity

Denisa E. Ferastraoar, Robert Tamayev, and Harris Goldstein

OVERVIEW OF IMMUNITY

The discipline of Immunology is focused on studying the function of the immune system, including the mechanisms utilized by our body to defend itself against different types of infections and malfunctions that result in immunological disorders. Since we are constantly exposed to innumerable microorganisms (normal microflora or pathogenic ones), our immune system has to identify foreign pathogens from self and prevent them from causing disease. This process is generally termed the *immune response*.

There have been numerous advances in our current understanding of how the immune system functions through its immune responses. Given the complexity of this subject, we can only provide in this chapter a basic introduction to the main components and functions of the immune system. We highlight the most common terms used in immunology and how the immune system is involved in the pathophysiology of ear, nose, and throat disorders.

One of the main functions of the immune response is to identify the microorganisms that threaten the human body, by recognizing any molecule or part of a molecule that is present in potentially harmful or foreign substances. These foreign molecules are termed *antigens* (*antibody generators*)¹ and are usually proteins or polysaccharides, and less frequently lipids, and can be endogenous or exogenous. Specific cells use a variety of mechanisms to take up or bind the antigens and to degrade them once captured.

Highly specialized structures expressed by lymphocytes recognize antigens, and these lymphocytes along with a number of other cells, effector molecule and enzymes, constitute the immune system. The immune system is considered to have 2 basic types of defense mechanisms. The adaptive immune response consists of responses that develop during the lifetime of an individual in response to exposure to new antigens. Its main function is to protect against infections by producing antibodies and forming memory cells. The innate immune response is present from birth and consists of a number of different components, including physical barriers (skin, mucous membranes, and low gastric pH), enzymes, and cells that act nonspecifically against infectious organisms.^{2,3}

There are 2 types of immune responses that work closely together: adaptive and innate.

THE INNATE IMMUNE SYSTEM

The innate immune system, the nonspecific portion of the immune response, is primed to respond immediately to and provide host defenses against microorganisms. It is capable of mounting a rapid response against any pathogenic invader that infiltrates the skin and mucous membranes, and to initiate signals that recruit and activate a subsequent adaptive immune response. The innate and adaptive immune responses work in close conjunction.

Innate and adaptive immune responses work closely together.

The innate immune system consists of fixed barriers such as the skin, which prevents entry of a pathogen into the body, and epithelial and mucosal layers that possess different factors that prevent pathogen invasion (eg, cytotoxic molecules such as defensins, or cells with beating cilia that clear exterior pathogens). In addition, environmental conditions, such as the acidity of the stomach, and resident normal flora of the gastrointestinal and urogenital tracts prevent unrestricted entrance of pathogens into the bloodstream.⁴

The innate system relies on a limited number of genetically encoded receptors (pattern recognition receptors, PRRs) that recognize structural motifs common to bacterial or viral pathogens (pathogen-associated molecular patterns, PAMPs).² Other distinct receptors recognize molecules expressed normally by cells of the body (“self” molecules). Identification of these self molecules delivers an inhibitory signal to immune cells that prevents activation of the immune response against host tissues. Natural killer (NK) cells are another type of protective cell that kills abnormal cells that have downregulated their molecular histocompatibility complex (MHC) class I proteins due to pathogen infection or neoplastic transformation.⁵

Skin, mucosa, stomach acidity, NK cells, complement system, toll-like receptors (TLRs), and chemokines are all components of the innate immune system.

Components of the Innate Immune System

Cells of the Innate Immune System

Phagocytes. Phagocytic cells (neutrophils and macrophages) are 2 of the major cellular components of the innate immune system. Their main function is to identify and kill pathogens that enter the body through a process called *phagocytosis*. Through this process, bacteria and other foreign substances

are ingested after PAMPs on the pathogen surface are recognized by PRRs or after pathogens have been opsonized by specific molecules (such as C3 molecules of the complement or immunoglobulin G). The foreign particle is trapped in a phagocytic vesicle (phagosome) inside the phagocytic cell. The phagosome then fuses with a lysosome forming a phagolysosome where the foreign substances are degraded by different enzymatic processes⁴ (Figure 1–1).

An important mechanism by which phagocytes kill ingested bacteria is through the release of bacteriolytic enzymes that break down the pathogen. This activity is augmented by a respiratory burst, where the cells utilize different enzymes (NADPH [nicotine adenine dinucleotide phosphate] oxidase, myeloperoxidase, and nitric oxide) to produce bactericidal-free oxygen radicals. Lack of NADPH oxidase results in chronic granulomatous disease, an X-linked recessive disorder characterized by recurrent infections with catalase positive organisms such as *Staphylococcus aureus*. Although the phagocytes of these patients can ingest the pathogen, they cannot kill it, leading to chronic infection and abscess formation (reviewed in Chapter 15).

Lack of NADPH oxidase results in chronic granulomatous disease (CGD), characterized by infections with catalase-positive organisms (eg, *S aureus*).

An alternative mechanism for attacking an endocytosed pathogen is by producing small molecules such as defensins, bacteriocidal peptides that perforate bacterial cell walls, and lactoferrin, which decreases iron stores available to pathogens thereby slowing their growth.

In addition, phagocytes send out other signals, either through immunologic proteins or peptides (cytokines and chemokines), or through cell-surface receptors that initiate activation of the adaptive immune response.

Neutrophils. Neutrophils play a crucial role in the innate inflammatory response and are the first circulating cells to migrate toward the site of infection. Neutrophils are produced and mature in the bone marrow and then are released into the bloodstream.

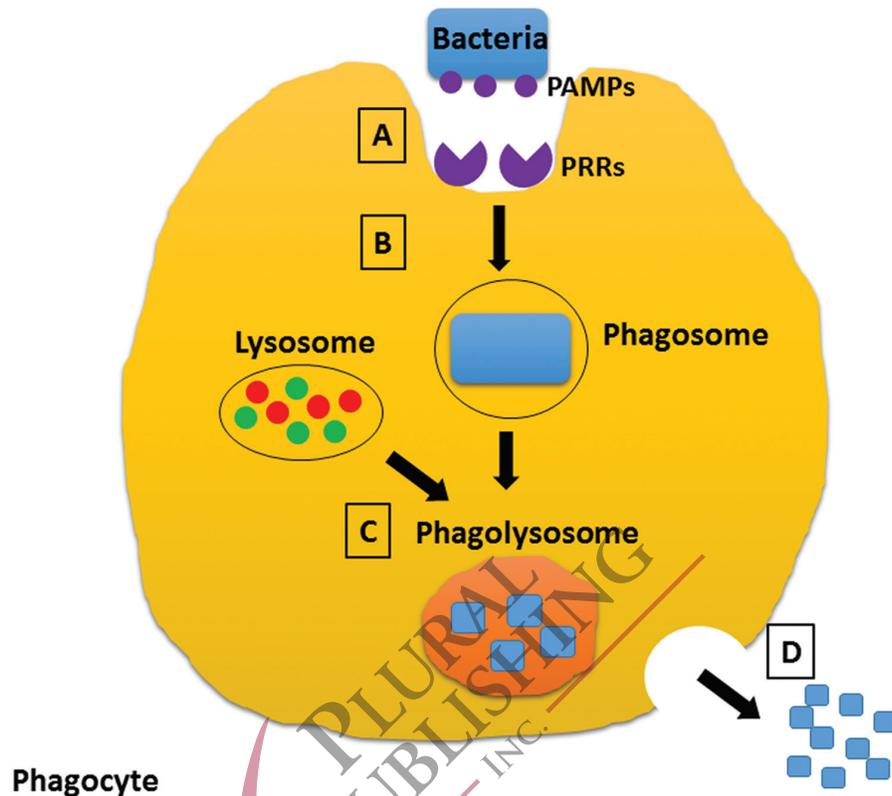


Figure 1-1. The process of phagocytosis. A. PAMPs on the surface of bacteria are recognized by PRRs on the surface of phagocytes. B. The bacteria are internalized in the phagosome. C. The phagosome fuses with a lysosome (which contains different bactericidal enzymes) forming the phagolysosome where the bacteria are lysed. D. The lysed bacterial particles are removed through the process of exocytosis.

They are the main phagocytic population in the body and are found in great numbers in the bloodstream and in infected areas.

Activation of neutrophils involves the detection of PAMPs through PRRs which stimulates activation of the nuclear factor (NF)- κ B pathway. This initiates activation of different effector cell functions including degranulation, the oxidative burst, and mediators production.⁶

Neutrophils have surface receptors for immunoglobulin G (IgG) and the C3b component of the complement system, which enable them to identify their targets after they have been opsonized by these molecules. Neutrophils target binding causes internalization of the pathogen followed by the release of bactericidal enzymes and bacterial death.

The main cytotoxic mediators produced by neutrophils include serine proteases, reactive oxygen species, defensins, and cytokines:

- Serine proteases (neutrophil elastase and proteinase 3) are found in neutrophil granules. Their main function is to degrade and kill phagocytosed pathogens.⁷
- Reactive oxygen species (superoxide, hydrogen peroxide, and hydroxyl radical) are generated by the actions of different enzymes such as NADPH oxidase, superoxide dismutase, and myeloperoxidase. They also kill phagocytosed pathogens.

- Defensins are small peptides that exert their antimicrobial activity through increasing microbe cell membrane permeability.⁸
- Cytokines are proinflammatory, anti-inflammatory, and/or growth inducers. Neutrophils produce a diverse repertoire of cytokines. Cytokine production is increased by inflammatory stimuli such as the Gram-negative bacterial cell wall lipopolysaccharide (LPS) and the lipoteichoic acids of the Gram-positive bacterial cell walls.⁹

After neutrophil activation, digestion and killing of the engulfed microorganisms, the neutrophils die through the process of programmed cell death (apoptosis) or via necrosis. Apoptosis is induced by cellular enzymes (caspases) which lead to nuclear collapse, cytosolic vacuolization, and cell shrinkage. Necrosis is the process where the neutrophil bursts and releases its contents. This cycle of formation and death of neutrophils is a very important homeostatic mechanism for maintaining the correct amount of neutrophils in the blood, enabling them to exert their functions but also allowing for the eventual resolution of the inflammatory process.¹⁰

Macrophages. Macrophages develop from the differentiation of blood-derived monocytes. This differentiation process takes place in most tissues, especially in those where pathogens are likely to enter such as the skin and gastrointestinal and respiratory tracts.

Macrophage cell surface receptors recognize danger signals (eg, bacterial LPS) that trigger activating signals resulting in a proinflammatory response that kills phagocytosed intracellular pathogens.

Macrophage activation also leads to release of cytokines such as interleukin (IL)-1, -12, and TNF (tumor necrosis factor) which stimulate the adaptive immune response. One of these cytokine functions is to induce the differentiation of T helper (T_H) 1 cells. In addition to phagocytosis and stimulation of T_H1 cell differentiation, macrophages can act as antigen-presenting cells (APCs) and present processed peptides to T cells.

Similar to neutrophils, macrophages secrete a variety of pro-inflammatory and cytotoxic molecules

including enzymes, growth factors, lipid mediators (leukotrienes and prostaglandins), and reactive oxygen species.¹¹

Dendritic Cells. Dendritic cells (DCs) are the most important APCs in the body. Their cell surface is characterized by long membrane projections called dendrites, which give the cell its name. The DCs develop in the bone marrow, circulate in the blood, and then migrate into different peripheral tissues such as the skin (Langerhans cells) and the mucosa of the upper and lower airways and gastrointestinal tract. They remain in the tissues in an inactive state until they bind antigen. Once they encounter an antigen, they upregulate specific surface receptors and become mature DCs. They then migrate into draining lymph nodes where they activate B and T cells by presenting the bound processed antigen.

The APCs such as dendritic cells can take up antigens through different processes, including endocytosis, macropinocytosis, or phagocytosis.

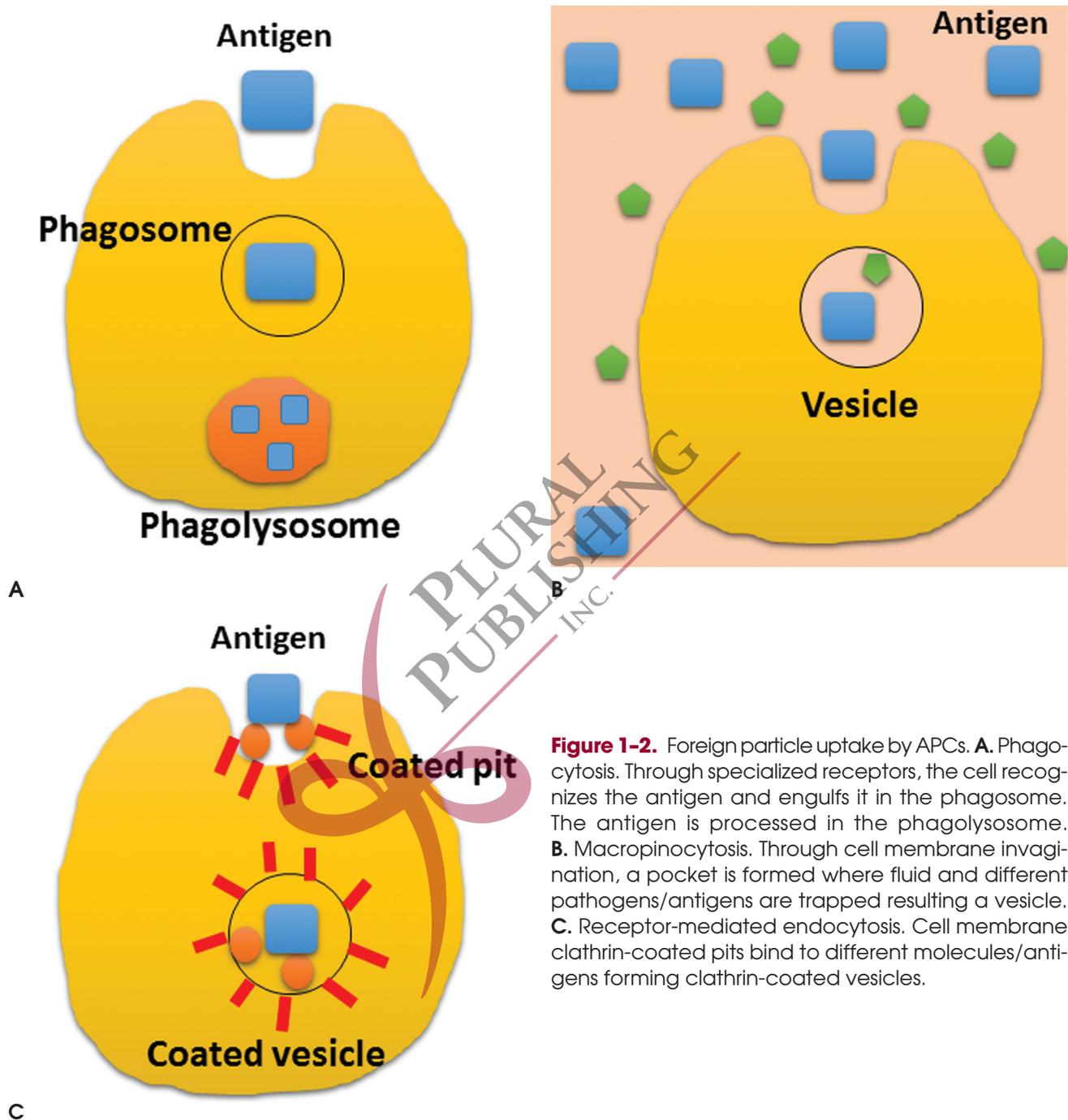
Endocytosis is a receptor-mediated process in which cell membrane clathrin-coated pits bind antigens forming clathrin-coated vesicles.¹² In the process of macropinocytosis, the invagination of the membrane forms a pocket that develops into a vesicle filled with a large amount of fluid and diverse pathogens or antigens.¹³ This vesicle then fuses with a lysosome resulting in antigen digestion and processing (Figure 1–2).

As described earlier in the chapter, through the process of phagocytosis the foreign substances are opsonized by C3 or IgG, ingested by the phagocytic cells, and processed with the use of different enzymes leading to their removal.

Through these 3 processes, extracellular allergens are processed and bound to MHC class II molecules for subsequent presentation to CD4⁺ T cells. The details of antigen presentation and T-cell activation are discussed later in this chapter.

Natural Killer (NK) Cells. Natural killer (NK) cells are effector cells of the innate immune system whose role is to identify and mark for death, cells that are infected with viruses or tumor cells that attempt to evade killing by effector (CD8⁺) T cells.

The NK cells are derived from bone marrow stem cells and circulate in the blood. They have both



cell surface-activating receptors (that activate the NK cells when they bind to target cells) and inhibitory receptors (that transmit an inhibitory signal if the NK cells bind to a cell which has MHC class I molecules on its surface). The NK cells identify potential

targets by evaluating target cell class I MHC expression using special receptors (killer immunoglobulin-like receptors, KIRs).

If the potential target cells are normal and not malignant or infected, and have normal MHC class