Introductory Immunology

Basic Concepts for Interdisciplinary Applications

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Introductory Immunology

PREFACE

DEDICATION

To my father, Paul Actor, PhD, who instilled in me a sense of excitement about the wonders of science and the curiosity to seek questions about how biological systems function.

PREFACE

Our bodies have evolved a protective set of mechanisms, comprised of cells and organs, as a primary defense to maintain health. In essence, we have developed internal tools to preserve health and homeostasis. Indeed, a working definition for "health" embraces the effective elimination or control of life-threatening agents. This includes both infectious agents attacking from the outside and internal threats, such as tumors. Immune responses are therefore designed to interact with, and respond to, the environment to protect the host against pathogenic invaders and internal dangers. The goal of this book is to appreciate the components of the human immune system that work together to confer protection.

We will begin our discussion by establishing a foundation for subsequent chapters, through presentation of the systems and cells involved in immune responses. **Chapter 1** will give a general overview on mechanisms in place to fight against disease. Components and pathways will be defined to allow presentation of concepts of innate (always present) and adaptive (inducible and specific) responses, and how these responses interact with one another to form the basis for everyday protection. These concepts will form the foundation to examine the process of defense against different classes of pathogens. **Chapter 2** will examine the coordinated effort of cells and blood components in development of inflammation as related to protection against infection. **Chapter 3** will introduce the basis for function of adaptive components, exploring the generation of B lymphocytes and

the nature of antibodies. **Chapter 4** will extend this discussion to T-lymphocyte populations and examine how they serve as ringleaders for immune function. **Chapter 5** will discuss immune responses with an element of detail focused on infectious organisms commonly encountered. This overview will also contain how initial engagement of pathogens by innate components leads to triggering of pathways to cause inflammation. A special section will introduce opportunistic infections and diminished response when individuals are immunocompromised.

Effective immune surveillance is paramount to maintaining health. **Chapter 6** will examine basic disorders of immune function. Too little of a response results in an inability to control threats, thus is ineffective to eliminate infectious agents. This lack of reactivity (hyporeactivity) leads to holes in our immune repertoire. This may be the result of genetic deficiencies or due to acquired compromisation of immune function. In the same manner, responses representing excessive activity can also lead to damage to the host. This overaggressive response, a state of hyperreactivity, may reflect a productive response that increases in intensity and duration without effective control. The dysregulation leads to tissue-damaging events and eventual states of disease.

The chief function of the immune system is to distinguish between what is you and what constitutes external threats. When the ability to distinguish these elements is compromised, autoimmunity may arise. In **Chapter 7**, autoimmune dysfunction will be addressed, moving from basic concepts to specific mechanisms involved in major clinical disorders. This includes a detailed discussion of how "self" is recognized, as well as mechanisms involved in tolerance to limit reactivity to our own tissues. The goals are to present clinical manifestation of autoimmunity in a manner so that outward symptoms are understood through investigation of the molecular targets involved in the host immune self-recognition response. At other times, misdirected recognition of nonself elements, such as environmental allergens that typically are considered harmless, result in development of clinical presentations. **Chapter 8** will therefore examine the processes involved in manifestation of immune dysfunction, examining the concepts of immune hypersensitivities which lead to clinical disease.

The general topic of vaccines will be addressed in **Chapter 9**, including both how they work and a frank discussion of the relative truths and myths surrounding their use. This chapter will also contain

information on "newer" therapeutics that are grounded in methods that lead to immune modification and factors which promote a healthy immune response (for example, lifestyle activities and good common practices). Indeed, it is critical that we maintain a healthy balance throughout our lives to ensure functional immune response as we age. The challenges faced at each stage of our lives, from that found in the prenatal/newborn to midlife to "mature" status, are mentioned in a way to encourage a healthy condition to allow optimization of immune function.

A discussion of natural (effective) response to tumor development in **Chapter 10** will allow an investigation into components of immune function to naturally eliminate potentially dangerous precancerous events. This will be followed by a discussion of the challenges faced when protective responses fail and tumors develop. A section will also contain information on cancers of the immune system, and the problems that arise when the protective cells themselves become the cause of tumorigenic activity.

Chapter 11 will delve once more into details underlying concepts of "self" versus "nonself" and blood types, with the goal to present genetic relationships (similarities as well as differences) between individuals. The mechanisms of the immunobiology of transplantation will be discussed, with details on the contributing cells and factors involved in transplant acceptance versus rejection. The challenge is to appreciate the importance of innate and adaptive components in graft recognition, as well as to recognize clinical consequences of transplantation that affect aspects of daily activities. Rejection topics will be discussed, including graft versus host disease, as well as modern immune-based therapeutics designed to alter immune function to limit graft rejection.

Finally, additional information and resources will be provided in **Chapter 12** to allow the reader to develop an immune-based knowledge foundation to understand clinical tests associated with identifying immune parameters that arise during development of disease states. As such, this includes an introduction to mechanisms that form the basis of immune-related diagnostics and identification of immune properties of the blood during disorders.

All in all, the hope is to present a working understanding of the concept of the immune system so that the reader may better

understand immune-based diseases resulting from either immune system component deficiencies or excess activity. This book is aimed at those who want to know more and to encourage the reader to explore deeper. It is aimed at the curious who have never previously considered facets underlying effective immune function. To the student who wishes to expand upon basic knowledge of biological systems. To the physician seeking a refreshed understanding of immune concepts that cause clinical disease. To the nurse who desires to expand their view of symptom development in patients. To the patient who desires a simple explanation for the complex way their bodies respond in the context of the world they inhabit. To all who seek to ask how the body confers protection against infectious agents, maintains everyday homeostasis, and guards against dysregulation of normal response to confer health and control development of disease.

ACKNOWLEDGMENTS

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CONTENTS

CHAPTER 1

A Functional Overview of the Immune System and Immune Components

Chapter Focus: To establish a foundation to appreciate how components of the immune system work together to protect against development of clinical disease. The basic systems and cells involved in immune responses will be presented to give a general overview of functional immunity. Components and systems will be defined to allow an understanding of concepts of innate (always present) and adaptive (inducible and specific) responses, and how these responses interact with one another to form the basis for protection against disease.

IMMUNE HOMEOSTASIS

A functional immune system offers constant surveillance of ourselves in relationship to the world. It confers a balanced state of health through effective elimination of infectious agents (bacteria, viruses, fungi, and parasites) and through control of malignancies. Indeed, the immune system has evolved to allow cells and organs to interact with the environment to protect against harmful invaders. At the same time, mechanisms are in place for tolerance toward the naturally occurring microbiome (microbial and viral agents) that reside within us in symbiotic ways. Taken together, these responses represent a balance of components that ward off development of clinical disease.

SELF VS. NON-SELF

Discrimination between "self" and "non-self" is considered the chief function of the immune system. We are under constant assault by invaders. Our bodies represent prime substrates for organisms to grow and reside, with an abundance of nutrients, warmth, and protection from the outside elements. The immune system is basically a series of obstacles to limit and inhibit pathogen entry and then attack and

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destroy those organisms once they enter the body. The immune response is exquisitely designed to recognize these invaders as "foreign." In fact, the major feature that renders our immune system so effective is its ability to distinguish our body's own cells ("**self**") from that which it considers foreign (termed "**non-self**"). Each one of our cells carries specific tags, or molecular markers, that label it as "self." These markers are important, as they not only determine what is unique about us, but they also distinguish one person from another.

Almost anything and everything that registers as "non-self" will trigger an immune response. An intricate system of molecular communication and cellular interactions allows immune components to function in concert to combat disease-causing organisms. The foreign agent (microbe, virus, parasite, etc.), or any part of it that can be specifically recognized, is called an **antigen**. Simply put, an antigen is defined as any substance that can be recognized by the immune system. Major classes of antigens include proteins, carbohydrates, lipids, and nucleic acids. If an antigen is of high complexity and weight, it can trigger full immune activity and become **immunogenic**.

The ability to distinguish our own cells from the outside world is critical in maintaining functional protection. If this ability is lost, e.g., when "self" tissue is seen as foreign, then our immune system launches an aggressive response against our own tissues. This is what happens during **autoimmunity**, where destruction of "self" leads to clinical disease.

The immune system maintains a balance of responsiveness. Too little a response is ineffective, while too aggressive a response can lead to targeted destruction of bystander tissues. Both scenarios are equally as devastating and may result in clinical disease. The regulation of immune function and overall immuno-homeostasis is under control of multiple factors that include genetic components and environmental cues. The intensity and duration of response must be sufficient to protect against invading pathogens, with prompt and specific downregulation when the foreign material (the antigen) is no longer present. The clinical state that arises when immune responses are not properly regulated is termed **hypersensitivity**; a state of excessive or inappropriate responses leads to disease. As one might imagine, hypersensitivity can occur in many different forms, depending upon which arm of the immune system is dysregulated.

INNATE AND ADAPTIVE IMMUNITY

The immune system is loosely divided into two major functional categories termed **innate** and **adaptive immunity**. Innate immune mechanisms provide the first line of defense from infectious disease (Table 1.1). The innate immune components are present from birth and consist of components available prior to the onset of infection. These defensive components include both physical barriers and biochemical factors. Defensive innate mechanisms may be anatomic (skin, mucous membranes), physiologic (temperature, low pH, chemical mediators), phagocytic (digestion of microorganisms), or inflammatory (vascular fluid leakage).

Innate mechanisms are particularly powerful at limiting infections. However, once the infectious agent is established inside the body, a more focused set of reactive molecules and cellular components are required to specifically combat the organism. An intricate system of molecular communication and cellular contact allows components of the innate immune group to trigger cells involved in adaptive immunity. In essence, both innate and adaptive components must function in concert to combat and control disease.

Table 1.1 Innate Defensive Components

Component	Effectors	Function
Anatomic and physiologic barriers	Skin and mucous membranes	– Physical barriers to limit entry, spread and replication of pathogens
	Temperature, acidic pH, lactic acid	
	Chemical mediators	
Inflammatory mediators	Complement	– Direct lysis of pathogen or infected cells
	Cytokines and interferons	– Activation of other immune components
	Lysozymes, defensins	– Bacterial destruction
	Acute phase proteins and lactoferrin	– Mediation of response
	Leukotrienes and prostaglandins	– Vasodilation and increased vascular permeability
Cellular components	Polymorphonuclear cells • Neutrophils, eosinophils • Basophils, mast cells	– Phagocytosis and intracellular destruction of microorganisms
	Phagocytic–endocytic cells • Monocytes and macrophages • Dendritic cells	– Presentation of foreign antigen to lymphocytes

The adaptive (also called "**acquired**") immune response accounts for specificity in recognition of foreign antigenic substances. It is critical to understand that specificity of the adaptive immune response lies within two distinct subsets of white blood cells, called **lymphocytes**. Lymphocyte recognition of unique shapes associated with foreign antigens is accomplished by functional receptors residing on their cellular surface. Key elements of the acquired immune responses are compared to innate functional elements, as listed in Table 1.2.

The adaptive immune response is subdivided into functional groups representing **humoral and cellular immunity**, based on participation of the two major cell types. Humoral immunity involves **B lymphocytes** (also called **B cells**) which synthesize and secrete **antibodies**. Cellular immunity involves effector **T lymphocytes** (also called **T cells**) which secrete immune regulatory factors following interaction with specialized processing cells (called **antigen presenting cells**; **APCs**) that show the lymphocytes foreign material in the context of self-molecules.

ANATOMY OF THE IMMUNE SYSTEM

The immune system is just that: a "system." It is a network of protective barriers, organs, cells, and molecules. Specifically, there are subsets of primarily bone-marrow-derived cells which circulate throughout the body. Indeed, the power of the "system" is that contributing immune cells can be found within every major organ and in every tissue. These cells are available to be called into action at very short notice.

Table 1.2 Key Elements of Innate and Acquired Immune Responses

Innate	Adaptive
Rapid response (minutes to hours)	Slow response (days to weeks)
PMNs and phagocytes NK cells	B cells and T cells NKT cells
Preformed effectors with limited variability Pattern recognition molecules recognizing structural motifs	B-cell and T-cell receptors with highly selective specificities to foreign agents
Soluble activators Proinflammatory mediators	Antibodies (humoral) Cytokines (cellular)
Nonspecific	Specific
No memory, no increase in response upon secondary exposure	Memory, maturation of secondary response upon reexposure

The interactions are managed by a series of central **lymphoid organs** (e.g., bone marrow, thymus, spleen, and lymph nodes) containing high levels of lymphocytes. The immune-based lymphoid organs are where leukocytes of myeloid and lymphoid origin mature, differentiate, and multiply (Figure 1.1). Cells also accumulate outside these major organs, residing in less defined areas (e.g., throughout the gut or skin), to allow for protective responses at local sites when responses are rapidly needed.

Primary lymphoid organs are the sites where lymphoid cells are generated. This act of cellular development, or **lymphopoiesis**, occurs in the liver in the fetus, and then in the bone marrow after birth. Islands or progenitor stem cells give rise to immune system cells that are subsequently released into the blood. A specialized primary lymphoid organ is the **thymus**, a pyramid-shaped gland that is located beneath the

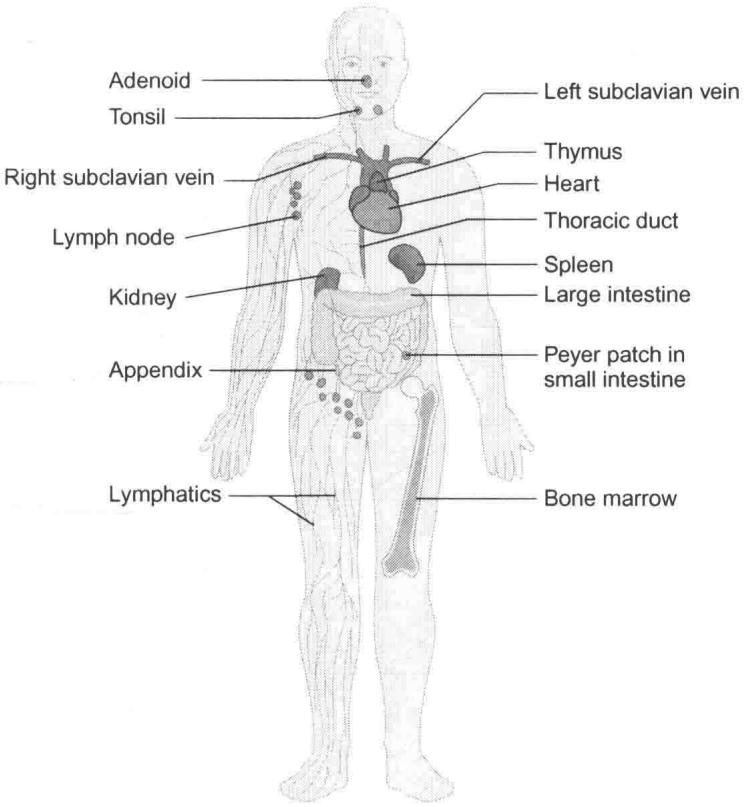

Figure 1.1 ***Distribution of lymphoid tissues.*** *Primary lymphoid organs, such as the bone marrow and thymus, are the major sites of lymphopoiesis and where lymphocytes differentiate. Secondary lymphoid organs, such as the spleen and lymph nodes, are sites where antigen-driven proliferation and maturation of lymphocytes occur.*

breastbone at the same level as the heart (Figure 1.2). Immature lymphocytes leave the bone marrow and circulate directly through the thymus. The principal function of the thymus gland is to educate T lymphocytes to distinguish between what is you (self) and what is not (non-self). When lymphocytes leave the thymus, they are committed along a certain pathway of activity and are ready to perform their effector functions. The other set of lymphoid organs, called **secondary lymphoid** organs, are structured compartments that provide a favorable environment for cell contact and activation of committed cells.

Lymphocytes continuously leave the blood vessels, migrating throughout the body where they perform surveillance activities. The return path to circulation begins when cells mix with fluids that naturally bathe tissues. The mixture eventually "drains" through small vessels to return materials into the blood supply. The fluid in the tissue is called **lymph**, and it carries cells and debris through small vessel **lymphatics**. The lymphatics direct the lymph and cells through secondary lymphoid organs before reaching the thoracic duct, where fluid and cells are returned to the venous circulation of the blood supply.

Lymph nodes are focal nodules connected by way of the draining lymphatic highway. They are placed throughout the body, with groupings found in the groin, armpits, and abdomen. They represent local nodes for antigen and cellular drainage. It is here where lymphocytes can interact and communicate with APCs, allowing a local presentation of antigenic particulates found in nearby regions of the body. Think of the regional lymph nodes as reststops along the highway, where cells can mingle and discuss local and system-wide information. If there is need for immediate response, cells can actively mobilize efforts to defend or repair tissues. In essence, this is where antigen-driven proliferation and differentiation occurs. Local lymph nodes become swollen and painful as cells respond to regional damage and drained materials lead to activation of the immune response team. Within the lymph nodes, the areas of response are called **germinal centers**. Indeed, the term "germinal center" is used to describe any local foci of responding lymphocytes in secondary immune reactive sites.

Just as the lymph nodes are connecting nodes for the lymphatics, the **spleen** is a filtering organ for circulating blood. The spleen, located in the upper portion of the abdomen, can be considered a holding facility where both innate and resting adaptive cells reside in specialized compartments.

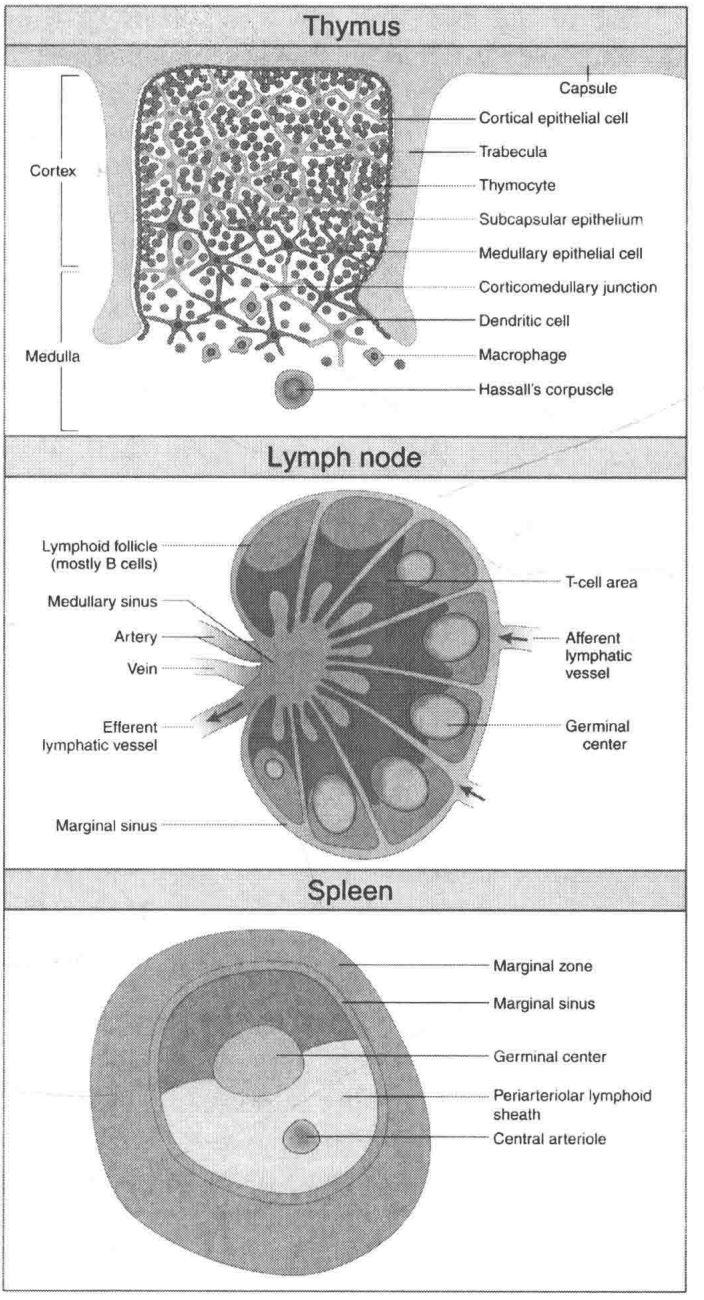

Figure 1.2 ***Major organs of the immune system.*** *The thymus is a primary organ responsible for education of lymphocytes to differentiate between self and non-self. The lymph nodes are secondary organs placed throughout the body, as focal nodules where lymphocytes interact and communicate with APCs. The spleen is a secondary organ, where resting lymphocytes reside to readily mobilize in response to detection of foreign materials.*

The main areas of the tissue are either comprised of lymphoid cells (called the "white pulp") where immune cells interact or comprised of red blood cells (RBCs) and associated areas where RBCs flow (called the "red pulp"). These different compartments for cellular activation allow cells to readily activate and mobilize in response to communication signals indicating foreign materials have been identified.

Another major secondary immune organ is not a truly defined organ, but rather represents a loosely associated cellular aggregation in areas where contact with foreign material is common. This type of immune aggregation is found in tissue layers that line the intestines, the lung, and the nasal cavities. These aggregates are called **mucosa-associated lymphoid tissue**, or **MALT**, and represent areas of rapid surveillance and detection for organisms entering through major openings in our bodies. The tonsils, adenoids, appendix, and Peyer's patches (organized tissue in the large intestines) represent a more formal association of parenchyma that shares the same functional parameters as the MALT. In an analogous manner, aggregates lining bronchial regions are called **BALT (bronchial/tracheal-associated lymphoid tissue)**, and those lining the intestinal tract are referred to as the **GALT (gut-associated lymphoid tissue)**. There are specialized cells in some of these aggregates; **M cells**, or microfold cells, can be found in the follicle-associated epithelium of the Peyer's patch. M cells sample antigen from the lumen of the small intestine and deliver it via transcytosis to immune cells located on their basolateral side.

CELLS OF THE IMMUNE SYSTEM

A **leukocyte** is the term given to any white blood cells that play a functional role in either innate or adaptive responses. This population of cells can be broken into two main groups, referred to as **myeloid** or **lymphoid** cells, depending on which developmental path was taken by the stem cells in the bone marrow during development (Figure 1.3). Myeloid cells are considered as the first line of defense and thus constitute the major cells involved in innate immunity (Table 1.3). Myeloid cells include highly phagocytic, motile **neutrophils**, **monocytes** and **macrophages**, and **dendritic cells** that provide relatively immediate protection against most pathogens. The other myeloid cells, including **eosinophils**, **basophils**, and their tissue counterparts, **mast cells**, are involved in defense against parasites and in the genesis of allergic reactions. In contrast, lymphoid cell types include