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医学免疫学

Textbook of Medical Immunology

主　编 Chief Editors

何　维（Hei Wei）LIM Pak Leong

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LIM Pak Leong（香港中文大学）

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全国高等学校临床医学专业规划教材
“英文版”出版说明

2001 年 8 月，教育部制定并下发《关于加强高等学校本科教学工作提高教学质量的若干意见》（教高[2001]4 号），指出：按照“教育面向现代化、面向世界、面向未来”的要求，为适应经济全球化和科技革命的挑战，本科教育要创造条件使用英语等外语进行公共课和专业课教学。对高新技术领域的生物技术、信息技术等专业，更要先行一步，力争三年内，外语教学课程达到所开课程的 5%～10%。2005 年 1 月，又印发了《关于进一步加强高等学校本科教学工作的若干意见》（教高〔2005〕1 号），指出：高等学校要全面推广和使用大学英语教学改革的成果，要提高双语教学课程的质量，继续扩大双语教学课程的数量。要加强教材建设，确保高质量教材进课堂。

双语教育是提高学生英语水平的一个途径，尽管我国高等医学院校双语教学探索已有若干年，但教材的跟进始终显得滞后。没有合适的教材是目前双语教学面临的困难之一。2006 年初，为推进双语教学的发展，经全国高等医药教材建设研究会和卫生部教材办公室审议，决定根据国家、地方和学生未来发展的需要，组织国内专家结合双语教学的经验，编写出版一套适应当前双语教学现状的教材。

此套教材的特点在于：

- 汇集名师。各教材主编均由卫生部规划的五年制、八年制教材的主编担任。
- 适合国情。教材的编写内容和体系主要参考我国医学院校长期使用并多次修订的五年制、八年制规划教材，更符合我国的教学模式。
- 语言纯正。根据引进的经典英文原版教材改编，聘请国外作者或编辑参与审校工作。
- 篇幅适中。由于双语教学的课时数有限，因此在编写时只选取各门学科需要重点掌握的内容（占中文教材内容的 1/2～2/3）进行编写，也可减轻学生的负担。
- 丰富的教辅资源。教辅资源一直是外版教材的核心资源，因此，在本套教材编写的同时，我社引进了国外畅销的系列案例教材《Case Files》，以配合教学使用。
- 制作精美。为满足广大读者的阅读需要，全套教材采用双色印刷，图文并茂，版式清新美观。

本套教材共 16 种，全部为卫生部“十一五”规划教材。全套教材将于 2007 年秋季和 2008 年春季分两批出版发行。可供各医学院校针对五年制、七年制、八年制等不同层次学生开展双语教学使用。

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Preface

Essential Medical Immunology is written for medical students in the People's Republic of China and is adapted largely from *Immunology* (Seventh Edition) by David Male, Jonathan Brostoff, David B Roth and Ivan Roit, with the permission of Mosby Elsevier Publishers. Information from other sources, including research articles, has also been included.

Immunology is an experimental biomedical science concerned with the study of the structure and function of the immune system in all life-forms, while medical immunology emphasizes on the human system and the diseases associated with it. Starting from the pioneering observations of people like Edward Jenner, who in 1798 performed the first vaccination, or Frank Widal who, in 1896, developed the first serological test, immunology has grown enormously to become an important, complex discipline that has permeated into many other fields of biology, including such diverse areas as neuroscience and biotechnology.

The book attempts to provide a brief account of immunology to medical students and is divided broadly into 'Basic Immunology and Clinical Immunology'. Although the aim is to keep the text simple and concise, depth has been given to some areas to provide a more comprehensive understanding for the more enthusiastic students. We hope students will find the book both informative and user-friendly.

We are indebted to Associate Professor Yang Gao, Ms. Xianqian Kong and Ms. Peggy Fung for their secretarial assistance.

HE Wei

LIM Pak Leong

Essential Medical Immunology

Section I Basic Immunology

Section I
Basic Immunology

Chapter 1 Overview of the Immune System

"Immunity" is derived from the Latin word *immunitas*, which in ancient Roman times meant the exemption of an individual from service or duty to the country. In medical usage, immunity has been used to denote the resistance of a person to infection by a particular microorganism or infectious agent. The organs, tissues, cells and molecules of the body responsible for immunity constitute the immune system, while the body's response to the infectious agent is called the **immune response.** The various components of the immune system, comprising both cells and serum proteins, are illustrated in Fig. 1.1. There are two types of immunity. **Innate immunity** (also called **natural** or **native immunity**) consists of those cellular and molecular defense mechanisms that allow the body to respond quickly to infections as a first line of defense, while **adaptive immunity** (also called **specific** or **acquired immunity**) develops later, which engages the specialized functions of cells (B and T lymphocytes) and proteins (antibodies) that have exquisite specificities. While the immune system has evolved primarily to protect the host from infectious agents that are "foreign" to the host, the same surveillance function also operates against tumors and other non-infectious substances that are foreign (allergens) or non-foreign, but mistaken as foreign (autoantigens).

INNATE IMMUNITY

Innate immunity is present from birth in all animals to protect the host from injury or infection. Innate immune responses are simple but sophisticated and rapid, which represent the first line of defense against any infectious agent (pathogen) encountered even for the first time. The magnitude of response is the same regardless of how many times the infectious agent has been encountered previously. The innate immune system includes both physical and chemical barriers, such as the epithelium and antimicrobial substances produced at epithelial surfaces, phagocytic cells (neutrophils, macrophages), natural killer (NK) cells, and various blood proteins including complement cytokines (Fig. 1.1).

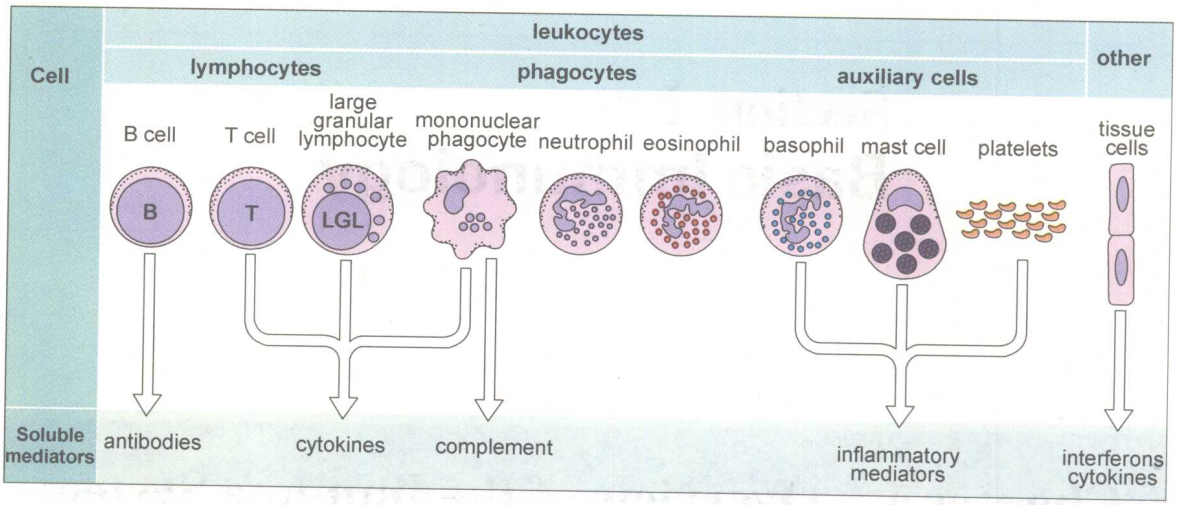

Fig. 1.1 Components of the immune system. The principal cells of the immune system and the mediators they produce are shown. Neutrophils, eosinophils and basophils are collectively known as polymorphonuclear granulocytes. Cytotoxic cells include cytotoxic T lymphocytes (CTLs), natural killer (NK) cells [large granular lymphocytes (LGLs)], and eosinophils. Complement is made primarily by the liver, though there is some synthesis by mononuclear phagocytes. Note that each cell produces and secretes only a particular set of cytokines or inflammatory mediators.

Physical and Chemical Barriers

The exterior defenses of the body (Fig. 1.2) present an effective barrier to most organisms. Very few infectious agents can penetrate intact skin. In contrast, many infectious agents gain access to the body across the epithelia of the gastrointestinal or urogenital tracts. Others, such as the virus responsible for the common cold, infect the respiratory epithelium of nasopharynx and lungs. A small number of infectious agents infect the body only if they enter into blood directly (e.g. malaria parasite, through mosquito bite).

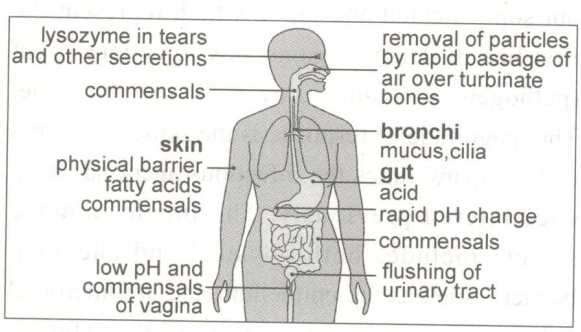

Fig. 1.2 Exterior defenses. Most infectious agents are prevented from entering the body by physical and biochemical barriers. The body tolerates a number of commensal organisms, which compete effectively with many potential pathogens.

Phagocytic Cells

Phagocytic cells are important components of innate immunity. They function by capturing and internalizing the pathogen and destroying it subsequently. These cells include monocytes, macrophages and neutrophils. Mononuclear phagocytic cells include the long-lived **monocytes** in peripheral blood and the **macrophages** in tissues. Monocytes migrate from the blood to the tissues where they develop into tissue macrophages, which are very effective at presenting antigens to T lymphocytes (see later). **Polymorphonuclear neutrophils** (often just called **neutrophils** or **PMNs**) are another important group of phagocytic cells. Neutrophils constitute the majority of the blood leukocytes and develop from the same

early precursors as monocytes and macrophages (Fig. 1.1). Like monocytes, neutrophils migrate into tissues, particularly at sites of inflammation. However, neutrophils are short-lived cells that phagocytose material, destroy it, and then die. Phagocytic cells bind to invading organisms using a variety of receptors such as **pattern-recognition receptors (PRRs)**. Phagocytosis describes the internalization (endocytosis) of large particles such as bacteria to form a phagosome, which later becomes fused with the granules and lysosome of the cell that contain degradative enzymes and toxic substances. Killing of the organism is thus effective including the damage caused by oxygen radicals generated by enzymic activity.

Auxiliary Cells

The main purpose of inflammation is to attract leukocytes and the soluble mediators of immunity towards a site of infection. Inflammation is mediated by a variety of other cells including basophils, mast cells and platelets. **Basophils** and **mast cells** have granules that contain a variety of mediators, which induce inflammation in surrounding tissues and are released when the cells are triggered.

Basophils and mast cells can also synthesize and secrete a number of mediators that control the development of immune reactions. Mast cells lie close to blood vessels in all tissues, and some of their mediators act on cells in the vessel walls. Basophils are functionally similar to mast cells, but are mobile, circulating cells. Platelets are essential in blood clotting, but can also be activated during immune response to release mediators of inflammation.

Soluble Mediators

A wide variety of molecules are involved in the development of immune responses, including **antibodies** and **cytokines** that are produced by lymphocytes, and other proteins that are normally present in serum.

The serum concentration of a number of these proteins increases rapidly during infection and they are therefore called acute phase proteins. One example of an acute phase protein is C reactive protein (CRP), so-called because of its ability to bind to the C protein of pneumococci. This promotes the uptake of pneumococci by phagocytic cells, a process known as opsonization. Molecules such as antibody and CRP that promote phagocytosis are said to act as opsonins. Another important group of molecules that can act as opsonins is components of the complement system.

Complement Proteins

The **complement** system is a group of about 20 serum proteins whose overall function is the control of inflammation (Fig. 1.3). The components interact with each other, and with other elements of the immune system. For example, a number of microorganisms spontaneously activate the complement system, via the so-called 'alternative pathway', which is an innate immune defense - this results in the microorganism being opsonized (i.e. coated by complement molecules, leading to its uptake by phagocytic cells). The complement system can also be activated by antibodies or by mannose binding lectin bound to the pathogen surface via the 'classical pathway'. Complement activation is a cascade reaction, where one component acts on enzymatically on the next component in the cascade to generate an enzyme, which mediates the following step in the reaction sequence, and so on. Activation of the complement system generates protein molecules or peptide fragments, which have the following effects: opsonization of microorganisms for uptake by phagocytic cells and eventual intracellular killing; attraction of

phagocytic cells to sites of infection (chemotaxis); increased blood flow to the site of activation and increased permeability of capillaries to plasma molecules; damage to plasma membranes on cells, Gram-negative bacteria, enveloped viruses, or other organisms that have induced the activation, which in turn can result in lysis of the cell or virus and so reduce the infection; release of inflammatory mediators from mast cells.

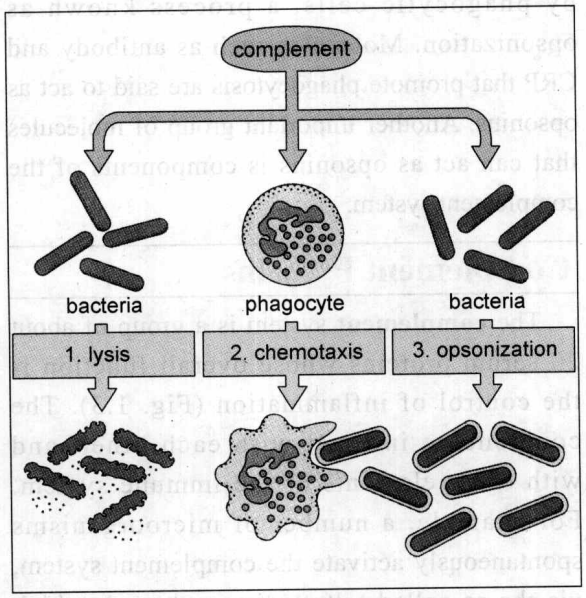

Fig. 1.3 Function of complement. Components of the complement system can lyse many bacterial species (1). Complement fragments released in this reaction attract phagocytes to the site of the reaction (2). Complement components opsonize the bacteria for phagocytosis (3). In addition to the responses shown here, activation of the complement system increases blood flow and vascular permeability at the site of activation. Activated components can also induce the release of inflammatory mediators from mast cells.

Toll–like Receptors

Toll-like receptors (TLRs) have recently been discovered to play a critical role in early innate immunity. These evolutionary conserved receptors, which are homologues of the Drosophila Toll gene product, are expressed on the surfaces of phagocytic cells and some other cells. They recognize highly conserved structural motifs expressed only by microbial pathogens called **pathogen-associated molecule patterns (PAMPs)**. PAMPs include various bacterial cell wall components such as lipopolysaccharides (LPs), peptidoglycans and lipopeptides, as well as flagellin, bacterial DNA and viral double-stranded RNA. The receptors for PAMPs are PRRs, which are encoded by germline genes. TLR is one kind of PRRs, which signals macrophages to respond to microbial products such as endotoxin. TLRs share signal transduction pathways with the type I IL-1 (cytokine) receptor.

ADAPTIVE IMMUNITY

In contrast to innate immunity, adaptive immunity protects a person from an infectious agent after a previous clinical or subclinical infection with that agent or following deliberate immunization with the particular agent. This type of immunity is mediated by B and T lymphocytes following activation by the infectious agent or antigens (i.e. components) derived from the agent. Unlike innate immunity, it is characterized by specificity and immunological memory, that is, the responses get stronger and are generated earlier when the same infectious agent is encountered again after previous times.

B and T Cells

Lymphocytes are wholly responsible for the specific immune recognition of pathogens, and they initiate the adaptive immune responses. All lymphocytes are derived from bone marrow stem cells, but **T lymphocytes (T cells)** then develop in the thymus, while **B lymphocytes (B cells)** develop in the bone marrow (in adult mammals). These cells populate the blood, where they form important members of the white blood cells or, as

commonly known, leukocytes (other important members being the monocytes and PMNs), and the lymphoid tissues.

B cells express unique surface receptors for native antigen

Each B cell is genetically programmed to express a surface receptor specific for a particular antigen, termed the **B cell receptor (BCR).** Each cell has only one type of BCR but many copies of it. B cells differ from one another by the unique specificity of the BCR each cell has. When the BCR is bound by the appropriate antigen (in its native form), the cell proliferates and differentiates into plasma cells, which produce and secrete large amounts of immunoglobulins or antibodies as they are commonly called (especially when the antigen specificity is known). The secreted antibody molecules are large glycosylated proteins found in the blood and tissue fluids, which are really a soluble version of the BCR associated with the original cell that later became the antibody-secreting cell.

T cells express unique surface receptors for processed antigen

There are several different types of T cells, each with a distinct function: One group interacts with mononuclear phagocytes and helps them to destroy intracellular pathogens - these are called **type 1 helper T (TH1) cells**. Another group interacts with B cells and helps them to divide, differentiate, and make antibody - these are the **type 2 helper T (TH2) cells**. A third group of T cells is responsible for the destruction of host cells that have become infected with viruses or other intracellular pathogens - this kind of action is called cytotoxicity and these T cells are thus called **cytotoxic T lymphocytes (CTLs or Tc cells)**. In all cases, T cells recognize antigens present on the surface of other cells using a specific receptor- **the T cell antigen receptor (TCR)**. TCR is structurally distinct from but related to BCR. However, it does not recognize the native antigen but rather, short peptides of the antigen derived from intracellular digestion following uptake of the antigen by the cell, and these peptides have to be presented by another cell surface receptor called Major Histocompatibility Complex (MHC). As the case with B cells, each T cell is equipped with multiple copies of a unique TCR. T cells generate their effects either by releasing soluble proteins (called cytokines) to signal other cells, or by direct cell-cell interactions.

Cytotoxic T cells recognize and destroy infected cells

Several cell types of immune cells have the capacity to kill other cells that have become infected. Cytotoxic cells include CTLs, NK cells (large granular lymphocytes), and eosinophils. Of these, the CTL is especially important, but other cell types may be particularly active against certain types of infection.

All cytotoxic cells damage their different targets by releasing the contents of their intracellular granules close to them. Cytokines secreted by these cells also contribute to the damage. Lymphocytes known as **large granular lymphocytes (LGLs)** or **NK cells** have the capacity to recognize the surface changes that occur on a variety of tumor cells and virally infected cells. LGLs damage these target cells using a different recognition system to CTLs that is sometimes called NK cell activity. Eosinophils are a specialized group of leukocytes that have the ability to engage and damage large extracellular parasites, such as schistosomes.

Cytokines

Cytokine is the general term for a large group of molecules involved in signaling between cells