英文原版

免疫学

SIXTH EDITION

IMMUNOLOGY

Roitt • Brostoff • Male

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SIXTH EDITION

IMMUNOLOGY

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Preface

As we started to plan the 6th edition of Immunology, it soon became clear that the steady progress in the subject during the last few years has lead to a new way of understanding immune responses. So we have completely reorganised the first half of the book which covers basic immunology. In addition, all sections have been thoroughly revised and updated to reflect the continuing rapid progress in both basic and clinical immunology.

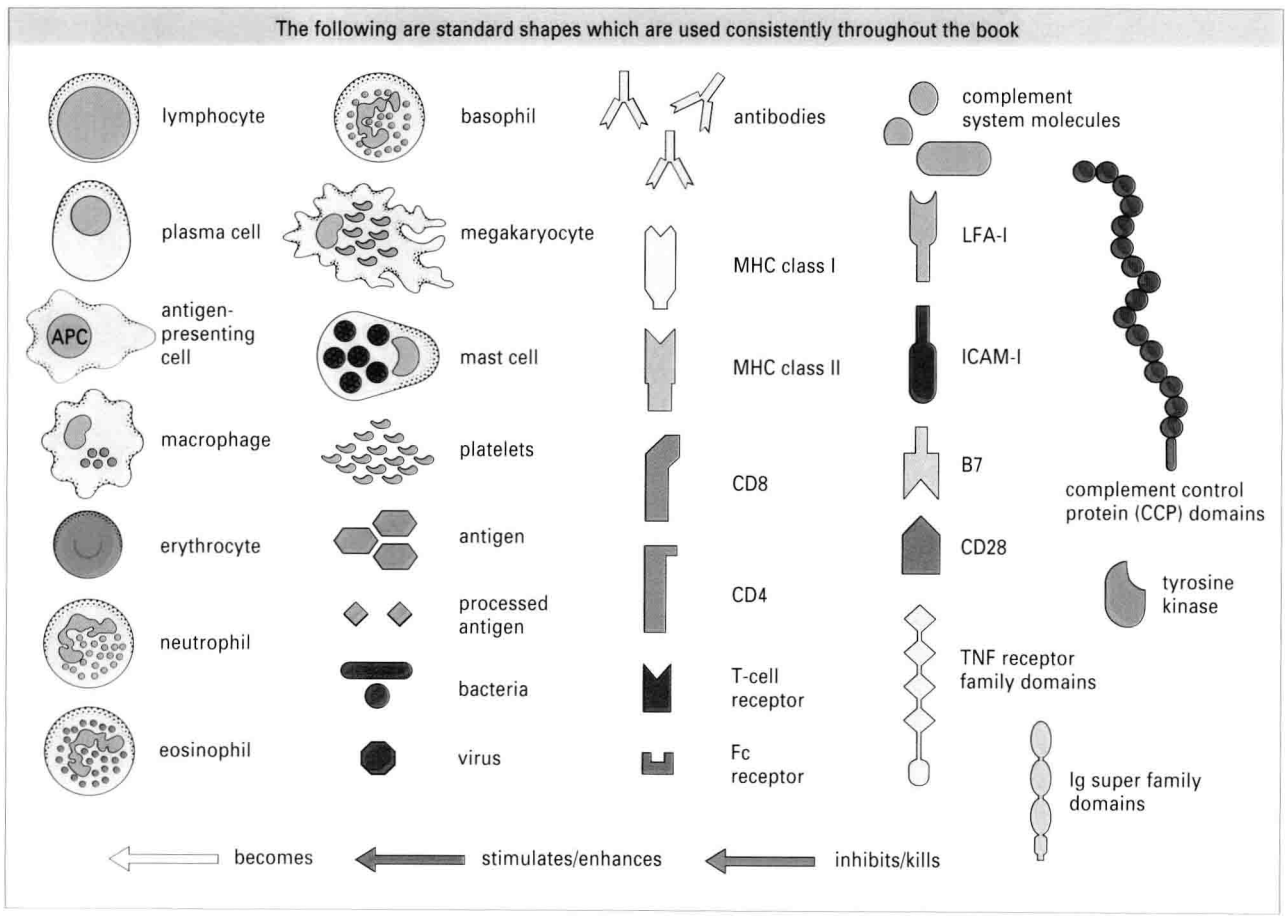
The opening chapters describe the building blocks of the immune system – cells, organs and the major receptor molecules, including antibodies, T cell receptors and MHC molecules. Information on the development of the leucocyte populations and antigen receptors has now been placed alongside the text describing their functions.

The following chapters deal with the initiation of the immune response, leading from antigen presentation and co-stimulation through cell activation pathways to the actions of cytokines. Finally three chapters discuss the principle effector arms of the immune response, TH2 responses with antibody production, TH1 responses and mononuclear phagocytes, and cytotoxicity, including Tc cells and NK cells. The chapter on immunoregulation has been revised to reflect this way of thinking, while the chapter on tolerance has been extensively rewritten to provide a bridge to the understanding of autoimmunity.

Our aim in this revision has been to provide readers with a sound understanding of the immune responses which underlie clinically important areas, namely defence against infection, hypersensitivity states and allergy, immunopathology, tumour immunotherapy and transplantation. We have maintained what we believe to be an important feature of the book, namely a clear description of the scientific principles of clinical immunology, integrated with histology, pathology, and clinical examples.

A new feature of the book is the use of problem-based learning for basic immunology and clinical case studies as appropriate. A set of solutions to the problems is also included, although some of the questions are open ended and would form a good basis for class discussion or tutorials.

A great strength of this book is the interlinked products which enhance learning and provide different ways of approaching the subject. Free with this book is a disk containing three sample animations taken from the highly successful Immunology Interactive CD-ROM (Male, Brostoff, Gray, Roitt) and a link to a supporting website:



www.fleshandbones.com/immunology/roitt. This website hosts the illustrations from the book in downloadable format. Also available separately is *Immunology: An Illustrated Outline*, Third edition (Male).

We wish our readers well in their study of immunology, a subject which continues to excite and surprise us, and which underpins many other areas of biology and biomedical sciences.

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1 Introduction to the immune system

- **The immune system has evolved to protect us from pathogens.** Some, such as viruses, infect individual cells; others, including many bacteria, divide extracellularly within tissues or the body cavities.
- **The cells which mediate immunity include lymphocytes and phagocytes.** Lymphocytes recognize antigens on pathogens. Phagocytes internalize pathogens and degrade them.
- **An immune response consists of two phases.** In the first phase, antigen activates specific lymphocytes that recognize it; in the effector phase, these lymphocytes coordinate an immune response that eliminates the source of the antigens.
- **Specificity and memory** are two essential features of adaptive immune responses. The immune system mounts a more effective response on second and subsequent encounters with a particular antigen.
- **Lymphocytes have specialized functions.** B cells make antibodies; cytotoxic T cells kill virally infected cells; helper T cells coordinate the immune response by direct cell–cell interactions and the release of cytokines, which help B cells to make antibody.
- **Antigens are molecules which are recognized by receptors on lymphocytes.** B lymphocytes usually recognize intact antigen molecules, while T lymphocytes recognize antigen fragments on the surface of other cells.
- **Clonal selection involves recognition of antigen by a particular lymphocyte;** this leads to clonal expansion and differentiation to effector and memory cells.
- **The immune system may break down.** This can lead to immunodeficiency or hypersensitivity diseases or to autoimmune diseases.

Our environment contains a great variety of infectious microbes – viruses, bacteria, fungi, protozoa and multicellular parasites. These can cause disease, and if they multiply unchecked they will eventually kill their host. Most infections in normal individuals are short-lived and leave little permanent damage. This is due to the immune system, which combats infectious agents.

Because microorganisms come in many different forms, a wide variety of immune responses are required to deal with each type of infection. In the first instance, the exterior defences of the body present an effective barrier to most organisms, and very few infectious agents can penetrate intact skin (*Fig. 1.1*). However, many gain access across the epithelia of the gastrointestinal or urogenital tracts. Others can infect the nasopharynx and lung. A small number, such as malaria and hepatitis B, can only infect the body if they enter the blood directly.

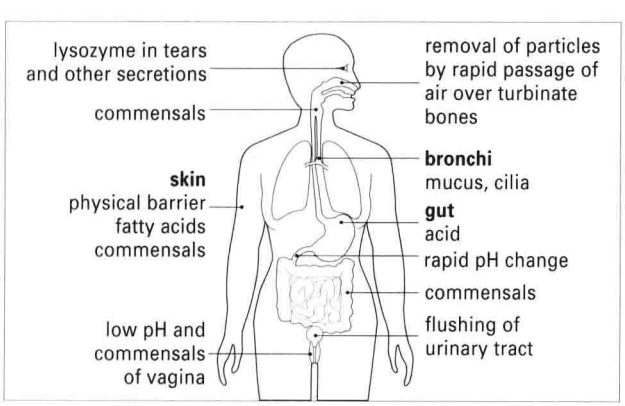

Fig. 1.1 Most of the infectious agents that an individual encounters do not penetrate the body surface, but are prevented from entering by a variety of biochemical and physical barriers. The body tolerates a number of commensal organisms, which compete effectively with many potential pathogens.

The site of the infection and the type of pathogen largely determine which immune responses will be effective. The most important distinction is between pathogens which invade the host's cells and those which do not. All viruses, some bacteria and some protozoan parasites replicate inside host cells, and to clear an infection the immune system must recognize and destroy these infected cells. Many bacteria and larger parasites live in tissues, body fluids or other extracellular spaces, and the responses to these pathogens are quite different. During the course of an infection, however, even intracellular pathogens must reach their target cells by moving through the blood and tissue fluid. At this time they are susceptible to elements of the immune system, which normally counter extracellular pathogens (*Fig. 1.2*).

This chapter introduces the basic elements of the immune system and of immune responses, which are detailed in Chapters 2–18. There are various ways in which the immune system can fail, leading to immunopathological reactions, and these are outlined in the second half of the book. However, it is important to stress that the primary function of the immune system is to eliminate infectious agents and to minimize the damage they cause.

ADAPTIVE AND INNATE IMMUNITY

Any immune response involves, firstly, recognition of the pathogen or other foreign material, and secondly a reaction to eliminate it. Broadly, the different types of immune response fall into two categories: innate (or non-adaptive) immune responses and adaptive immune responses. The important difference between these is that an adaptive

Intracellular and extracellular pathogens

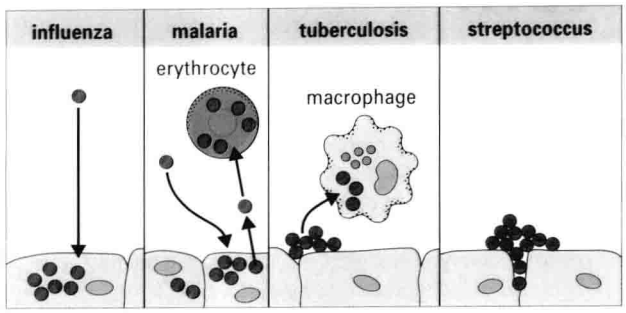

Fig. 1.2 All infectious agents spread to infect new cells by passing through the body fluids or tissues, but many pathogens must infect cells of the body to divide. For example, viruses such as influenza must invade cells to reproduce, while *Plasmodium* spp. (malaria) have two separate phases of division, either in cells of the liver or in erythrocytes. The mycobacteria which cause tuberculosis can divide extracellularly or within macrophages. Some bacteria such as the streptococci, which produce sore throats and wound infections, generally divide outside cells.

Interaction between lymphocytes and phagocytes

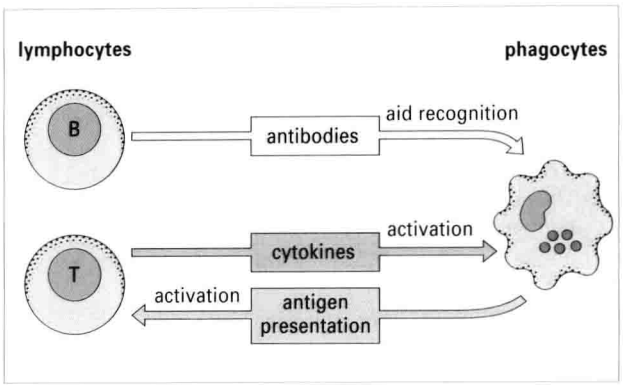

Fig. 1.3 B lymphocytes release antibodies, which bind to pathogens and their products and so aid recognition by phagocytes. Cytokines released by T cells activate the phagocytes to destroy the material they have taken up. In turn, mononuclear phagocytes can present antigen to T cells, thereby activating them.

immune response is highly specific for a particular pathogen. Moreover, although the innate response does not alter on repeated exposure to a given infectious agent, the adaptive response improves with each successive encounter with the same pathogen: in effect the adaptive immune system 'remembers' the infectious agent and can prevent it from causing disease later. For example, diseases such as measles and diphtheria induce adaptive immune responses which generate a life-long immunity following an infection. The two key features of the adaptive immune response are thus specificity and memory.

Immune responses are produced primarily by leucocytes, of which there are several different types.

Phagocytes and innate immune responses – One important group of leucocytes is the phagocytic cells, such as the monocytes, macrophages and polymorphonuclear neutrophils. These cells bind to microorganisms, internalize them and then kill them. Because they use primitive non-specific recognition systems which allow them to bind to a variety of microbial products, they mediate innate immune responses. In effect they act as a first line of defence against infection.

Lymphocytes and adaptive immune responses – Another important set of leucocytes is the lymphocytes. These cells are central to all adaptive immune responses, because they specifically recognize individual pathogens, whether they are inside host cells or outside in the tissue fluids or blood. In fact there are several different types of lymphocyte, but they fall into two basic categories, T lymphocytes (or T cells) and B lymphocytes (or B cells). B cells combat extracellular pathogens and their products by releasing antibody, a molecule which specifically recognizes and binds to a particular target molecule, called the antigen. The antigen may be a molecule on the surface of a pathogen, or a toxin which it produces. T lymphocytes have a wider range of activities. Some are involved in the control of B lymphocyte development and antibody production. Another group of T lymphocytes interacts with phagocytic cells to help them destroy pathogens they have taken up. A third set of T lymphocytes recognizes cells infected by virus and destroys them.

Interaction between lymphocytes and phagocytes – In practice there is considerable interaction between the lymphocytes and phagocytes. For example, some phagocytes can take up antigens and show them to T lymphocytes in a form they can recognize, a process which is called antigen presentation. In turn, the T lymphocytes release soluble factors (cytokines), which activate the phagocytes and cause them to destroy the pathogens they have internalized. In another interaction, phagocytes use antibodies released by B lymphocytes to allow them to recognize pathogens more effectively (*Fig. 1.3*). One consequence of these interactions is that most immune responses to infectious organisms are made up of a variety of innate and adaptive components. In the earliest stages of infection, innate responses predominate, but later the lymphocytes start to generate adaptive immune responses. They then 'remember' the pathogen, and mount more effective and rapid responses should the individual become reinfected with the same pathogen at a later date.

CELLS OF THE IMMUNE SYSTEM

Immune responses are mediated by a variety of cells, and by the soluble molecules which they secrete. Although the leucocytes are central to all immune responses, other cells in the tissues also participate, by signalling to the lymphocytes and responding to the cytokines released by

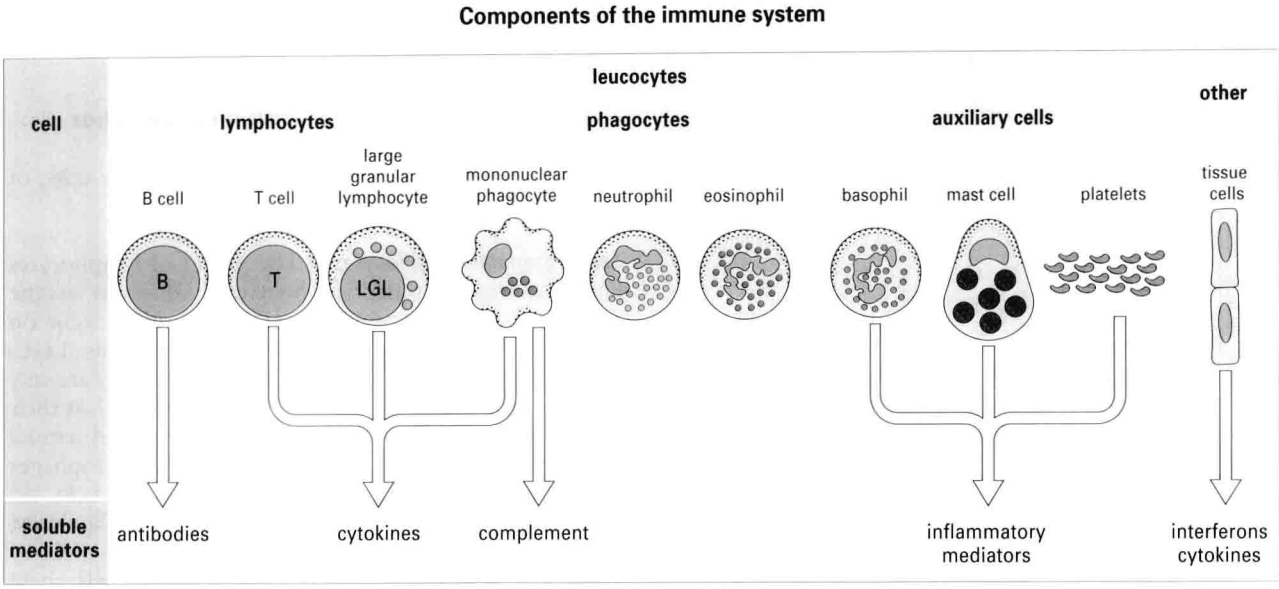

Fig. 1.4 The principal components of the immune system are shown, indicating which cells produce which soluble mediators. Complement is made primarily by the liver, although there is some synthesis by mononuclear phagocytes. Note that each cell produces and secretes only a particular set of cytokines or inflammatory mediators.

T lymphocytes and macrophages. *Figure 1.4* lists the main cells and molecules involved in immune reactions.

Phagocytes internalize antigens and pathogenic microorganisms and degrade them

Mononuclear phagocytes – The most important group of long-lived phagocytic cells belongs to the mononuclear phagocyte lineage. These cells are all derived from bone marrow stem cells, and their function is to engulf particles, including infectious agents, internalize them and destroy them. For this purpose they are strategically placed where they will encounter such particles. For example, the Kupffer cells of the liver line the sinusoids along which blood flows, while the synovial A cells line the synovial cavity (*Fig. 1.5*). Blood cells belonging to this lineage are called monocytes. In time, these migrate from the blood into the tissues, where they develop into tissue macrophages. These cells are very effective at presenting antigens to T lymphocytes (see Chapter 2).

Polymorphonuclear neutrophils – Polymorphonuclear neutrophils, often just called neutrophils or PMN, are another important group of phagocytes. Neutrophils constitute the majority of the blood leucocytes and develop from the same early precursors as monocytes and macrophages. Like monocytes, they migrate into tissues, particularly at sites of inflammation, but neutrophils are short-lived cells, which engulf material, destroy it and then die.

Lymphocytes occur as two major types, B cells and T cells, which are responsible for specific recognition of antigens

Lymphocytes are wholly responsible for the specific immune recognition of pathogens, so they initiate adaptive immune responses. All lymphocytes are derived from bone-marrow stem cells, but T lymphocytes then develop in the thymus, while B lymphocytes develop in the bone marrow (in adult mammals).

B cells – Each B cell is genetically programmed to encode a surface receptor specific for a particular antigen. Having recognized its specific antigen, the B cells multiply and differentiate into plasma cells, which produce large amounts of the receptor molecule in a soluble form that can be secreted. This is known as antibody. These antibody molecules are large glycoproteins found in the blood and tissue fluids: because they are virtually identical to the original receptor molecule, they bind to the antigen that initially activated the B cells.

T cells – There are several different types of T cells, and they have a variety of functions. One group interacts with mononuclear phagocytes and helps them destroy intracellular pathogens; they are called type-1 T-helper cells or TH1 cells. Another group interacts with B cells and helps them to divide, differentiate and make antibody: these are the TH2 cells. A third group of T cells is responsible for the destruction of host cells which have become infected by viruses or other intracellular pathogens – this kind of action is called cytotoxicity and these T cells are hence called T-cytotoxic (TC) cells. In every case, the T cells recognize antigens, but only when they are presented on the surface of the other cell by so-called major histocompatibity complex (MHC) molecules. They use a specific receptor to do this, termed the T-cell antigen receptor (TCR). This is related, both in function and structure, to the surface antibody which B cells use as their antigen receptors. T cells generate their effects, either by releasing soluble proteins, called cytokines,

Cells of the mononuclear phagocyte lineage

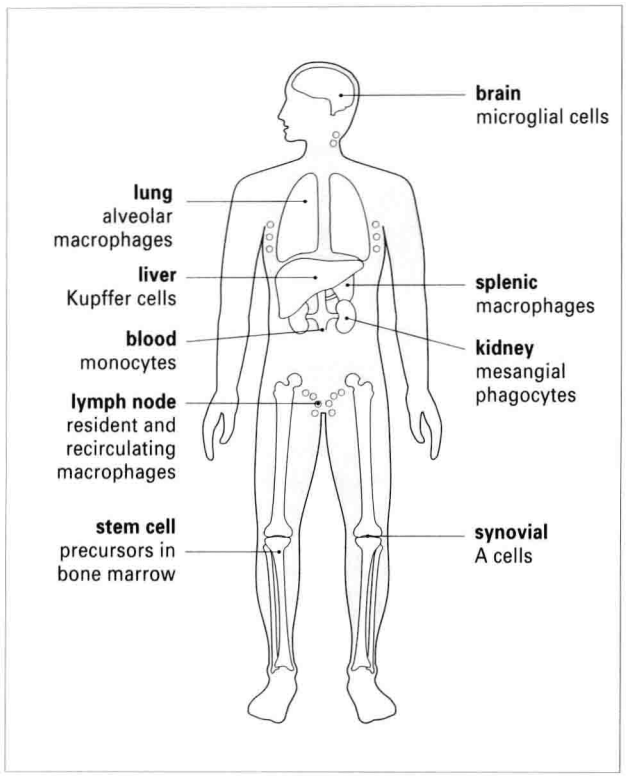

Fig. 1.5 Many organs contain phagocytic cells derived from blood monocytes which are manufactured in the bone marrow. Monocytes pass out of the blood vessel and become macrophages in the tissues. Resident phagocytic cells of different tissues were previously referred to as the reticuloendothelial system, but they too appear to belong to the monocyte lineage.

which signal to other cells, or by direct cell–cell interactions. The principal functions of lymphocytes are summarized in *Figure 1.6*.

Cytotoxic cells recognize and destroy other cells that have become infected

Several cell types have the capacity to kill other cells, of which the Tc cell is especially important.

Large granular lymphocytes – The group of lymphocytes known as large granular lymphocytes (LGLs) also has the capacity to recognize the surface changes that occur on a variety of tumour cells and virally infected cells. LGLs damage these target cells, but unlike Tc cells, they are very effective at recognizing cells which lack, or have lost their MHC molecules. This action is sometimes called natural killer (NK) cell activity. Additionally, both macrophages and LGLs recognize and destroy some target cells (or pathogens) which have become coated with specific antibody.

Eosinophil polymorphs – Also known as eosinophils, these are a specialized group of leucocytes which have the ability to engage and damage large extracellular parasites, such as schistosomes.

All of these cell types damage their different targets by releasing the contents of their intracellular granules close to them. Other molecules secreted by the cytotoxic cells, but not stored in granules, contribute to the damage.

Auxiliary cells control inflammation

A number of other cells mediate inflammation, the main purpose of which (see below) is to attract leucocytes and the soluble mediators of immunity towards a site of infection.

Basophils and mast cells – These have granules containing a variety of mediators that produce inflammation in surrounding tissues. These mediators are released when the cells are triggered. They can also synthesize and secrete a number of mediators which control the development of immune reactions. Mast cells lie close to blood vessels

Functions of lymphocytes

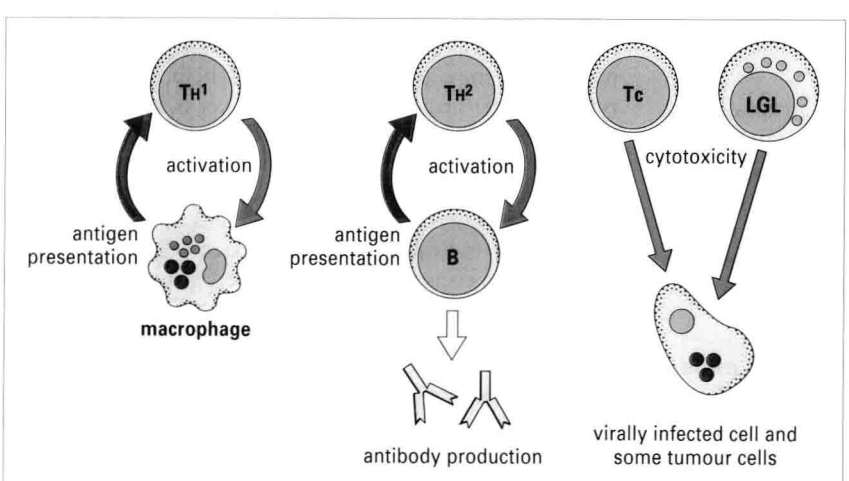

Fig. 1.6 Macrophages present antigen to type-1 T helper cells (TH1) which release cytokines that activate the macrophages to destroy microorganisms they have phagocytosed. B cells present antigen to TH2 cells, which release cytokines which activate them, causing them to divide and differentiate. Cytotoxic T cells (Tc) and large granular lymphocytes (LGL) recognize and destroy virally infected cells.

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 – These can also release inflammatory mediators when activated during thrombogenesis or by means of antigen–antibody complexes.

SOLUBLE MEDIATORS OF IMMUNITY

A wide variety of molecules are involved in the development of immune responses. These include antibodies and cytokines, produced by lymphocytes, and a variety of other molecules 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 is C-reactive protein (CRP), so called because of its ability to bind to the C-molecule of pneumococci. This promotes their uptake by phagocytes, a process known as opsonization (see *Fig. 1.10*). Molecules such as antibody, complement and C-reactive protein that promote phagocytosis are said to act as opsonins.

Complement proteins mediate phagocytosis, control inflammation and interact with antibodies in immune defence

The complement system is a group of about 20 serum proteins whose overall function is the control of inflammation. 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, non-specific reaction. This results in the microorganism being coated by complement molecules, leading to its uptake by phagocytes. The complement system can also be activated by antibodies bound to the pathogen surface (via the 'classical pathway'), when it co-mediates a specific, adaptive response.

Complement activation is a cascade reaction, with each component sequentially acting on others, in a similar way to the blood-clotting system. Activation by either the classical or the alternative pathway generates protein molecules or peptide fragments which have the following effects:

- Opsonization of microorganisms for uptake by phagocytes and eventual intracellular killing.
- Attraction of phagocytes 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 which have induced the activation. This in turn can produce lysis of the cell or virus and reduce the infection.
- Release of further inflammatory mediators from mast cells.

These functions are outlined in *Figure 1.7* and detailed in Chapter 3.

Cytokines signal between lymphocytes, phagocytes and other cells of the body

Cytokine is the general term for a large group of molecules involved in signalling between cells during immune responses. All cytokines are proteins, some with sugar molecules attached (glycoproteins). The different cytokines fall into a number of categories, and those produced by lymphocytes may be called lymphokines. The principal sets of cytokines are outlined below.

Complement functions

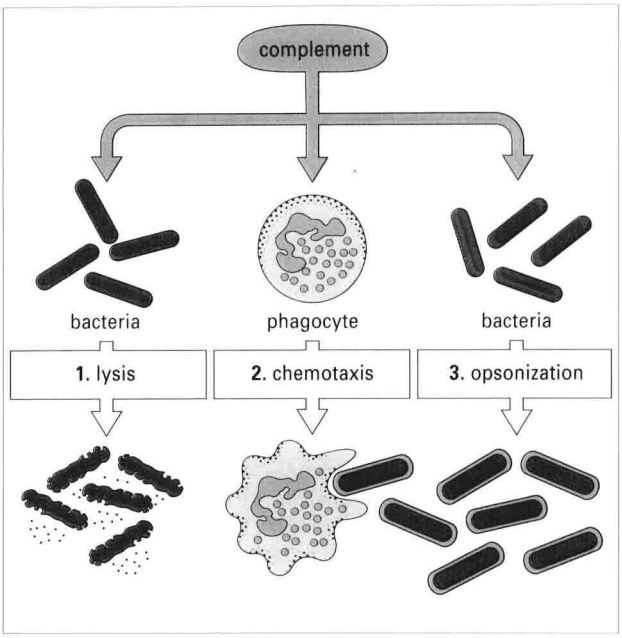

Fig. 1.7 (**1**) The complement system has an intrinsic ability to lyse the cell membranes of many bacterial species. (**2**) Complement products released in this reaction attract phagocytes to the site of the reaction – chemotaxis. (**3**) Complement components coat the bacterial surface – opsonization – allowing the phagocytes to recognize the bacteria and engulf them. These reactions may be triggered by the intrinsic ability of the complement system to recognize microbial components or by antibodies bound to the microorganism.

Interferons (IFNs) – These are particularly important in limiting the spread of certain viral infections. One group of interferons (IFNα and IFNβ) is produced by cells which have become virally infected; another type, IFNγ, is released by certain activated T cells. IFNs induce a state of antiviral resistance in uninfected tissue cells (*Fig. 1.8*). They are produced very early in infection and are the first line of resistance to a great many viruses.

Interleukins (ILs) – These are a large group of cytokines (IL-1 to IL-22) produced mainly by T cells, although some are also produced by mononuclear phagocytes, or by tissue cells. They have a variety of functions, but most of them are involved in directing other cells to divide and differentiate.

Colony-stimulating factors (CSFs) – These are primarily involved in directing the division and differentiation of bone-marrow stem cells, and the precursors of blood

Interferons (IFNs)

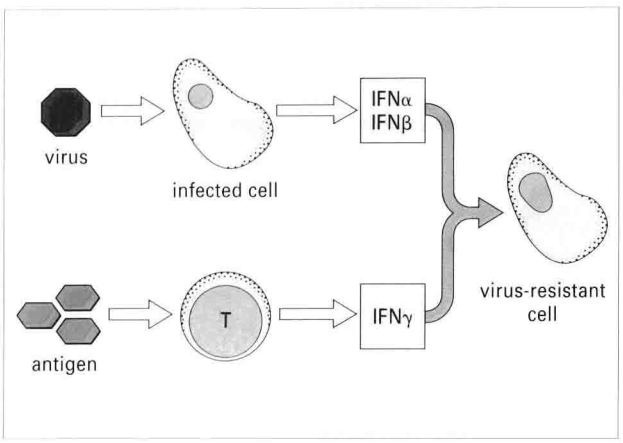

Fig. 1.8 When host cells become infected by virus, they may produce interferon. Different cell types produce interferon-α (IFNα) or interferon-β (IFNβ); interferon-γ (IFNγ) is produced by some types of lymphocyte (T) after activation by antigen. Interferons act on other host cells to induce a state of resistance to viral infection. IFNγ has many other effects as well.

leucocytes. The balance of different CSFs is partially responsible for the proportions of different cell types that will be produced. Some CSFs also promote further differentiation of cells outside the bone marrow. For example, macrophage-CSF (M-CSF) promotes the development of monocytes in bone marrow and macrophages in tissues.

Chemokines – This large group of chemotactic cytokines direct movement of cells around the body, from the blood stream into tissues and to the appropriate location within each tissue. Some of the chemokines also activate cells to carry out particular functions.

Other cytokines – Of these, the tumour necrosis factors, TNFα and TNFβ and transforming growth factor-β (TGFβ), have a variety of functions, but are particularly important in mediating inflammation and cytotoxic reactions.

Each set of cells releases a particular blend of cytokines, depending on the type of cell and whether it has been activated. For example, the TH1 cells release one set of cytokines which promote their interactions with mononuclear phagocytes, while the TH2 cells release a different set which allow them to activate B cells. Some cytokines may be produced by all T cells, and some just by a specific subset. Equally important is the expression of cytokine receptors. Only a cell which has the appropriate receptors can respond to a particular cytokine. For example the receptors for interferons, mentioned above, are present on all nucleated cells in the body, but other cytokines are much more restricted in their distribution. In general, cytokine receptors are specific for their own individual cytokine, but this is not always so. In particular many of the chemokine receptors respond to several different chemokines. This is discussed in more detail in Chapters 3 and 7.

Antibody specifically binds to antigen and then mediates secondary effects

Antibodies (Ab), also called immunoglobulins (Ig), are a group of serum molecules produced by B lymphocytes. In fact, as explained earlier, they are the soluble form of the B cells' surface antigen receptor. All antibodies have the same basic structure, but they differ in the region that binds to the antigen. In general, each antibody can bind specifically to just one antigen.

While one part of an antibody molecule (the Fab portion) binds to antigen, other parts interact with other elements of the immune system, such as phagocytes, or one of the complement molecules. In effect, antibodies act as flexible adaptors, allowing various elements of the immune system to recognize specific pathogens and their products (*Fig. 1.9*).

The part of the antibody molecule that interacts with cells of the immune system, is termed the Fc portion. Neutrophils, macrophages and other mononuclear phagocytes have Fc receptors on their surface. Consequently, if antibody binds to a pathogen, it can link to a phagocyte via the Fc portion. This allows the pathogen to be ingested and destroyed by the phagocyte (phagocytosed) – the antibody acts as an opsonin. Phagocytes can recognize

Antibody – a flexible adaptor

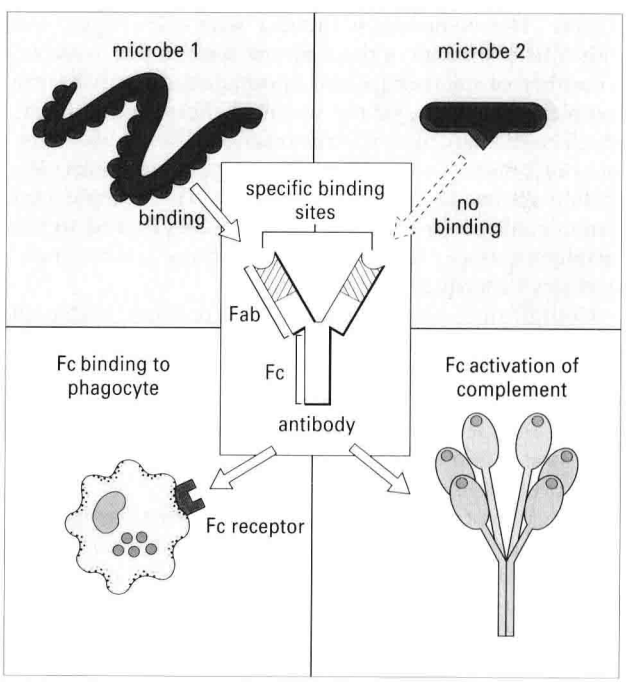

Fig. 1.9 When a microorganism lacks the inherent ability to activate complement or bind to phagocytes, the body provides antibodies as flexible adaptor molecules. The body can make several million different antibodies able to recognize a wide variety of infectious agents. Thus the antibody illustrated binds microbe 1, but not microbe 2, by its 'antigen-binding portion' (Fab). The Fc portion may activate complement or bind to Fc receptors on host cells, particularly phagocytes.