INNATE IMMUNITY: A Non Specific Immunity

UNIT-I: Chapter 1
MSc 3rd Sem General Microbiology and Applied Microbiology
Course: Molecular Immunology

Compiled By: Dr Dinesh Kumar Sharma

INTRODUCTION

The immune system has evolved to protect us from pathogens. Intracellular pathogens infect individual cells (e.g. viruses), whereas extracellular pathogens divide extracellularly within tissues or the body cavities (e.g. many bacteria). Immunity is the capability of multicellular organisms to resist harmful microorganisms from entering their cells. Immunity involves both specific and nonspecific components. The nonspecific components act as barriers or eliminators of a wide range of pathogens irrespective of their antigenic make-up. Other components of the immune system adapt themselves to each new disease encountered and can generate pathogen-specific immunity.

The discipline of immunology grew out of the observation that individuals who had recovered from certain infectious diseases were thereafter protected from the disease. The Latin term *immunis,* meaning "exempt," is the source of the English word **immunity**, a state of protection from infectious disease.

Innate immunity serves three important functions: 1. Innate immunity is the initial response to microbes that prevents, controls, or eliminates infection of the host by many microbes, 2. Innate immune mechanisms recognize the productsof damaged and dead host cells and serve to eliminate these cells and to initiate the process of tissue repair, 3. Innate immunity to microbes stimulates adaptive immune responses and can influence the nature of the adaptive responses to make them optimally effective against different types of microbes

TYPES OF IMMUNITY:

The Immune System Includes Innate and Adaptive Components:

Immunity—the state of protection from infectious disease has both a nonspecific and specific component.

INNATE IMMUNITY: non Specific Component

Innate immune responses are not specific to a particular pathogen in the way that the adaptive immune responses are. They depend on a group of proteins and phagocytic cells that recognize conserved features of pathogens and become quickly activated to help destroy invaders. The less specific component, **innate immunity,** provides the first line of defense against infection. Most components of innate immunity are present before the onset of infection and constitute a set of disease-resistance mechanisms that are not specific to a particular pathogen but that include cellular and molecular components that recognize classes of molecules peculiar to frequently encountered pathogens. Phagocytic cells, such as macrophages and neutrophils, barriers such as skin, and a variety of antimicrobial compounds synthesized by the host all play important roles in innate immunity.

TABLE 1-2 Summary of nonspecific host defenses

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

Innate immunity can be seen to comprise four types of defensive barriers: anatomic, physiologic, phagocytic, and inflammatory

1. **Anatomic Barrier-**(Skin and Mucous Membrane)

Intact skin contributes greatly to innate host resistance because it is a very effective mechanical barrier to microbial invasion. Its outer layer consists of thick, closely packed cells called keratinocytes, which produce keratins. Keratins are scleraproteins (i.e., insoluble proteins) that are the main components of hair, nails, and the outer skin cells. These outer skin cells shed continuously, removing microorganisms that manage to adhere to their surface. The skin is slightly acidic (around pH 5 to 6) due to sebum, secretions from sweat glands, and organic acids produced by commensal staphylococci. It also contains a high concentration of sodium chloride and is subject to periodic drying.

The skin consists of two distinct layers: a thinner outer layer—the **epidermis**—and a thicker layer—the **dermis.** The epidermis contains several layers of tightly packed epithelial cells. The outer epidermal layer consists of dead cells and is filled with a waterproofing protein called keratin. The dermis, which is composed of connective tissue, contains blood vessels, hair follicles, sebaceous glands, and sweat glands. The sebaceous glands are associated with the hair follicles and produce an oily secretion called **sebum.** Sebum consists of lactic acid and fatty acids, which maintain the pH of the skin between 3 and 5; this pH inhibits the growth of most microorganisms. A few bacteria that metabolize sebum live as commensals on the skin and sometimes cause a severe form of acne.

The mucous membranes of the eye (conjunctiva) and the respiratory, digestive, and urogenital systems withstand microbial invasion because the intact stratified epithelium and mucus form a protective covering that resists penetration and traps microorganisms. Many mucosal surfaces are bathed in specific antimicrobial secretions. For example, cervical mucus, prostatic fluid, and

tears are toxic to many bacteria. The conjunctiva that lines the interior surface of each eyelid and the exposed surface of the eyeball is a good example of how a mucous membrane functions to provide chemical as well as physical protection from microorganisms. It is kept moist by the continuous flushing action of tears from the lacrimal glands. Tears contain large amounts of lysozyme, lactoferrin, and other antimicrobial chemicals.

2. Physiologic Barrier

The physiologic barriers that contribute to innate immunity include temperature, pH, and various soluble and cell associated molecules. Many species are not susceptible to certain diseases simply because their normal body temperature inhibits growth of the pathogens. Chickens, for example, have innate immunity to anthrax because their high body temperature inhibits the growth of the bacteria. Gastric acidity is an innate physiologic barrier to infection because very few ingested microorganisms can survive the low pH of t he stomach contents. A variety of soluble factors contribute to innate immunity, among them the soluble proteins lysozyme, interferon, and complement.

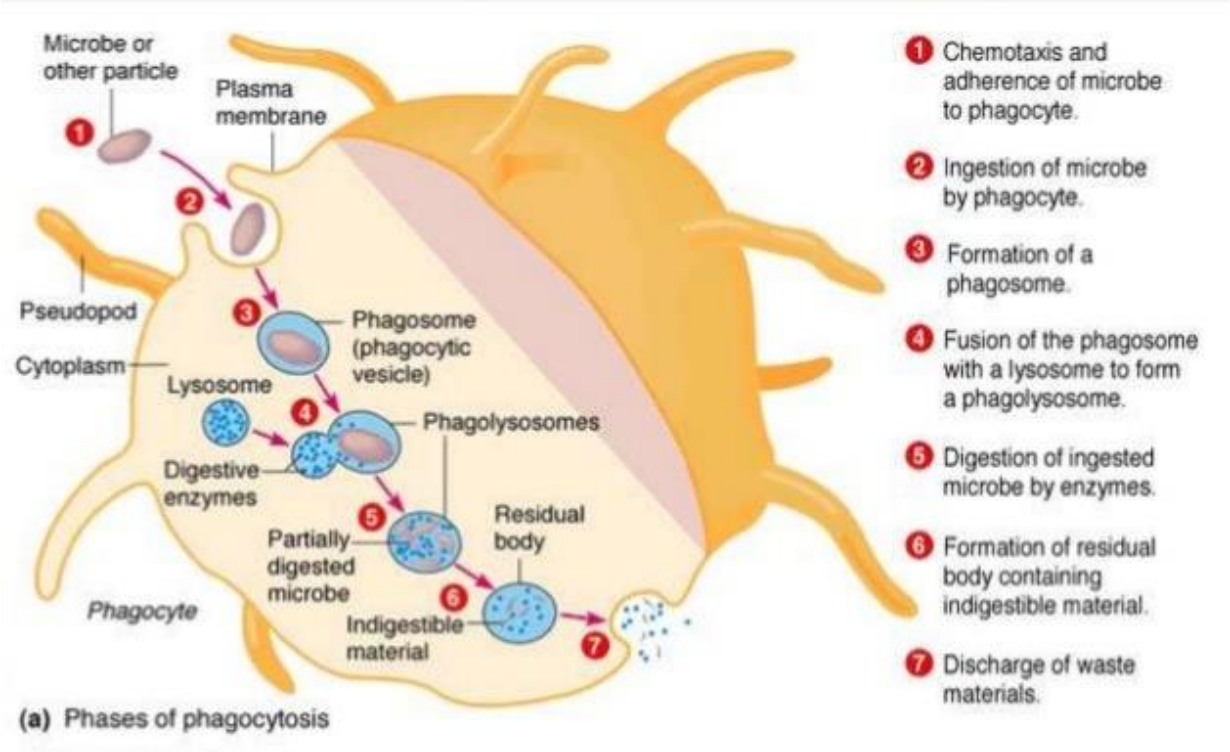
Lysozyme, a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall.

Interferon comprises a group of proteins produced by virus-infected cells. Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state.

Complement is a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance.

3. Phagocytic Barrier

Phagocytosis is one type of **endocytosis,** the general term for the uptake by a cell of material from its environment. In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms, to form large vesicles called **phagosomes**. Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages. Most cell types are capable of other forms of endocytosis, such as *receptor-mediated endocytosis,*in which extracellular molecules are internalized after binding by specific cellular receptors, and *pinocytosis,* the process by which cells take up fluid from the surrounding medium along with any molecules contained in it.



4. **Inflammatory Barrier**

Tissue damage caused by a wound or by an invading pathogenic microorganism induces a complex sequence of events collectively known as the **inflammatory response.** a molecular component of a microbe, such as LPS, may trigger an inflammatory response via interaction with cell surface receptors. The end result of inflammation may be the marshalling of a specific immune response to the invasion or clearance of the invader by components of the innate immune system.

In the first century AD, the Roman physician Celsus described the "four cardinal signs of inflammation" as *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, another physician, Galen, added a fifth sign: *functio laesa* (loss of function). The cardinal signs of inflammation reflect the three major events of an inflammatory response

1. ***Vasodilation***—an increase in the diameter of blood vessels—of nearby capillaries occurs as the vessels that carry blood away from the affected area constrict, resulting in engorgement of the capillary network. The engorged capillaries are responsible for tissue redness (*erythema*) and an increase in tissue temperature.
2. **An *increase in capillary permeability*** facilitates an influx of fluid and cells from the engorged capillaries into the tissue. The fluid that accumulates **(exudate)** has a much higher protein content than fluid normally released from the vasculature. Accumulation of exudate contributes to tissue swelling **(edema)**.
3. ***Influx of phagocytes*** from the capillaries into the tissues is facilitated by the increased permeability of the capillaries. The emigration of phagocytes is a multistep process that includes adherence of the cells to the endothelial wall of the blood vessels **(margination)**, followed by their emigration between the capillaryendothelial cells into the tissue **(diapedesis** or **extravasation)**, and, finally, their migration through the tissue to the site of the invasion

(chemotaxis). As phagocytic cells accumulate at the site and begin to phagocytose bacteria, they release lytic enzymes, which can damage nearby healthy cells. The accumulation of dead cells, digested material, and fluid forms a substance called pus.

The events in the inflammatory response are initiated by a complex series of events involving a variety of chemical mediators whose interactions are only partly understood. Some of these mediators are derived from invading microorganisms, some are released from damaged cells in response to tissue injury, some are generated by several plasma enzyme systems, and some are products of various white blood cells participating in the inflammatory response.

Among the substances that contribute to vasodilation, increased permeability, and other aspects of the inflammatory response are the following:

Histamine. In response to injury, mast cells in connective tissue and basophils and platelets in blood release **histamine**. Neutrophils and macrophages attracted to the site of injury also stimulate the release of histamine, which causes vasodilation and increased permeability of blood vessels.

Kinins. Polypeptides formed in blood from inactive precursors called kininogens, (**kinins**), induce vasodilation and increased permeability and serve as chemotactic agents for phagocytes. An example of a kinin is bradykinin.

Prostaglandins. **Prostaglandins (PGs)**, especially those of the E series, are released by damaged cells and intensify the effects of histamine and kinins. PGs also may stimulate the emigration of phagocytes through capillary walls.

Leukotrienes. Produced by basophils and mast cells, **leukotrienes (LTs)** cause increased permeability; they also function in adherence of phagocytes to pathogens and as chemotactic agents that attract phagocytes.

Complement. Different components of the complement system stimulate histamine release, attract neutrophils by chemotaxis, and promote phagocytosis; some components can also destroy bacteria.

Dilation of arterioles and increased permeability of capillaries produce three of the signs and symptoms of inflammation: heat, redness (erythema), and swelling (edema). Heat and redness result from the large amount of blood that accumulates in the damaged area. As the local temperature rises slightly, metabolic reactions proceed more rapidly and release additional heat. Edema results from increased permeability of blood vessels, which permits more fluid to move from blood plasma into tissue spaces.

Pain is a prime symptom of inflammation. It results from injury to neurons and from toxic chemicals released by microbes. Kinins affect some nerve endings, causing much of the pain associated with inflammation. Prostaglandins intensify and prolong the pain associated with inflammation. Pain may also be due to increased pressure from edema. The increased permeability of capillaries allows leakage of blood-clotting factors into tissues. The clotting sequence is set into motion, and fibrinogen is ultimately converted to an insoluble, thick mesh of fibrin threads that localizes and traps invading microbes and blocks their spread.

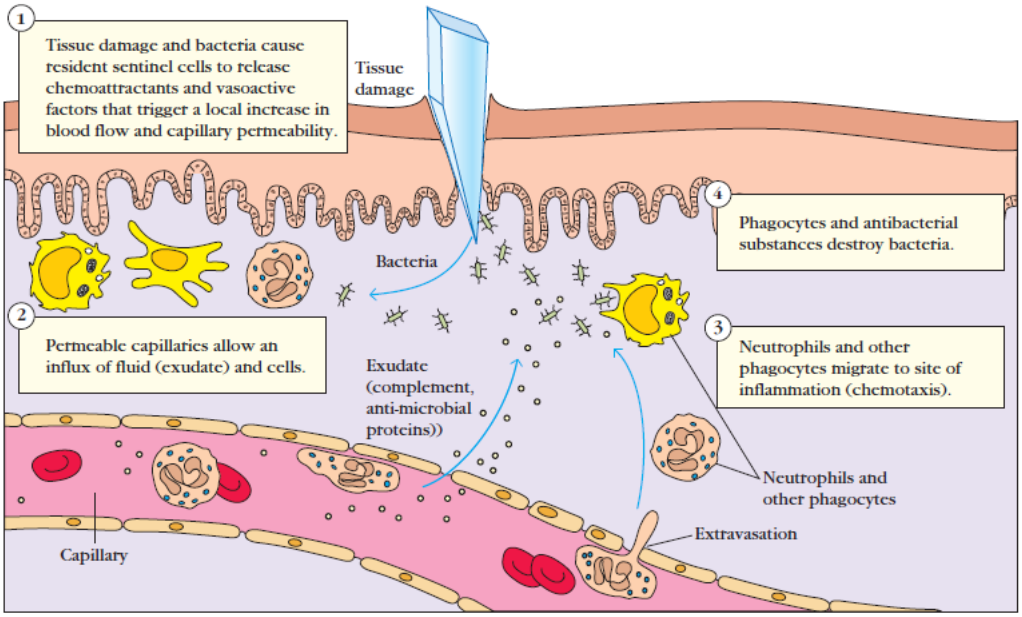


FIGURE 5-17 Initiation of a local inflammatory response. Bacterial entry through wounds activates initial innate immune mechanisms, including phagocytosis by and activation of resident cells, such as macrophages and dendritic cells. Recognition of bacteria by soluble and cellular pattern recognition molecules initiates an inflammatory response that recruits antimicrobial substances and phagocytes (first neutrophils and then monocytes) to the site of infection.

RECOGNITION OF MICROBES AND DAMAGED SELF BY THE INNATE IMMUNE SYSTEM

The specificities of innate immune recognition have evolved to combat microbes and are different from the specificities of the adaptive immune system in several respects. The innate immune system recognizes molecular structures that are characteristic of microbial pathogens but not mammalian cells. The microbial substances that stimulate innate immunity are called **pathogen-associated molecular patterns (PAMPs)**. Different classes of microbes (e.g., viruses, gram-negative bacteria, gram positive bacteria, fungi) express different PAMPs. These structures include nucleic acids that are unique to microbes, such as double-stranded RNA found in replicating viruses and unmethylated CpG DNA sequences found in bacteria; features of proteins that are found in microbes, such as initiation by *N*-formylmethionine, which is typical of bacterial proteins; and complex lipids and carbohydrates that are synthesized by microbes but not by mammalian cells, such as lipopolysaccharide (LPS) in gram-negative bacteria, lipoteichoic acid in gram positive bacteria, and mannose-rich oligosaccharides found in microbial but not in mammalian glycoproteins. In actuality, there are only a limited number of fundamental differences between microbial molecules and the molecules that higher organisms produce. Thus, the innate immune system has evolved to recognize only a limited number of molecules, most of which are unique to microbes, whereas the adaptive immune system is capable of recognizing a much wider array of foreign substances whether or not they are products of microbes.

TABLE 4–2 Examples of PAMPs and DAMPs

Pathogen-Associated Molecular Patterns		Microbe Type
Nucleic acids	ssRNA	Virus
	dsRNA	Virus
	CpG	Virus, bacteria
Proteins	Pilin	Bacteria
	Flagellin	Bacteria
Cell wall lipids	LPS	Gram-negative bacteria
	Lipoteichoic acid	Gram-positive bacteria
Carbohydrates	Mannan	Fungi, bacteria
	Dectin glucans	Fungi
Damage-Associated Molecular Patterns		
Stress-induced proteins	HSPs	
Crystals	Monosodium urate	
Nuclear proteins	HMGB1	

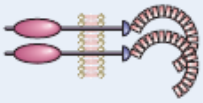
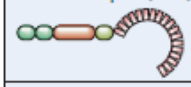
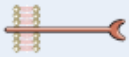
CpG, cytidine-guanine dinucleotide; dsRNA, double-stranded RNA; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; LPS, lipopolysaccharide; ssRNA, single-stranded RNA.

The innate immune system recognizes microbial products that are often essential for survival of the microbes. This feature of innate immune recognition is important because it ensures that the targets of innate immunity cannot be discarded by microbes in an effort to evade recognition by the host. An example of a target of innate immunity that is essential for microbes is double-stranded viral RNA, which plays a critical role in the replication of certain viruses. Similarly, LPS and lipoteichoic acid are structural components of bacterial cell walls that are recognized by innate immune receptors; both are required for bacterial survival and cannot be discarded. In contrast, microbes may mutate or lose many of the antigens that are recognized by the adaptive immune system, thereby enabling the microbes to evade host defense without compromising their own survival.

The innate immune system also recognizes endogenous molecules that are produced by or released from damaged and dying cells. These substances are called **damage associated molecular patterns (DAMPs).** DAMPs may be produced as a result of cell damage caused by infections, but they may also indicate sterile injury to cells caused by any of myriad reasons, such as chemical toxins, burns, trauma, or decreased blood supply. DAMPs are generally not released from cells dying by apoptosis. In some cases, healthy cells of the immune system are stimulated to produce and release DAMPs, which enhances an innate immune response to infections.

The innate immune system uses several types of cellular receptors, present in different locations in cells, and soluble molecules in the blood and mucosal secretions to recognize PAMPs and DAMPs. Cell-associated recognition molecules of the innate immune system are expressed by phagocytes (primarily macrophages and neutrophils), dendritic cells, epithelial cells that compose the barrier interface between the body and the external environment, and many other types of cells that occupy tissues and organs. These cellular receptors for pathogens and damage-associated molecules are often called **pattern recognition receptors**. They are expressed on the plasma membrane or endosomal membranes of various cell types and also in

the cytoplasm of these cells. These various locations of the receptors ensure that the innate immune system can respond to microbes that may be present outside cells or within different cellular compartments. When these cell-associated pattern recognition molecules bind to PAMPs and DAMPs, they activate signal transduction events that promote the antimicrobial and proinflammatory functions of the cells in which they are expressed. In addition, there are many proteins present in the blood and extracellular fluids that recognize PAMPs. These soluble molecules are responsible for facilitating the clearance of microbes from blood and extracellular fluids by enhancing uptake into cells or by activating extracellular killing mechanisms.

Cell-Associated Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Toll-like receptors (TLRs) 	Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells endothelial cells, and many other cell types	TLRs 1-9	Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids
NOD-like receptors (NLRs) 	Cytoplasm of phagocytes epithelial cells, and other cells	NOD1/2 NALP family (inflammasomes)	Bacterial cell wall peptidoglycans Flagellin, muramyl dipeptide, LPS; urate crystals; products of damaged cells
RIG-like receptors (RLRs) 	Cytoplasm of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
C-type lectin–like receptors 	Plasma membranes of phagocytes	Mannose receptor Dectin	Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides
N-Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing *N*-formylmethionyl residues

SUMMARY:-

Immunity is the state of protection against foreign organisms or substances (antigens). There are two interdependent components of the immune response to invading microorganisms and foreign material; innate resistance and adaptive immune responses.

Innate immune system lacks any form of memory. As a result the intensity and duration of processes such as inflammation remain unchanged no matter how often a specific invader is encountered. On the other hand, it is always ready to respond immediately once an invading pathogen encountered. It is not specific to any one pathogen but rather constitutes a first line of defense, which includes anatomic, physiologic, endocytic and phagocytic, and inflammatory barriers.

Innate and adaptive immunity operate in cooperative and interdependent ways. The activation of innate immune responses produces signals that stimulate and direct subsequent adaptive immune responses.

The receptors of the innate immune system recognize conserved pathogen-associated molecular patterns (PAMPs), which are molecular motifs found in microbes, and damage- associated

molecular patterns (DAMPs) from aging, damaged, or dead cells. Therefore these receptors are called pattern-recognition receptors (PRRs).

Phagocytosis—engulfment and internalization of particulate materials such as microbes—is mediated by receptors on phagocytes (monocytes, macrophages, neutrophils, and dendritic cells) that either directly recognize PAMPs on the surface of microbes or recognize soluble proteins (opsonins) that bind to the microbes.

TOPIC RELATED QUESTIONS

1. Outline the sequence of innate host responses that result in inflammation.
2. Describe the differences between specific and nonspecific immunity.
3. What is acquired immunity? How do you get it?
4. Discuss about phagocytosis. Give suitable diagram.
5. Briefly describe the three major events in the inflammatory response.
6. Discuss abouts PAMPs.

REFFERENCES:

1. Judith A. Owen, Jenni Punt, Sharon A. Stranford and Patricia P. Jones (2013). Kuby Immunology, 7th Edition, W. H. Freeman and Company. New York.
2. David Male, Jonathan Brostoff, David B Roth and Ivan Roitt (2006). Immunology, 7th Edition Mosby Elsevier.
3. Ian R Tizard (2009). Immunology, an Introduction, 4th Edition; Cengage Learning.
4. Gerard J. Tortora and Bryan Derrickson(2014). Principles of Anatomy and Physiology, 14th Edition; Wiley.
5. Joanne M. Willey, Linda M. Sherwood, and Christopher J. Woolverton(2014). Prescott's Microbiology, 9th Edition; The McGraw-Hill.
6. Abul K. Abbas, Andrew H. Lichtman and Shiv Pillai (2012). Cellular and Molecular Immunology, 7th Edition, Elsevier Saunders.