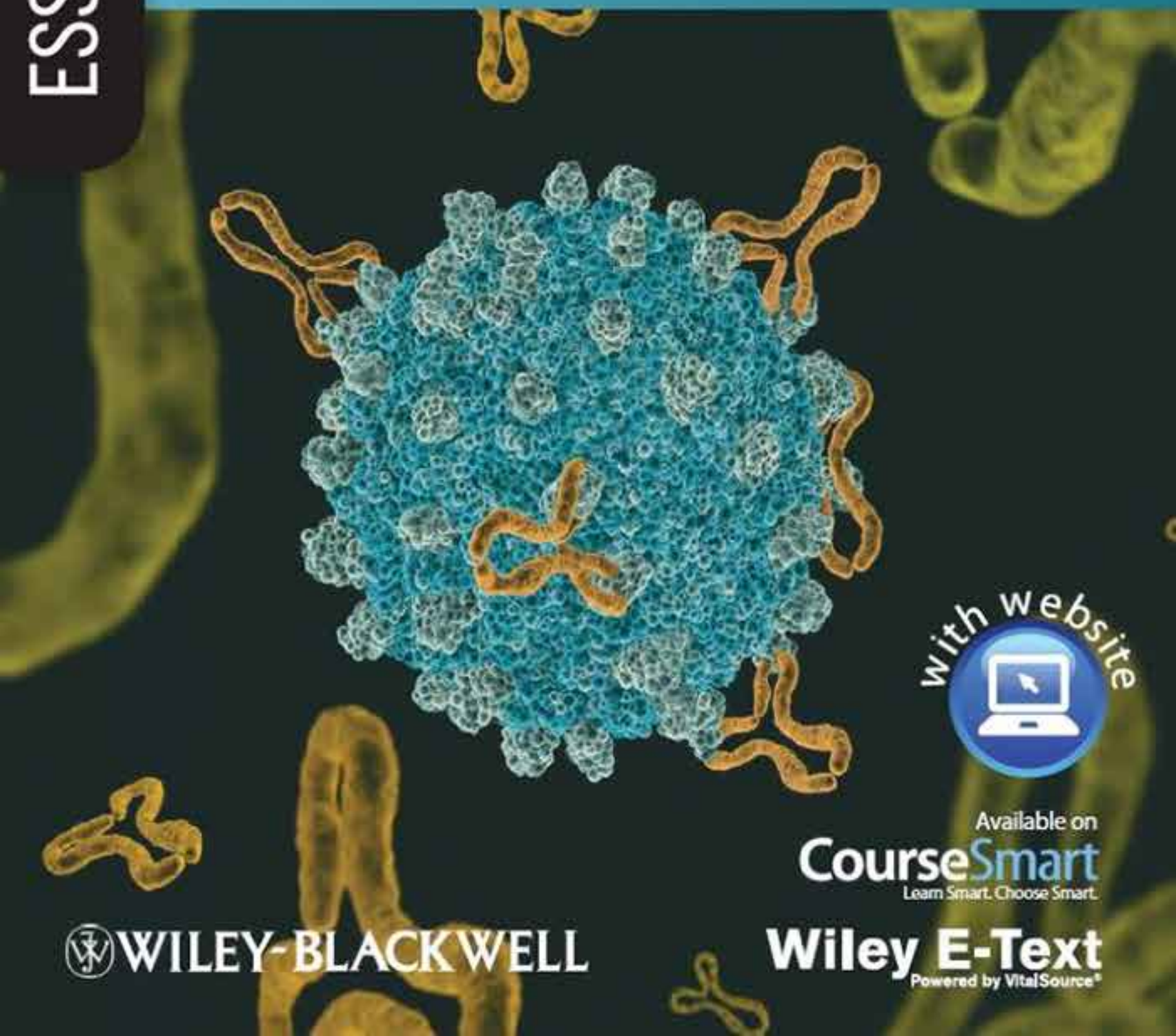
ESSENTIALS

ESSENTIALS OF CLINICAL IMMUNOLOGY

HELEN CHAPEL, MANSEL HAENEY
SIRAJ MISBAH AND NEIL SNOWDEN

6TH EDITION



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Essentials of Clinical Immunology

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Preface to the Sixth Edition

This is the last edition of the book in this format and the first as a digital edition; some progress since the first edition in 1984. During this time there have been fantastic advances in basic immunology and clinical applications, so that many of the earlier concepts are outmoded, redundant or just wrong. Keeping up to date is an increasingly time consuming and difficult task, not least to keep pruning exciting new findings in basic immunology that do not yet add much to our overall understanding of the important role of the immune system in health and disease.

Since the fifth edition in 2006, Mansel Haeney has finally retired completely and sadly could not be persuaded that his help would be invaluable (it would have been); I have missed the laughter generated over many years about 'pompous text' and 'over-researched detail'. In addition, Neil Snowden has moved to full-time rheumatology and clinical administration and was not able to take part and Siraj Misbah has become Clinical Lead in Immunology and is active on any number of national and international committees. So that left only one of the four, who is therefore responsible for all the mistakes in this edition.

Blackwell Scientific – now Wiley-Blackwell – were very persuasive and hence assistance was found in the form of Tom Hills, a Rhodes scholar from New Zealand, formerly an MSc student on the Integrated Immunology course in Oxford and currently a DPhil student. Tom has read and updated all the clinical chapters with me, as well as providing enthusiasm and encouragement to complete the task. I am indebted to him.

I am also grateful to Vojtech Thon, Associate Professor in Brno, who has not only translated this edition into the Czech language but checked the English version as he went along; a mammoth task that he has undertaken with great determination and precision. My grateful thanks to him too.

This edition includes a rewrite of Chapter 1 since there is so much new information about Basic Immunology compared with only 6 years ago. The chapter on Pregnancy has been revised to include associated immunological diseases only, since the basic immunology of pregnancy is an area of specialised interest rather than mainstream Clinical Immunology. For the same reason, I have resisted adding a whole chapter on Tumour Immunology (though this can be found in the French edition for those who are really keen!), settling instead to expand the chapter on Immune Manipulation. For students who may read older texts, I have left in comments on some of the now outdated tests or therapies and, where I can, have provided explanations as to why they have been superseded, so that students are not misled. The biggest change in the clinical sections relates to the genetic insights provided by the many genome-wide association studies (GWAS) now undertaken for most immunological diseases. These studies have provided both new understanding and many 'red herrings'. The rapid growth in primary immunodeficiencies and the discovery of the many new genes in various complex conditions have shown that many of the genes mutated in primary immunodeficiencies are multifunctional; furthermore, some are involved in several important/central pathways whilst others are redundant. It has been difficult to choose those that are important to students of Clinical Immunology and I have included only a small selection of examples.

As before, the bold type in the text indicates the content of each paragraph; really important points are identified by italics. Since several student reviews, while generous in their comments, requested more MCQs for each section, these are on the website, with answers as before: **www.immunologyclinic.com**.

My thanks for help with particular chapters go to Beth Psaila (also my daughter-in-law), who rewrote much of the lymphoproliferation chapter, Georg Hollander, who kept me straight on autoimmunity and tolerance as well as new basic concepts, Meilyn Hew for reading the practical chapter and Siraj Misbah for making sure that my rheumatology was up to date.

This edition would not have happened without Martin Davies at Wiley-Blackwell, who talked me into it, and Karen Moore, who edited the final revised version. I thank them for their persistence and help in achieving a final edition.

Finally, I thank my family once again – and, I promise, for the last time. They have been most long-suffering, allowing 'the seeming endless intrusion of Clinical Immunology into their lives' – as Mansel wrote for the first edition in 1984.

Helen Chapel

Preface to the First Edition

Immunology is now a well-developed basic science and much is known of the normal physiology of the immune system in both mice and men. The application of this knowledge to human pathology has lagged behind research, and immunologists are often accused of practising a science which has little relevance to clinical medicine. It is hoped that this book will point out to both medical students and practising clinicians that clinical immunology is a subject which is useful for the diagnosis and management of a great number and variety of human disease.

We have written this book from a clinical point of view. Diseases are discussed by organ involvement, and illustrative case histories are used to show the usefulness (or otherwise) of immunological investigations in the management of these patients. While practising clinicians may find the case histories irksome, we hope they will find the application of immunology illuminating and interesting. The student should gain some perspective of clinical immunology from the case histories, which are selected for their relevance to the topic we are discussing, as this is not a textbook of general medicine. We have pointed out those cases in which the disease presented in an unusual way.

Those who have forgotten, or who need some revision of, basic immunological ideas will find them condensed in Chapter 1. This chapter is not intended to supplant longer texts of basic immunology but merely to provide a springboard for chapters which follow. Professor Andrew McMichael kindly contributed to this chapter and ensured that it was up-to-date. It is important that people who use and request immunological tests should have some idea of their complexity, sensitivity, reliability and expense. Students who are unfamiliar with immunological methods will find that Chapter 17 describes the techniques involved.

Helen Chapel
Mansel Haeney
1984

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4.1 Introduction

'Allergy' is a much-misunderstood term that is used wrongly in general parlance. Unfortunately, the term is often used loosely to describe any intolerance of environmental factors irrespective of any objective evidence of immunological reactivity to an identified antigen. In this chapter, we distinguish those conditions in which immunological reactivity to key antigens is well defined from the rest, since such patients often present to an allergy clinic because of a popular public perception that they are 'allergic' in origin. In order to avoid any confusion the relationship of these terms is shown in Box 4.1.

Key topics

Case studies and other boxes give further insight into topics.

Case 6.1 Acute leukaemia (common type)

A 7-year-old boy presented with malaise and lethargy of 6 days duration. He had become inattentive at school, anorexic and had lost 3 kg in weight. On examination he was thin, anxious and clinically anaemic. There was mild, bilateral, cervical lymphadenopathy and moderate splenomegaly.

On investigation, he was pancytopenic with a low haemoglobin (80 g/l), platelet count (30×10^9/l) and white cell count (1.2×10^9/l). The blood film showed that most leucocytes were blasts; the red cells were normochromic and normocytic. Bone marrow examination showed an overgrowth of primitive white cells with diminished numbers of normal erythroid and myeloid precursors. Acute leukaemia was diagnosed.

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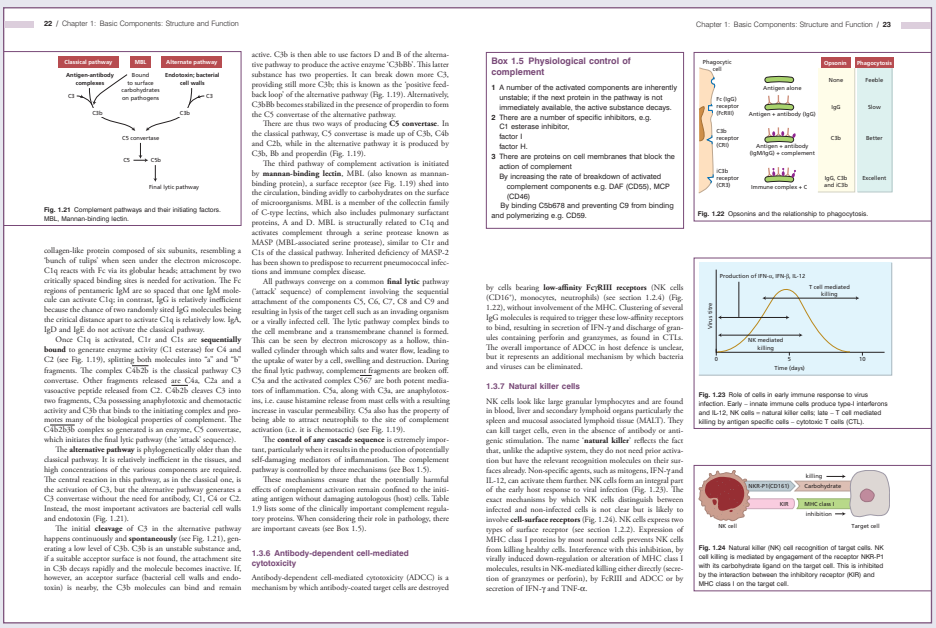

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Classical pathway | MBL | Alternate pathway

Antigen-antibody complexes | Bound to surface carbohydrates on pathogens | Endotoxin, bacterial cell walls

C3 | C3 | C3

C3b | C3b

C5 convertase

C5 → C5b

Final lytic pathway

Fig. 1.21 Complement pathways and their initiating factors. MBL, Mannan-binding lectin.

collagen-like protein composed of six subunits, resembling a 'bunch of tulips' when seen under the electron microscope. C1q reacts with Fc via its globular heads; attachment by two critically spaced binding sites is needed for activation. The Fc regions of pentameric IgM are so spaced that one IgM molecule can activate C1q; in contrast, IgG is relatively inefficient because the chance of two randomly sited IgG molecules being the critical distance apart to activate C1q is relatively low. IgA, IgD and IgE do not activate the classical pathway.

Once C1q is activated, C1r and C1s are **sequentially bound** to generate enzyme activity (C1 esterase) for C4 and C2 (see Fig. 1.19), splitting both molecules into "a" and "b" fragments. The complex $\overline{C4b2b}$ is the classical pathway C3 convertase. Other fragments released are C4a, C2a and a vasoactive peptide released from C2. $\overline{C4b2b}$ cleaves C3 into two fragments, C3a possessing anaphylotoxic and chemotactic activity and C3b that binds to the initiating complex and promotes many of the biological properties of complement. The $\overline{C4b2b3b}$ complex so generated is an enzyme, C5 convertase, which initiates the final lytic pathway (the 'attack' sequence).

The **alternative pathway** is phylogenetically older than the classical pathway. It is relatively inefficient in the tissues, and high concentrations of the various components are required. The central reaction in this pathway, as in the classical one, is the activation of C3, but the alternative pathway generates a C3 convertase without the need for antibody, C1, C4 or C2. Instead, the most important activators are bacterial cell walls and endotoxin (Fig. 1.21).

The initial **cleavage** of C3 in the alternative pathway happens continuously and **spontaneously** (see Fig. 1.21), generating a low level of C3b. C3b is an unstable substance and, if a suitable acceptor surface is not found, the attachment site in C3b decays rapidly and the molecule becomes inactive. If, however, an acceptor surface (bacterial cell walls and endotoxin) is nearby, the C3b molecules can bind and remain active. C3b is then able to use factors D and B of the alternative pathway to produce the active enzyme '$\overline{C3b}$Bb'. This latter substance has two properties. It can break down more C3, providing still more C3b; this is known as the 'positive feedback loop' of the alternative pathway (Fig. 1.19). Alternatively, $\overline{C3b}$Bb becomes stabilized in the presence of properdin to form the C5 convertase of the alternative pathway.

There are thus two ways of producing **C5 convertase**. In the classical pathway, C5 convertase is made up of C3b, C4b and C2b, while in the alternative pathway it is produced by C3b, Bb and properdin (Fig. 1.19).

The third pathway of complement activation is initiated by **mannan-binding lectin**, MBL (also known as mannan-binding protein), a surface receptor (see Fig. 1.19) shed into the circulation, binding avidly to carbohydrates on the surface of microorganisms. MBL is a member of the collectin family of C-type lectins, which also includes pulmonary surfactant proteins, A and D. MBL is structurally related to C1q and activates complement through a serine protease known as MASP (MBL-associated serine protease), similar to C1r and C1s of the classical pathway. Inherited deficiency of MASP-2 has been shown to predispose to recurrent pneumococcal infections and immune complex disease.

All pathways converge on a common **final lytic** pathway ('attack' sequence) of complement involving the sequential attachment of the components C5, C6, C7, C8 and C9 and resulting in lysis of the target cell such as an invading organism or a virally infected cell. The lytic pathway complex binds to the cell membrane and a transmembrane channel is formed. This can be seen by electron microscopy as a hollow, thin-walled cylinder through which salts and water flow, leading to the uptake of water by a cell, swelling and destruction. During the final lytic pathway, complement fragments are broken off. C5a and the activated complex C567 are both potent mediators of inflammation. C5a, along with C3a, are anaphylotoxins, i.e. cause histamine release from mast cells with a resulting increase in vascular permeability. C5a also has the property of being able to attract neutrophils to the site of complement activation (i.e. it is chemotactic) (see Fig. 1.19).

The **control of any cascade sequence** is extremely important, particularly when it results in the production of potentially self-damaging mediators of inflammation. The complement pathway is controlled by three mechanisms (see Box 1.5).

These mechanisms ensure that the potentially harmful effects of complement activation remain confined to the initiating antigen without damaging autologous (host) cells. Table 1.9 lists some of the clinically important complement regulatory proteins. When considering their role in pathology, there are important caveats (see Box 1.5).

1.3.6 Antibody-dependent cell-mediated cytotoxicity

Antibody-dependent cell-mediated cytotoxicity (ADCC) is a mechanism by which antibody-coated target cells are destroyed by cells bearing **low-affinity FcγRIII receptors** (NK cells (CD16$^+$), monocytes, neutrophils) (see section 1.2.4) (Fig. 1.22), without involvement of the MHC. Clustering of several IgG molecules is required to trigger these low-affinity receptors to bind, resulting in secretion of IFN-γ and discharge of granules containing perforin and granzymes, as found in CTLs. The overall importance of ADCC in host defence is unclear, but it represents an additional mechanism by which bacteria and viruses can be eliminated.

Box 1.5 Physiological control of complement

1 A number of the activated components are inherently unstable; if the next protein in the pathway is not immediately available, the active substance decays.
2 There are a number of specific inhibitors, e.g.
C1 esterase inhibitor,
factor I
factor H.
3 There are proteins on cell membranes that block the action of complement
By increasing the rate of breakdown of activated complement components e.g. DAF (CD55), MCP (CD46)
By binding C5b678 and preventing C9 from binding and polymerizing e.g. CD59.

Phagocytic cell | Opsonin | Phagocytosis

Fc (IgG) receptor (FcRIII) | Antigen alone | None | Feeble

Antigen + antibody (IgG) | IgG | Slow

C3b receptor (CR1) | Antigen + antibody (IgM)/IgG + complement | C3b | Better

iC3b receptor (CR3) | Immune complex + C | IgG, C3b and iC3b | Excellent

Fig. 1.22 Opsonins and the relationship to phagocytosis.

1.3.7 Natural killer cells

NK cells look like large granular lymphocytes and are found in blood, liver and secondary lymphoid organs particularly the spleen and mucosal associated lymphoid tissue (MALT). They can kill target cells, even in the absence of antibody or antigenic stimulation. The name '**natural killer**' reflects the fact that, unlike the adaptive system, they do not need prior activation but have the relevant recognition molecules on their surfaces already. Non-specific agents, such as mitogens, IFN-γ and IL-12, can activate them further. NK cells form an integral part of the early host response to viral infection (Fig. 1.23). The exact mechanisms by which NK cells distinguish between infected and non-infected cells is not clear but is likely to involve **cell-surface receptors** (Fig. 1.24). NK cells express two types of surface receptor (see section 1.2.2). Expression of MHC class I proteins by most normal cells prevents NK cells from killing healthy cells. Interference with this inhibition, by virally induced down-regulation or alteration of MHC class I molecules, results in NK-mediated killing either directly (secretion of granzymes or perforin), by FcRIII and ADCC or by secretion of IFN-γ and TNF-α.

Production of IFN-α, IFN-β, IL-12

Virus titre

T cell mediated killing

NK mediated killing

0 | 5 | 10

Time (days)

Fig. 1.23 Role of cells in early immune response to virus infection. Early – innate immune cells produce type-I interferons and IL-12. NK cells – natural killer cells; late – T cell mediated killing by antigen specific cells – cytotoxic T cells (CTL).

killing

NKR-P1(CD161) | Carbohydrate

KIR | MHC class I

inhibition

NK cell | Target cell

Fig. 1.24 Natural killer (NK) cell recognition of target cells. NK cell killing is mediated by engagement of the receptor NKR-P1 with its carbohydrate ligand on the target cell. This is inhibited by the interaction between the inhibitory receptor (KIR) and MHC class I on the target cell.

Table 1.5 Effector molecules in immunity

	Innate	Adaptive
Humoral	Complement components for opsonization or lysis	Specific antibodies for opsonization and phagocytosis or lysis with complement
Cellular	Perforin in NK cells creates pores in target cell membranes	Perforin in cytolytic (CD8) T cells creates pores in specific target cell membranes, allowing entry of granzymes to cause apoptosis
	Granzymes in NK cells induce apoptosis in target cells	NKT cells induce apoptosis by perforin production
	Lysosomes in phagocytic vacuoles result in death of ingested microbes	
	Preformed histamine and related vasoactive substances as well as leukotrienes in mast cells	

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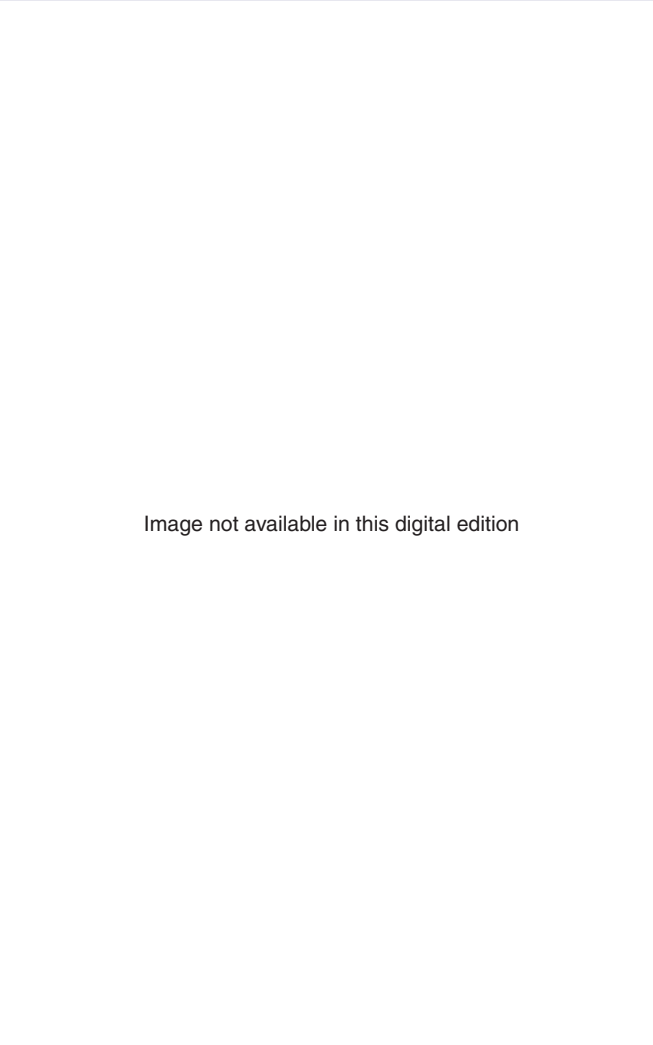

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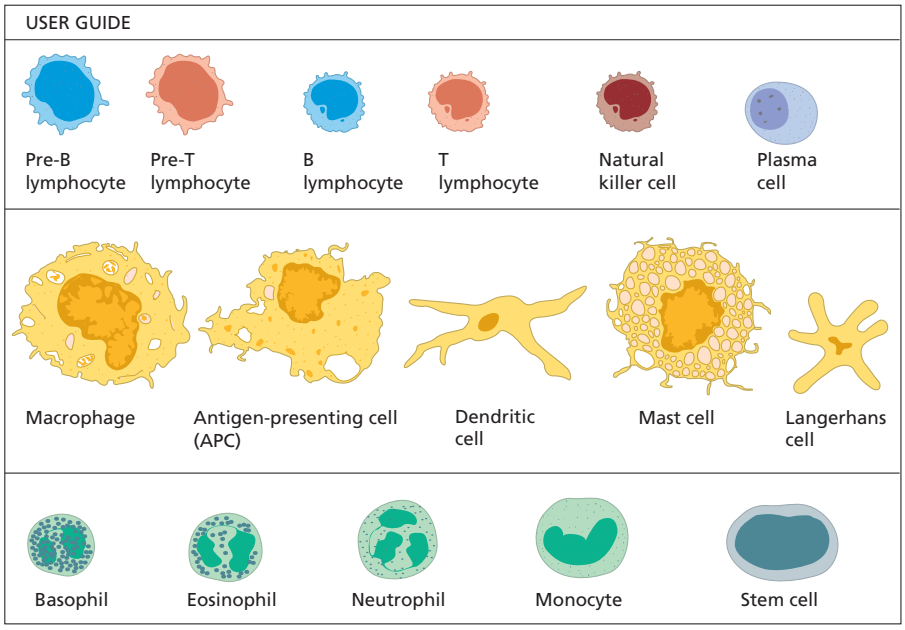
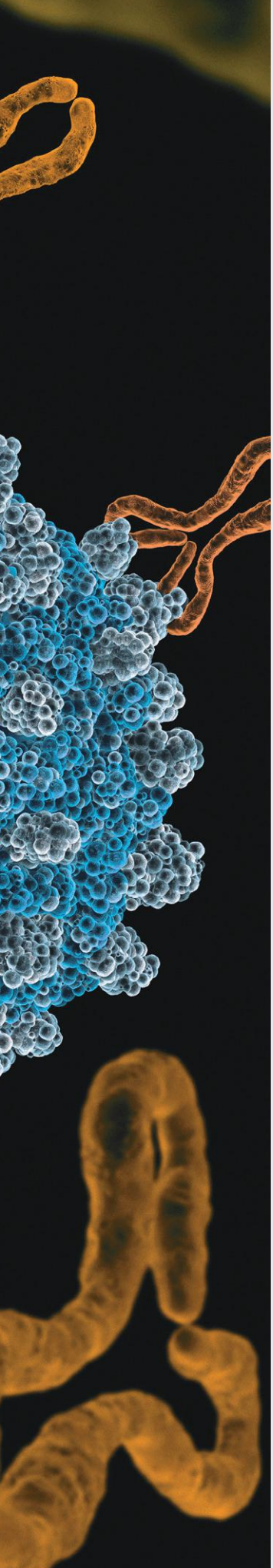
Key to Illustrations

Throughout the illustrations standard forms have been used for commonly-occurring cells and pathways. A key to these is given in the figure below.





CHAPTER 1

Basic Components: Structure and Function

Key topics

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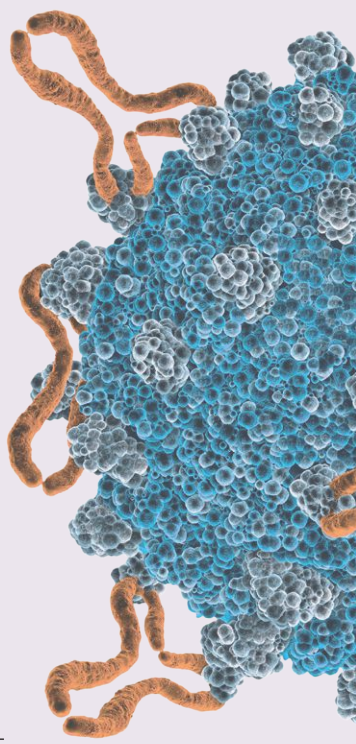


Essentials of Clinical Immunology, Sixth Edition. Helen Chapel, Mansel Haeney, Siraj Misbah, and Neil Snowden.

1.1 Introduction

The immune system evolved as a defence against infectious diseases. Individuals with markedly deficient immune responses, if untreated, succumb to infections in early life. There is, therefore, a selective **evolutionary pressure** for a really efficient immune system. Although innate systems are fast in response to pathogens, the evolution to adaptive responses provided greater efficiency. However a parallel evolution in pathogens means that all species, plants, insects, fish, birds and mammals, have continued to improve their defence mechanisms over millions of years, giving rise to some redundancies as well as resulting in apparent complexity. The aim of this chapter is to provide an initial description of the molecules involved, moving onto the role of each in the immune processes rather than the more traditional sequence of anatomical structure, cellular composition and then molecular components. It is hoped that this gives a sense of their relationship in terms of immediacy and dependency as well as the parallel evolution of the two immune systems. An immune response consists of **five parts**:

1. recognition of material recognized as foreign and dangerous;
2. an early innate (non-specific) response to this recognition;
3. a slower specific response to a particular antigen, known as adaptive responses;
4. non-specific augmentation of this response;
5. memory of specific immune responses, providing a quicker and larger response when that particular antigen is encountered the second time.

Innate immunity, though phylogenetically older and important in terms of speed of a response, is less efficient. Humoral components (soluble molecules in the plasma) and cells in blood and tissues are involved. Such responses are normally accompanied by inflammation and occur within a few hours of stimulation (Table 1.1).

Adaptive immune responses are also divided into humoral and cellular responses. Adaptive humoral responses result in the generation of antibodies reactive with a particular antigen. Antibodies are proteins with similar structures, known collectively as immunoglobulins (Ig). They can be transferred passively to another individual by injection of serum. In contrast, only cells can transfer cellular immunity. Good examples of cellular immune responses are the rejection of a graft by lymphoid cells as well as graft-versus-host disease, where viable transferred cells attack an immunologically compromised recipient that is unable to fight back.

Antibody-producing lymphocytes, which are dependent on the bone marrow, are known as B cells. In response to antigen stimulation, B cells will mature to antibody-secreting plasma cells. Cellular immune responses are dependent on an intact thymus, so the lymphocytes responsible are known as thymus-dependent (T) cells. The developmental pathways of both cell types are fairly well established (Fig. 1.1).

The **recognition phase is common to both adaptive and innate immunity.** It involves professional cells, known as classical dendritic cells, that recognize general pathogen features or specific antigenic molecules, process the antigens and present antigen fragments to the other cells of the immune systems as well as initiating non-specific inflammation to the pathogen. In the **effector phase**, neutrophils and macrophages (innate immunity) and antibodies and effector T lymphocytes (adaptive immunity) eliminate the antigen.

In terms of disease, like other organs, the immune system may fail (immunodeficiency), may be come malignant (lymphoid malignancies) or produce aberrant responses (such as in autoimmunity or allergy). This chapter describes the normal immune system in order to lay the basis for discussing these ways in which it can go wrong and so cause disease.

1.2 Key molecules

Many types of molecules play vital roles in both phases of immune responses; *some are shared by both the innate and the adaptive systems*. Antigens are substances that are recognized by immune components. Detection molecules on innate cells recognize general patterns of 'foreignness' on non-mammalian cells, whereas those on adaptive cells are specific for a wide range of very particular molecules or fragments of molecules. Antibodies are not only the surface receptors of B cells (BCRs) that recognize specific antigens, but, once the appropriate B cells are activated and differentiate into plasma cells, antibodies are also secreted into blood and body fluids in large quantities to prevent that antigen from causing damage. T cells have structurally similar receptors for recognizing antigens, known as T-cell receptors (TCRs). Major histocompatibility complex (MHC) molecules provide a means of self-recognition and also play a fundamental role in T lymphocyte effector functions.

Table 1.1 Components of innate and adaptive immunity

Features	Innate	Adaptive
Foreign molecules recognized	Structures shared by microbes, recognized as patterns (e.g. repeated glycoproteins) PAMPs	Wide range of very particular molecules or fragments of molecules on all types of extrinsic and modified self structures
Nature of recognition receptors	Germline encoded – limited PRRs	Somatic mutation results in wide range of specificities and affinities
Speed of response	Immediate	Time for cell movement and interaction between cell types
Memory	None	Efficient
Humoral components	Complement components	Antibodies
Cellular components	Dendritic cells, neutrophils, macrophages, NK cells, NKT cells, B1 cells, epithelial cells, mast cells	Lymphocytes – T (Th1, Th2, Th17, T regs) B
	iNKT cells, γδ T cells	

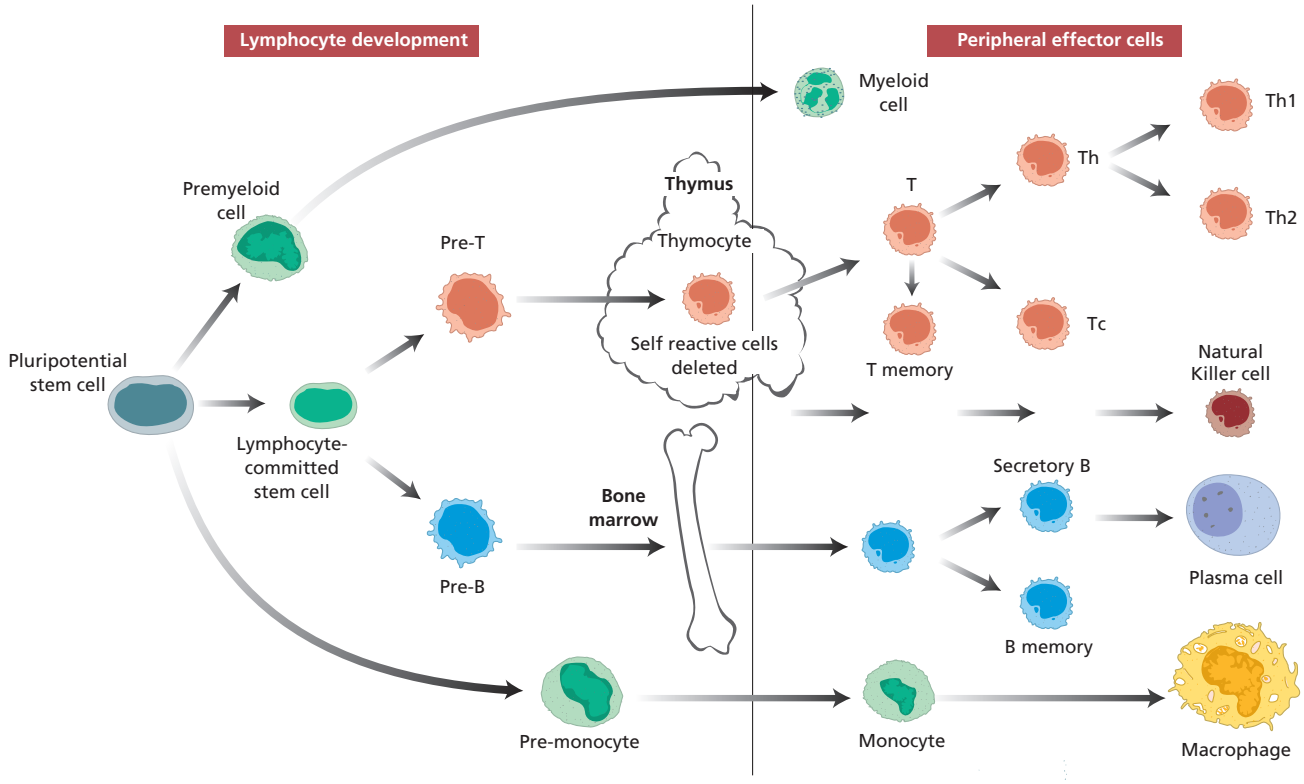


Fig. 1.1 Development of different types of blood from a pluripotential stem cell in the bone marrow. The developmental pathway for natural killer (NK) cells is shown separately because it is thought NK cells may develop in both the thymus and the bone marrow.

Effector mechanisms are often dependent on messages from initiating or regulating cells; soluble mediators, which carry messages between cells, are known as interleukins, cytokines and chemokines.

1.2.1 Molecules recognized by immune systems

Foreign substances are recognized by both the innate and adaptive systems, but in different ways, using different receptors (see section 1.2.2). The innate system is activated by 'danger signals', due to pattern recognition receptors (PRRs) on dendritic cells recognizing conserved microbial structures directly, often repeated polysaccharide molecules, known as **pathogen-associated molecular patterns (PAMPs)**. Toll-like receptors (receptors which serve a similar function to toll receptors in drosophila) make up a large family of **non-antigen-specific** receptors for a variety of individual bacterial, viral and fungal components such as DNA, lipoproteins and lipopolysaccharides. Activation of dendritic cells by binding to either of these detection receptors leads to inflammation and *subsequently activation of the adaptive system*.

Phagocytic cells also recognize particular patterns associated with potentially damaging materials, such as lipoproteins and other charged molecules or peptides.

Traditionally, **antigens** have been defined as molecules that interact with components of the adaptive system, i.e. T- and B-cell recognition receptors and antibody. *An antigenic molecule may have several antigenic determinants (epitopes)*; each **epitope** can bind with an individual antibody, and a single antigenic molecule can therefore provoke many antibody molecules with different binding sites. Some low-molecular-weight molecules, called **haptens**, are unable to provoke an immune response themselves, although they can react with existing antibodies. Such substances need to be coupled to a carrier molecule in order to have sufficient epitopes to be antigenic. For some chemicals, such as drugs, the carrier may be a host (auto) protein. The tertiary structure, as well as the amino acid sequence, is important in determining antigenicity. Pure lipids and nucleic acids are poor antigens, although they do activate the innate system and can be inflammatory.

Antigens are conventionally divided into thymus-dependent and thymus-independent antigens. **Thymus-dependent antigens** require T-cell participation to provoke the production of antibodies; most proteins are examples. **Thymus-independent antigens** require no T-cell cooperation for antibody production; they directly stimulate specific B lymphocytes by virtue of their ability to cross-link antigen receptors on the B-cell surface, produce predominantly IgM and IgG_2 antibodies and provoke poor immunological memory. Such antigens include bacterial polysaccharides, found in bacterial cell walls. Endotoxin, another thymus-independent antigen, not only causes specific B-cell activation and antibody production but also acts as a stimulant for all B cells regardless of specificity.

Factors other than the intrinsic properties of the antigen can also influence the quality of the immune response (Table 1.2). Substances that improve an immune response to a separate, often rather weak, antigen are known as **adjuvants**. The use of adjuvants in humans, important in vaccines against infective agents and tumours, is discussed in section 7.3.2.

Table 1.2 Factors influencing the immune response to an antigen, i.e. its immunogenicity

1	Nature of molecule: Protein content Size Solubility
2	Dose: Low doses provoke small amounts of antibody with high affinity and restricted specificity Moderate doses provoke large amounts of antibody but mixed affinity and broad specificity High doses provoke tolerance
3	Route of entry: ID, IM, SC→regional lymph nodes IV→spleen Oral→Peyer's patches Inhalation→bronchial lymphoid tissue
4	Addition of substances with synergistic effects, e.g. adjuvants,
5	Genetic factors of recipient animal: Species differences Individual differences

ID, Intradermal injection; IM, intramuscular injection; IV, intravenous injection; SC, subcutaneous injection.

Superantigen is the name given to those foreign proteins which are not specifically recognized by the adaptive system but do activate large numbers of T cells regardless of specificity, via direct action with an invariant part of the TCR (see section 2.4.2).

Self-antigens are not recognized by dendritic cells, so inflammation and co-stimulation of T cells (see section 1.4.1) is not induced. There are mechanisms to control any aberrant adaptive responses to self-antigens, by prevention of production of specific receptors and regulation of the response if the immune system is fooled into responding (see Chapter 5, Autoimmunity).

1.2.2 Recognition molecules

There are several sets of detection molecules on dendritic cells (Table 1.3): pattern recognition receptors (PRRs), such as Toll-like receptors, as well as chemotactic receptors and phagocytic receptors. **PRRs** may be soluble or attached to cell membranes. Mannan binding lectin is a protein that binds sugars on microbial surfaces; if attached to a macrophage, it acts as a trigger for phagocytosis and, if soluble, it activates the complement cascade resulting in opsonization. Others belonging to this family are less well defined.

Table 1.3 Markers on dendritic cells

	Immature dendritic cells	Mature myeloid dendritic cells
Function	Antigen capture	Antigen presentation to immature T cells for specific differentiation
Co-stimulatory molecule expression, e.g. CD80, CD86	Absent or low	++
Adhesion molecules, e.g. ICAM-1	Absent or low	++
Cytokine receptors, e.g. IL-12R	Absent or low	++
Pattern recognition receptors (PRRs), e.g. mannose receptor	++	–
MHC class II:		
turnover	Very rapid	Persist >100 h
density	Reduced (approx. 1×10^6)	Very high (approx. 7×10^6)

ICAM-1, Intercellular adhesion molecule-1.

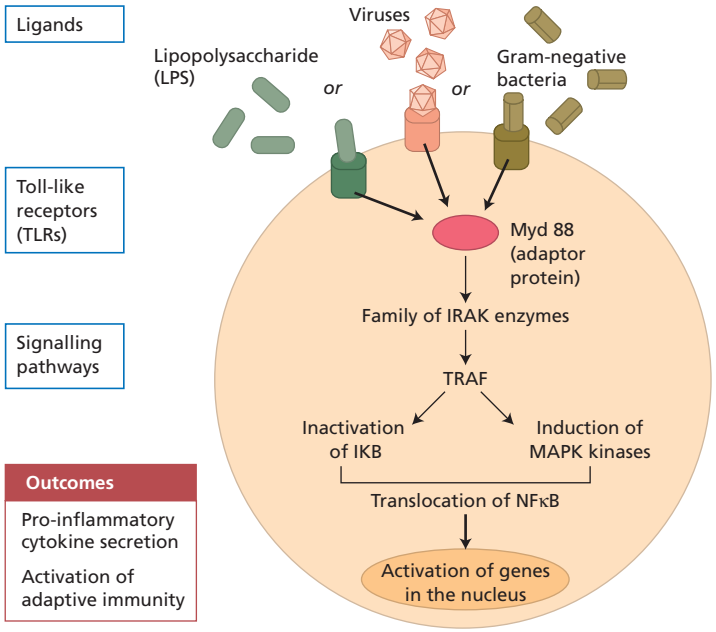


Fig. 1.2 Sequential cellular events induced by engagement of Toll-like receptors on dendritic cells neutrophils and macrophages by microbial ligands (TRAF, TNF receptor-associated factor; IKB, inhibitor kappa B; MAPK, mitogen-activated protein kinase; IRAK, interleukin-1 receptor-associated kinase).

Toll-like receptors (TLRs) are part of this family too. These are evolutionarily conserved proteins found on macrophages, dendritic cells and neutrophils. At least ten different TLRs are found in humans, each TLR recognizing a range of particular motifs on pathogens, such as double-stranded RNA of viruses (TLR3), lipopolysaccharides of Gram-negative bacterial cell walls (TLR4), flagellin (TLR5) and bacterial DNA (TLR9), all highly conserved motifs unique to microorganisms. Upon binding to their ligands, TLRs induce signal transduction, via a complex cascade of intracellular adaptor molecules and kinases, culminating in the induction of nuclear factor kappa B transcription factor (NFκB)-dependent gene expression and the induction of pro-inflammatory cytokines (Fig. 1.2). The clinical consequences of a defective TLR pathway are discussed in section 3.4.1 (see Box 1.1 in this chapter also).

CD1 molecules are invariant proteins (MHC-like and associated with β_2-microglobulin – see later), which are present on dendritic and epithelial cells. CD1 combine with lipids, which are poor antigens and not usually well presented to the adaptive immune system, and so act as recognition molecules for the intestine and other microbial rich surfaces. CD1 present lipids to the immune cells of the gut in particular, namely non-MHC-restricted natural killer (NKT) cells and γδ T cells in the epithelium.

Box 1.1 Clinical consequences of a defective Toll-like receptor pathway

In humans, deficiency of IRAK-4 (interleukin-1 receptor-associated kinase) or MyDD88, key intracellular molecules responsible for TLR signal transduction (Fig. 1.2) is associated with recurrent pyogenic bacterial infections accompanied by failure to mount an appropriate acute-phase response (Case 3.6).

Mice lacking TLR4 are exceptionally susceptible to infection with Gram-negative bacteria

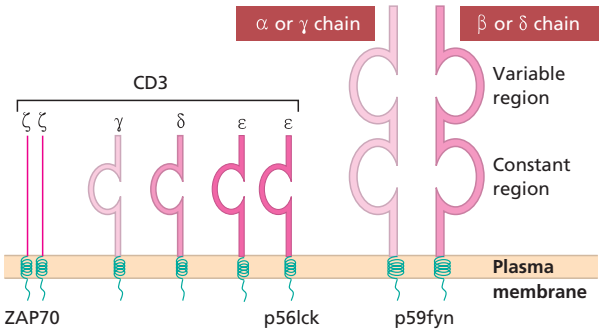


Fig. 1.3 Diagram of the structure of the T-cell receptor (TCR). The variable regions of the alpha (α) and beta (β) chains make up the T idiotype, i.e. antigen/peptide binding region. The TCR is closely associated on the cell surface with the CD3 protein that is essential for activation.

Antigenic epitopes, having been processed by dendritic cells, are recognized by cells of the adaptive system by means of specific receptors. *Each T cell, like B cells, is pre-committed to a given epitope*. It recognizes this by one of two types of **TCRs**, depending on the cell's lineage and thus its effector function. T cells have either αβTCR [a heterodimer of alpha (α) and beta β) chains] or γδTCR [a heterodimer of gamma γ and delta (δ) chains]. αβTCR cells predominate in adults, although 10% of T cells in epithelial structures are of the γδTCR type. In either case, TCRs are associated with several transmembrane proteins that make up the cluster differentiation 3 (CD3) molecule (Fig. 1.3), to make the CD3–TCR complex responsible for taking the antigen recognition signal inside the cell (signal transduction). Signal transduction requires a group of intracellular tyrosine kinases (designated p56 lck, p59 fyn, ZAP 70) to join with the cytosolic tails of the CD3–TCR complex and become phosphorylated. Nearby accessory molecules, CD2, LFA-1, CD4 and CD8, are responsible for increased adhesion (see section 1.2.6) but are not actually involved in recognizing presented antigenic fragments.

The genes for TCR chains are on different chromosomes: β and γ on chromosome 7 and α and δ on chromosome 14. Each of the four chains is made up of a variable and a constant domain. The variable regions are numerous (although less so than immunoglobulin variable genes; they are joined by D and J region genes to the invariant (constant) gene by recombinases, *RAG1 and RAG2, the same enzymes used for making antigen receptors on B cells (BCRs) and antibodies* (section 1.4.1). The **diversity of T-cell antigen receptors** is achieved in a similar way for immunoglobulin, although *TCRs are less diverse since somatic mutation is not involved*; perhaps the risk of 'self recognition' would be too great. The diversity of antigen binding is dependent on the large number of V genes and the way in which these may be combined with different D and J genes to provide different V domain genes. The similarities between TCRs and BCRs led to the suggestion that the genes evolved from the same parent gene and both are *members of a 'supergene' family*. Unlike immunoglobulin, TCRs are not secreted and are not independent effector molecules.

A particular TCR complex recognizes a processed antigenic peptide in the context of MHC class I or II antigens (section 1.4.1) depending on the type of T cell; helper T cells recognize class II with antigen, and this process is enhance by the surface accessory protein CD4 (see later) and intracellular signals. Cytotoxic T cells (CTL/Tc) recognize antigens with class I (see section 1.3.1) and use CD8 accessory molecules for increased binding and signalling. Since the number of variable genes available to TCRs is more limited, reactions with antigen might not be sufficient if it were not for the increased binding resulting from these **accessory mechanisms**. Recognition of processed antigen alone is not enough to activate T cells. Additional signals, through soluble cytokines (interleukins), are needed; some of these are generated during 'antigen processing' (see Antigen processing, section 1.4.1).

Major histocompatibility complex molecules (MHC) were originally known as 'histocompatibility antigens' because of the vigorous reactions they provoked during mismatched organ transplantation. However, these molecules are known to play a fundamental role in immunity by presenting antigenic peptides to T cells. Histocompatibility antigens in humans [known as human leucocyte antigens (HLA)] are synonymous with the MHC molecules. MHC molecules are cell-surface glycoproteins of two basic types: class I and class II (Fig. 1.5). They exhibit extensive genetic polymorphism with multiple alleles at each locus. As a result, genetic variability between individuals is very great and most unrelated individuals possess different MHC (HLA) molecules. This means that it is very difficult to obtain perfect HLA matches between unrelated persons for transplantation (see Chapter 8). The **extensive polymorphism in MHC molecules** is best explained by the need of the immune system to cope with an ever-increasing range of pathogens adept at evading immune responses (see Chapter 2).

The TCR of an individual T cell will only recognize antigen as a complex of antigenic peptide and self-MHC (Fig. 1.4).

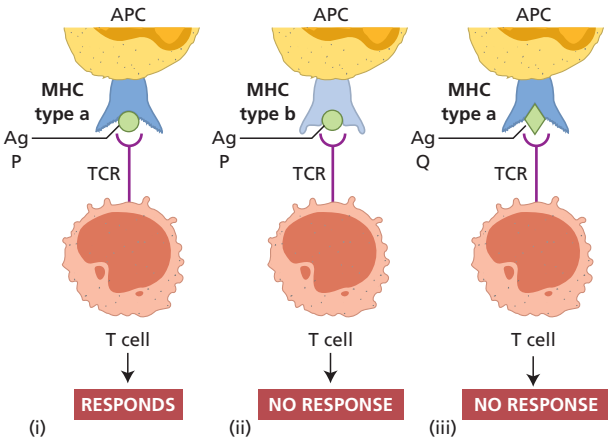


Fig. 1.4 MHC restriction of antigen recognition by T cells. T cells specific for a particular peptide and a particular MHC allele will not respond if the same peptide were to be presented by a different MHC molecule as in (ii) or as in (iii) if the T cell were to encounter a different peptide. APC, Antigen-presenting cell; TCR, T-cell receptor.

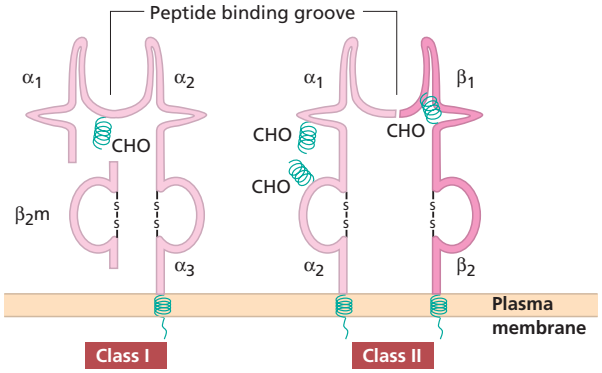


Fig. 1.5 Diagrammatic representation of MHC class I and class II antigens. β_2m, β_2-microglobulin; CHO, carbohydrate side chain.

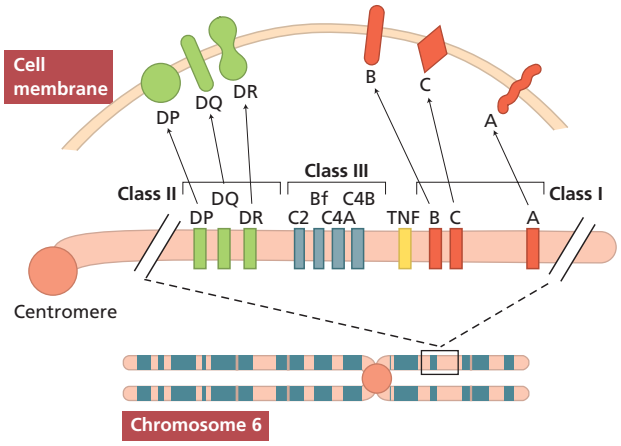


Fig. 1.6 Major histocompatibility complex on chromosome 6; class III antigens are complement components. TNF, Tumour necrosis factor.

This process of **dual recognition of peptide and MHC molecule** is known as MHC restriction, since the MHC molecule restricts the ability of the T cell to recognize antigen (Fig. 1.4). The importance of MHC restriction in the immune response was recognized by the award of the Nobel Prize in Medicine to Peter Doherty and Rolf Zinkernagel, who found that virus-specific CTLs would only kill cells of the same particular allelic form of MHC molecule.

MHC class I antigens are subdivided into three groups: A, B and C. Each group is controlled by a different gene locus within the MHC region on chromosome 6 (Fig. 1.6) in humans (different in mice). The products of the genes at all three loci are chemically similar. All MHC class I antigens (see Fig. 1.5) are made up of an α heavy chain, controlled by a gene in the relevant MHC locus, associated with a smaller chain called β_2-microglobulin, controlled by a gene on chromosome 12. The differences between individual MHC class I antigens are due to variations in the α chains; the β_2-microglobulin component is constant. The detailed structure of class I antigens was determined by X-ray crystallography. This shows that small antigenic peptides (approx. nine amino acids long) can be tightly bound to a groove produced by the pairing of the two extracellular domains (α_1 and α_2) of the α chain. The *affinity (tightness of binding) of individual peptide binding depends on the nature and shape of the groove*, and accounts for the MHC restriction mentioned earlier.

MHC class II antigens have two heavy chains, α and β, both coded for by genes in the MHC region of chromosome 6. The detailed structure of MHC class II antigens was also determined by X-ray crystallography. It has a folded structure similar to class I antigens with the peptide-binding groove found between the α and β chains (see Fig. 1.5). Whereas most nucleated cells express class I molecules, *expression of class II molecules is restricted to a few cell types*: dendritic cells, B lymphocytes, *activated* T cells, macrophages, *inflamed* vascular endothelium and some epithelial cells. However, other cells (e.g. thyroid, pancreas, gut epithelium) can be induced to express class II molecules under the influence of interferon (IFN)-γ released during inflammation. In humans, there are three groups of variable class II antigens: the loci are known as HLA-DP, HLA-DQ and HLA-DR.

In practical terms, there are different mechanisms by which antigens in different intracellular compartments can be captured and presented to $CD4^+$ or $CD8^+$ T cells (Fig. 1.7). **Endogenous antigens** (including viral antigens that have infected host cells) are processed by the endoplasmic reticulum and presented by MHC class I-bearing cells exclusively to

$CD8^+$ T cells. Prior to presentation on the cell surface, endogenous antigens are broken down into short peptides, which are then actively transported from the cytoplasm to endoplasmic reticulum by proteins. These proteins act as a shuttle and are so named 'transporters associated with antigen processing' (TAP-1 and TAP-2). TAP proteins (also coded in the MHC class II region) deliver peptides to MHC class I molecules in the endoplasmic reticulum, from whence the complex of MHC and peptide is delivered to the cell surface. Mutations that affect function in either TAP gene prevent surface expression of MHC class I molecules.

In contrast, **exogenous antigens** are processed by the lysosomal route and presented by MHC class II antigens to $CD4^+$ T cells (Fig. 1.7). As with MHC class I molecules, newly synthesized MHC class II molecules are held in the endoplasmic reticulum until they are ready to be transported to the cell surface. Whilst in the endoplasmic reticulum, class II molecules are prevented from binding to peptides in the lumen by a protein known as MHC class II-associated invariant chain.

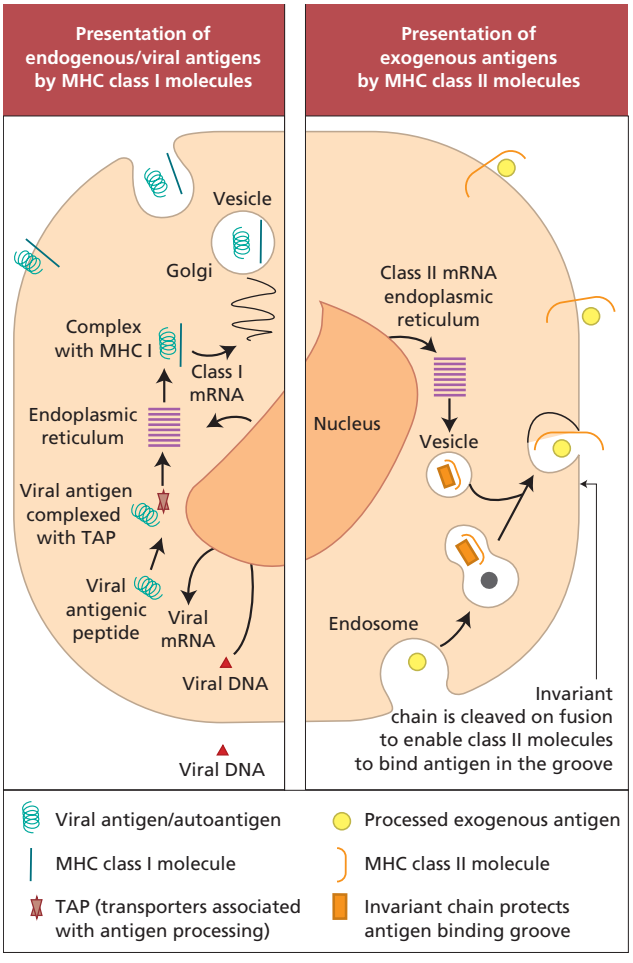


Fig. 1.7 Different routes of antigen presentation, depending on nature of antigen.

The invariant chain also directs delivery of class II molecules to the endosomal compartment where exogenous antigens are processed and made available for binding to class II molecules.

The **MHC class III region** (see Fig. 1.6) contains genes encoding proteins that are involved in the complement system (see section 1.4.1): the early components C4 and C2 of the classical pathway and factor B of the alternative pathway. Some inflammatory proteins, e.g. tumour necrosis factor (TNF), are also encoded in adjacent areas. Invariant MHC-like proteins, such as CD1 lipid-recognition receptors (see earlier), are not coded for on chromosome 6, despite being associated with β_2-microglobulin.

In contrast to TCRs, the antigen receptors on B cells **(BCRs) are surface-bound immunoglobulin** molecules that can be secreted as soluble molecules. As with TCRs, they have predetermined specificity for epitopes and are therefore extremely diverse. *The immune system has to be capable of recognizing all pathogens, past and future*. Such diversity is provided by the way in which all three types of molecules, TCR, BCR and antibody, are produced.

The **basic structure of the immunoglobulin** molecule is shown in Fig. 1.8. It has a four-chain structure: two identical heavy (H) chains (mol. wt. 50 kDa) and two identical light (L) chains (mol. wt. 25 kDa). Each chain is made up of domains of about 110 amino acids held together in a loop by a disulphide bond between two cysteine residues in the chain. The domains have the same basic structure and many areas of similarity in their amino acid sequences. The heavy chains determine the isotype of the immunoglobulin, resulting in

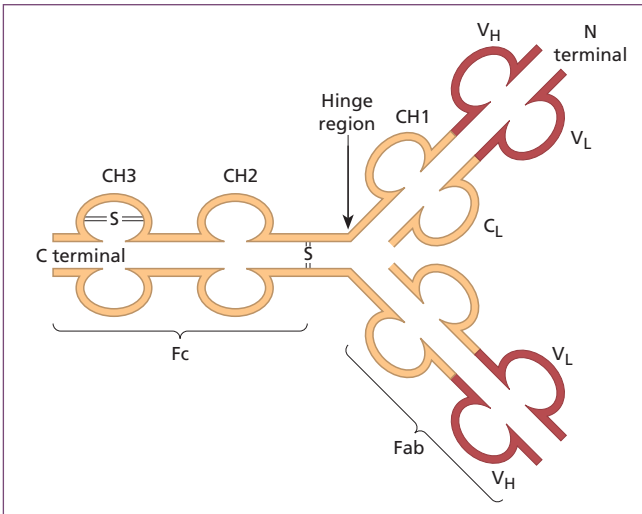


Fig. 1.8 Basic structure of an immunoglobulin molecule. Domains are held in shape by disulphide bonds, though only one is shown. C_{1-3}, constant domain of a heavy chain; C_L, constant domain of a light chain; V_H, variable domain of a heavy chain; V_L, variable domain of a light chain. =S=, disulphide bond.

pentameric IgM (Fig. 1.9), dimeric IgA (Fig. 1.10) or monomeric IgG.

The amino (N) terminal domains of the heavy and light chains include the **antigen-binding site**. The amino acid sequences of these N-terminal domains vary between different antibody molecules and are known as variable (V) regions. Most of these differences reside in three hypervariable areas of the molecule, each only 6–10 amino acid residues long. In the folded molecule, these hypervariable regions in each heavy and light chain come together to form, with their counterparts on the other pair of heavy and light chains, the antigen-binding site (Fig. 1.8). The structure of this part of the antibody molecule is unique to that molecule and is known as the **idiotypic determinant**. In any individual, approximately 10^6–10^7 different antibody molecules could be made up by 10^3 different heavy chain variable regions associating with 10^3 different light chain variable regions, though there are even more epitopes due to further variation during the later processing (see section 1.4.1).

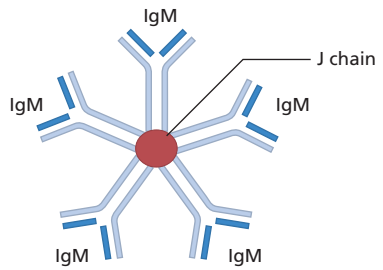


Fig. 1.9 Schematic representation of IgM pentamer (MW 800 kDA).

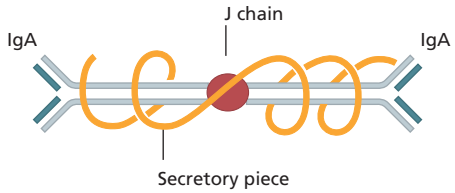


Fig. 1.10 Schematic representation of dimeric secretory IgA (MW 385 kDA).

The part of the immunoglobulin chain next to the V region in either heavy or light chains is the constant (C) region; this is made up of one domain in a **light chain** (C_L) and three or four in a **heavy chain** (C_H) (Fig. 1.8). There are two alternative types of C_L chain, known as kappa (κ) and lambda (λ); an antibody molecule has either two κ or two λ light chains, *never one of each*. Of all the antibodies in a human individual, roughly 60% contain κ and 40% contain λ light chains. There are no known differences in the functional properties between κ and λ light chains. In contrast, there are several possible different types of C_H domain, each with important functional differences (Table 1.4). The heavy chains determine the **isotype** of the antibody and the ultimate physiological function of the particular antibody molecule. Once the antigen-binding site has reacted with its antigen, the molecule undergoes a change in the conformation of its heavy chains in order to take part in effector reactions, depending on the isotype of the molecule.

Table 1.4 Immunoglobulin classes and their functions

Isotype	Heavy chain	Serum concentration*	Main function	Complement fixation†	Placental passage	Reaction with Fc receptors‡
IgM	μ	0.5–2.0	Neutralization and opsonization	+++	–	L
IgG_1	γ_1	5.0–12.0	Opsonization	+++	++	M, N, P, L, E
IgG_2	γ_2	2.0–6.0		+	±	P, L
IgG_3	γ_3	0.5–1.0	Opsonization	+++	++	M, N, P, L, E
IgG_4	γ_4	0.1–1.0		–	+	N, L, P
IgA_1	α_1	0.5–3.0	Neutralization at mucosal surfaces	–	–	M, N
IgA_2	α_2	0.0–0.2		–	–	–
IgD	δ	Trace	Lymphocyte membrane receptor	–	–	–
IgE	εΣ	Trace	Mast cell attachment	–	–	B, E, L

*Normal adult range in g/l.
†Classical pathway.
‡Fc receptors on: basophils/mast cells, B; on eosinophils, E; on lymphocytes, L; on macrophages, M; on neutrophils, N; on platelets, P.

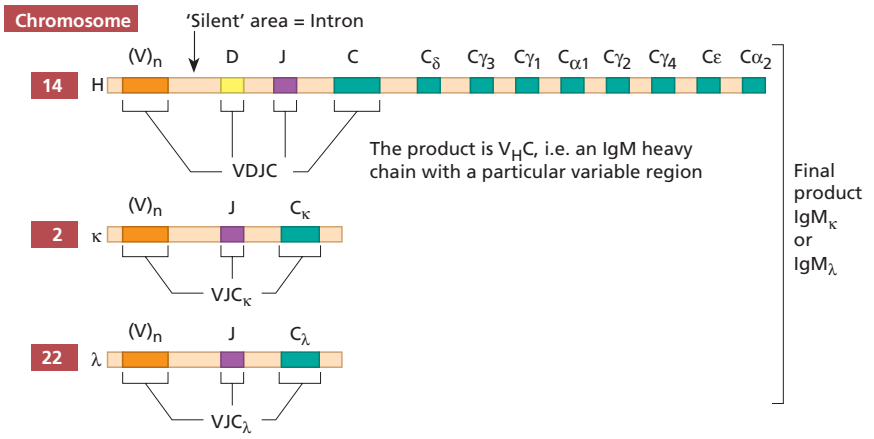


Fig. 1.11 Immunoglobulin genes (see text for explanation).

The processes by which the components of this supergene family are produced are identical for TCR and BCR and known as **recombination.** Immunoglobulin production, whether for BCR or antibody production, is the same initially. As for the TCR, the genes for the different chains in a BCR are carried on different chromosomes (Fig. 1.11). Like those coding for other macromolecules, the genes are broken up into coding segments (exons) with intervening silent segments (introns). The heavy chain gene set on chromosome 14 is made up of small groups of exons representing the constant regions of the heavy chains [e.g. mu (μ) chain] and a very large number of V region genes, perhaps as many as 10^3. Between the V and C genes are two small sets of exons, D and J (Fig. 1.11). In a single B cell, one V region gene is selected, joined to one D and J on the same chromosome; the VDJ product is then joined at the level of RNA processing to C_μ when the B cell is making IgM. The cell can make IgG by omitting the C_μ and joining VDJ to a C_γ. Thus, the cell can make IgM, IgD and IgG/A/E in sequence, while still using the same variable region. **The same enzymes are used for the TCRs, and coded for by two recombination-activating genes control VDJ gene recombination**: **RAG1 and RAG2**. Disruption of the RAG1 or RAG2 function in infants who have mutations in these genes causes profound immune deficiency, characterized by absent mature B and T cells, as neither TCR or BCR can be produced. On a different chromosome (either chromosome 22 for λ chains or chromosome 2 for κ chains) in the same cell, a V gene is joined to a J gene (there is no D on the light chain) and then the VJ product is joined at the RNA level to the Cκ or Cλ (Fig. 1.11).

The wide diversity of antigen binding is dependent on the large number of V genes and the way in which these may be combined with different D and J genes to provide different rearranged VDJ gene segments. Once V, D and J rearrangement has taken place to produce a functional immunoglobulin molecule, *further V region variations are introduced only at a much later stage*, when antibodies rather than BCRs are produced by the process of somatic mutation in germinal centres.

Natural killer cells also have recognition molecules. These cells are important in killing virally infected cells and tumour cells. They have to be able to recognize these targets and distinguish them from normal cells. They recognize and kill cells that have reduced or absent MHC class I, using two kinds of receptors [inhibitory (KIR) and activating (KAR)] to estimate the extent of MHC expression. They also have one type of Fc IgG (Fcγ) receptor, that for low-affinity binding of IgG antibodies, and so NK cells are able to kill some cells with large amounts of antibody on their surfaces. Further subsets of NK-like cells that contribute to innate immunity include NKT cells and invariant NKT cells (section 1.3.6); these are thought to be particularly important in tumour immunology (sections 1.5.1).

The major purpose of the complement pathways is to provide a means of removing or destroying antigens, regardless of whether or not these are coated with antibody. This requires that **complement components recognize** damaging material such as immune complexes (antigen combined with antibodies) or foreign antigens. The complement pathways are discussed in more detail in section 1.3.5.

1.2.3 Accessory molecules

The binding of a processed antigen–MHC class II complex on an antigen-presenting cell to the corresponding TCR provides an insufficient signal for T-cell activation; the binding of accessory molecules on the two cell surfaces provides additional stimuli. Accessory molecules are lymphocyte surface proteins, distinct from the antigen binding complexes, which are necessary for **efficient binding, signalling and homing**. *Accessory molecules are invariant, non-polymorphic proteins*. Each accessory molecule has a particular ligand – a corresponding protein to which it binds. These ligands are present on all cells which require close adhesion for functioning; for example, there are those on T cells for each of the many cell types that can activate or respond to T cells (antigen-presenting cells, endothelial cells, etc.); similar ligands are present on B cells for efficiency of T-cell help as well as stimulation by follicular dendritic cells.

There are several families of accessory molecules, but the most important appear to be the **immunoglobulin supergene family of adhesion molecules**, which derives its name from the fact that its members contain a common immunoglobulin-

like structure. Members of their family strengthen the interaction between antigen-presenting cells and T cells (Fig. 1.12); those on T cells include CD4, CD8, CD28, CTLA-4, CD45R, CD2 and lymphocyte function antigen 1 (LFA-1). For interaction with B cells, CD40 ligand and ICOS are important for class switching (see section 1.4.3). Adhesion molecules, for binding leucocytes (both lymphocytes and polymorphonuclear leucocytes) to endothelial cells and tissue matrix cells, are considered in section 1.2.6. On B cells, such molecules include CD40 (ligand for CD40L, now named CD154) (Case 3.2), B-7-1 and B7-2 (ligands for CD28).

1.2.4 Effector molecules for immunity

There are humoral and cellular effector molecules in both the innate and the adaptive immune systems (Table 1.5). Several of the same mechanisms are used in both types of immune responses, especially in killing of target cells, *suggesting that evolution of immune responses has been conservative in terms of genes, though with much redundancy to ensure the life-preserving nature of the immune systems* in the face of rapid evolution of pathogenic microbes.

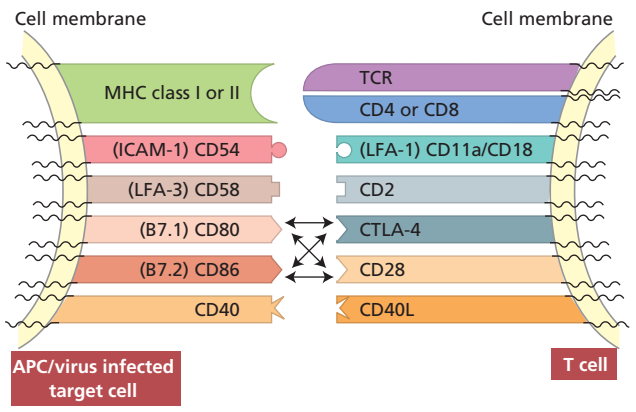


Fig. 1.12 Diagrammatic representation of adhesion molecules on T cells and their ligands on antigen-presenting cells/virus-infected target cells.

Antibodies

Antibodies are the best described effector mechanisms in adaptive immunity. They are the **effector arm of B cells** and are secreted as soluble molecules by plasma cells in large quantities, to be carried in the blood and lymph to distant sites. As shown in Table 1.4, there are five major isotypes of antibodies, each with different functions (see also Box 1.2).

IgM is a large molecule whose major physiological role is intravascular neutralization of organisms (especially viruses). **IgM** has five complement-binding sites, resulting in excellent complement activation and subsequent removal of the antigen–antibody–complement complexes by complement receptors on phagocytic cells or complement-mediated lysis of the organism (see section 1.4).

IgG is a smaller immunoglobulin which penetrates tissues easily. Placental transfer is an active process involving specific placental receptors for the Fc portion of the IgG molecule, termed FcRn (Fc receptor of the neonate). The FcRn receptor is also present on epithelial and endothelial cells and is an important regulator of IgG metabolism (see section 7.4 and Fig. 7.8). Of the four subclasses, IgG_1 and IgG_3 activate complement most efficiently and are responsible for clearing most protein antigens, including the removal of microorganisms by phagocytic cells (see section 1.5). IgG_2 and IgG_4 react predominantly with carbohydrate antigens (in adults) and are relatively poor opsonins.

IgA is the major mucosal immunoglobulin. Attachment of 'secretory piece' prevents digestion of this immunoglobulin in the intestinal and bronchial secretions. IgA_2 is the predominant subclass in secretions and neutralizes antigens that enter via these mucosal routes. IgA_1, the monomeric IgA in serum, is capable of neutralizing antigens that enter the circulation but IgA_1 is sensitive to bacterial proteases and therefore less useful

Table 1.5 Effector molecules in immunity

	Innate	Adaptive
Humoral	Complement components for opsonization or lysis	Specific antibodies for opsonization and phagocytosis or lysis with complement
Cellular	Perforin in NK cells creates pores in target cell membranes	Perforin in cytolytic (CD8) T cells creates pores in specific target cell membranes, allowing entry of granzymes to cause apoptosis
		NKT cells induce apoptosis by perforin production
	Granzymes in NK cells induce apoptosis in target cells	
	Lysosomes in phagocytic vacuoles result in death of ingested microbes	
	Preformed histamine and related vasoactive substances as well as leukotrienes in mast cells	

Box 1.2 Immunoglobulin isotypes and their significance

IgM is phylogenetically the oldest class of immunoglobulin. It is a large molecule (Fig. 1.9) and penetrates poorly into tissues. IgM has five complement-binding sites, which results in excellent activation of the classical complement pathway.

IgG is smaller and penetrates tissues easily. It is the only immunoglobulin to provide immune protection to the neonate (Table 1.4) as IgG is actively transported across the placenta. There are four subclasses of IgG, with slightly different functions.

IgA is the major mucosal immunoglobulin – sometimes referred to as 'mucosal antiseptic paint'. IgA in mucosal secretions consists of two basic units joined by a J chain (Fig. 1.10); the addition of a 'secretory piece' prevents digestion of this immunoglobulin in the intestinal and bronchial secretions.

IgD is synthesized by antigen-sensitive B lymphocytes, is not secreted, acting as a cell-surface receptor for activation of these cells by the specific antigen relating to the BCR; it is essential for activation of antigen-responsive B cells.

IgE is produced by plasma cells but is taken up by specific IgE receptors on mast cells and basophils. IgE then provides an antigen-sensitive way of expelling intestinal parasites by increasing vascular permeability and inducing chemotactic factors via mast cell degranulation (see section 1.7).

for host defence at mucosal surfaces. IgA has additional functions via its receptor (FcαR or CD89), present on mononuclear cells and neutrophils, for activation of phagocytosis, inflammatory mediator release and antibody-dependent cell-mediated cytotoxicity (ADCC) (see section 1.5).

There is little free **IgD or IgE** in serum or normal body fluids, since both act as surface receptors on mature B cells or mast cells respectively.

As mentioned previously, mechanisms of recombination in immunoglobulin production, whether for BCR or antibody production, are the same initially (Fig. 1.11). Once V, D and J region rearrangement has taken place, **further variation is introduced when antibodies are made**, by the introduction of point mutations in the V region genes. This process, known as **somatic hypermutation**, occurs in the lymphoid germinal centres and is critically dependent on activation-induced cytidine deaminase (AID), an enzyme responsible for deamination of DNA. Somatic hypermutation helps to increase the possible number of combinations and accounts for the enormous diversity of antibody specificities (10^{14}), which by far exceeds the number of different B cells in the body (10^{10}).

Box 1.3 Common features of cytokines

- Their half-lives are short so any potential harm due to persistent action is controlled.
- They are rapidly degraded as another method of regulation and thus difficult to measure in the circulation.
- Most act locally within the cell's microenvironment, which confines their action to a particular site.
- Some act on the cell of production itself, promoting self-activation and differentiation through high-affinity cell-surface receptors.
- Many cytokines are pleiotropic in their biological effects, i.e. affecting multiple organs in the body.
- Most exhibit biologically overlapping functions, illustrating the redundancy of the group. For this reason, therapeutic targeting of individual cytokines in disease has had limited success so far (effects of deletion of individual cytokine genes are listed in Table 1.7).

Cytokines and chemokines

Cytokines are soluble mediators secreted by macrophages or monocytes (monokines) or lymphocytes (lymphokines). These mediators act as **stimulatory or inhibitory signals** between cells; those between cells of the immune system were known as interleukins, (a phrase that has fallen out of general usage since the range of soluble molecules has widened so tremendously, though the individual names persist to avoid confusion). As a group, cytokines share several common features (see Box 1.3). Among the array of cytokines produced by macrophages and T cells, interleukin (IL)-1 and IL-2 are of particular interest due to their pivotal role in amplifying immune responses. IL-1 acts on a wide range of targets (Table 1.6), including T and B cells. In contrast, the effects of IL-2 are largely restricted to lymphocytes. Although IL-2 was originally identified on account of its ability to promote growth of T cells, it has similar trophic effects on IL-2 receptor-bearing B and NK cells. The considerable overlap between actions of individual cytokines and interleukins is summarized in Table 1.7.

Cytokines that induce chemotaxis of leucocytes are referred to as **chemokines**, a name derived from chemo + kine, i.e. something chemical to help movement. Some cytokines and interleukins have been redefined as chemokines as their function becomes clearer, e.g. IL-8 = CXCL8. Chemokines are structurally similar proteins of small molecule size (8–10 kDa), which are able to diffuse from the site of production to form a local concentration gradient along which granulocytes and lymphocytes can migrate towards the stimulus. There are two types of movement: migration of leucocytes to sites of inflammation and that of differentiating cells moving to a specific activation site (see section 1.2.5); chemokines are involved in

Table 1.6 Actions of interleukin-1

Target cell	Effect
T lymphocytes	Proliferation
	Differentiation
	Lymphokine production
	Induction of IL-2 receptors
B lymphocytes	Proliferation
	Differentiation
Neutrophils	Release from bone marrow
	Chemoattraction
Macrophages	Proliferation/activation
Fibroblasts	
Osteoblasts	
Epithelial cells	
Osteoclasts	Reabsorption of bone
Hepatocytes	Acute-phase protein synthesis
Hypothalamus	Prostaglandin-induced fever
Muscle	Prostaglandin-induced proteolysis

both. There are therefore two main types: the **inflammatory chemokines** (CXC) coded for by genes on chromosome 17 and attractants for granulocytes, and the **homeostatic chemokines** acting as attractants for lymphocytes (CC) and coded by genes on chromosome 4. The corresponding receptors on inflammatory cells are designated CXCR on neutrophils and CCR on lymphocytes; there are exceptions!

Molecules for lysis and killing

The other major sets of effector molecules are the cytolytic molecules, though less is known about their diversity or mechanisms of action. They include **perforin**, a C9 like molecule present in secretory lysosomes in CD8 T cells and in NK cells that polymerizes to form pores to enable large proteins to enter the cell. These cell types also secrete **granzymes**, enzymes that induce apoptosis in target cells (Table 1.5). Macrophages and polymorphonuclear leucocytes also contain many substances for the destruction of ingested microbes, some of which have multiple actions, such as TNF. The duplication of the functions of this essential phylogenetically ancient protein during evolution underlines the continued development of mammalian immunity to keep up with microbial invaders.

1.2.5 Receptors for effector functions

Without **specific cytokine receptors** on the surface of the target cells, cytokines are ineffective; this has been demonstrated in

Table 1.7 Clinically important cytokines grouped by effect on immune or inflammatory responses, to show source and site of action

Cytokines	Action
(a) Promotion of non-specific immunity and inflammation	
Interleukin-17 (IL-17)	Increases chemokine production for inflammatory cells
Interleukin-1 (IL-1)	(see Table 1.6)
Interleukin-6 (IL-6)	Growth and differentiation of T, B and haematopoietic cells
	Production of acute-phase proteins by liver cells
Interleukin-8 (now CXCL8)	Chemotaxis and activation of neutrophils, and other leucocytes
Interferon-α (IFN-α)	Antiviral action by: activation of natural killer (NK) cells, up-regulation of MHC class I antigens on virally infected cells, inhibition of viral replication
Interleukin-5 (IL-5)	Activation of B cells, especially for IgE production
	Activation of eosinophils
Tumour necrosis factor (TNF)	Promotion of inflammation by: activation of neutrophils, endothelial cells, lymphocytes, liver cells (to produce acute-phase proteins)
	Interferes with catabolism in muscle and fat (resulting in cachexia)
Interferon-γ (IFN-γ)	Activation of macrophages, endothelial cells and NK cells. Increased expression of MHC class I and class II molecules in many tissues; inhibits allergic reactions (↓IgE production)

(*Continued*)

Table 1.7 (*Continued*)

Cytokines	Action
(b) Lymphocyte activation, growth and differentiation, i.e. specific immunity	
Interleukin-2 (IL-2)	Proliferation and maturation of T cells, induction of IL-2 receptors and activation of NK cells
Interleukin-4 (IL-4) and interleukin-5 (IL-5)	Induction of MHC class II, Fc receptors and IL-2 receptors on B and T cells
	Induction of isotype switch in B cells Facilitation of IgE production (mainly IL-4) Activation of macrophages Proliferation of bone marrow precursors
Interleukin-12 (IL-12)†	Synergism with IL-2; regulates IFN-γ production Activation of NK cells
Interleukin-13 (IL-13)	Actions overlap with IL-4, including induction of IgE production
	IL-13 receptor acts as a functional receptor for IL-4
Interleukin-15 (IL-15)	Similar to IL-12
Interleukin-16 (IL-16)	Chemotaxis and activation of CD4 T cells
(c) Colony stimulation of bone marrow precursors	
GM-CSF	Stimulates growth of polymorph and mononuclear progenitors
G-CSF	Stimulates growth of neutrophil progenitors
M-CSF	Stimulates growth of mononuclear progenitors
(d) Regulatory cytokines	
Interleukin-10 (IL-10); also called cytokine synthesis inhibitory factor‡	Inhibition of cytokine production Growth of mast cells
Transforming growth factor-β (TGF-β)	Anti-inflammatory Inhibits cell growth
(e) Chemokines	
Interleukin-8 (IL-8)	See under section (a)
RANTES (regulated on activation, normal T cell expressed and secreted)	Chemoattractant for eosinophils, monocytes
Monocyte chemotactic protein (MCP 1, 2, 3)	Chemoattractant for monocytes
Exotaxin	Chemoattractant for eosinophils; synergistic with IL-5

*Evidence from murine models. See appendix for web address for update on knockout mice.
†IL-12 family of cytokines includes IL-23 and IL-27.
‡IL-10 family includes IL-19, IL-20 and IL-22.

those primary immune deficiencies in which gene mutations result in absence or non-functional receptors, such as the commonest X-linked form of severe combined immune deficiency (see Case 3.5), IL-12 receptor or IFN-γ receptor deficiencies (see Chapter 3). Some cytokines may have unique receptors but many others share a common structural chain, such as the γ-chain in the receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-23, suggesting that *these arose from a common gene originally*. There are other structurally similar cytokine receptors, leading to the classification of these receptors into five families of similar types of receptors, many of which have similar or identical functions, providing a safety net (redundancy) for their functions, which are crucial for both the innate and adaptive immune systems.

Chemokine receptors from a family of G protein coupled receptors – meaning that they are transmembrane and able to

activate internal signalling pathways. These receptors also function as differentiation 'markers', as they become expressed as an immune reaction progresses and cells move in inflammatory responses.

Receptors for the Fc portions of immunoglobulin molecules (FcR) are important for effector functions of phagocytic cells and NK cells. There are at least **three types of Fcγ receptors**: FcRγI are high-affinity receptors on macrophages and neutrophils that bind monomeric IgG for phagocytosis; FcRγII are low-affinity receptors for phagocytosis on macrophages and neutrophils and for feedback inhibition on B cells; and FcRγIII on NK cells as mentioned earlier. There are also FcRn involved in the transfer of IgG across the placenta and these receptors are also involved in IgG recirculation and catabolism. IgE receptors are found on mast cells, basophils and eosinophils for triggering degranulation of these cells. IgA receptors ensure the transport of polymeric IgA across the mucosal cells and other, possibly important, functions are slowly being defined.

Complement receptors for fragments of C3 produced during complement activation also provide a mechanism for phagocytosis and are found on macrophages and neutrophils. However, there are several types of **complement receptors**: those on red blood cells for transport of immune complexes for clearance (CR1), those on B cells and follicular dendritic cells in lymph nodes to trap antigen to stimulate a secondary immune response (CR2) (see section 1.4.3), those on macrophages, neutrophils and NK cells to provide adhesion of these blood cells to endothelium, prior to movement into tissues (CR3).

1.2.6 Adhesion molecules

Adhesion molecules comprise another set of cell surface glycoproteins with a pivotal role, not only in immune responses by **mediating cell-to-cell adhesion**, and for **adhesion between cells and extracellular matrix proteins**. Adhesion molecules are grouped into two major families: (i) integrins and (ii) selectins (Table 1.8). The migration of leucocytes to sites of inflammation is dependent on three key sequential steps mediated by adhesion molecules (Fig. 1.13): 1. rolling of leucocytes along activated endothelium is selectin dependent;

Table 1.8 Examples of clinically important adhesion molecules.

Adhesion molecule	Ligand	Clinical relevance of interaction	Consequences of defective expression
β_1 integrin family			
VLA-4 (CD49d–CD29) expressed on lymphocytes, monocytes	VCAM-1 on activated endothelium	Mediates tight adhesion between lymphocytes, monocytes and endothelium	? Impaired migration of lymphocytes and monocytes into tissue. Defective expression of either $\beta_1$integrins or VCAM-1 has not yet been described in humans
β_2 integrin family			
CD18/CD11 expressed on leucocytes	ICAM-1 on endothelium	Mediates tight adhesion between *all* leucocytes and endothelium	Defective expression of CD18/CD11 is associated with severe immunodeficiency, characterized by marked neutrophil leucocytosis, recurrent bacterial and fungal infection, and poor neutrophil migration into sites of infection
B_3 integrin family			
Expressed on platelets	Fibrinogen	Interacts during clotting	Clotting disorder *Glanzmann's disease*
Selectin family			
E-selectin (CD62E) expressed on activated endothelial cells	Sialyl Lewis X (CD15) on neutrophils, eosinophils	Mediates transient adhesion and rolling of leucocytes on monocytes	Defective expression of CD15 is associated with severe endothelium immunodeficiency – clinical features similar to CD18 deficiency. Mice deficient in both E- and P-selectin exhibit a similar clinical phenotype
L-selectin (CD62L) expressed on all leucocytes	CD34, Gly CAM on high endothelial venules	L-selectin mediates transient adhesion and rolling of leucocytes in lymph nodes, and also acts as a homing molecule directing lymphocytes into lymph nodes	L-selectin-deficient mice exhibit reduced leucocyte rolling and impaired lymphocyte homing

VLA, very late activation antigen; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule.

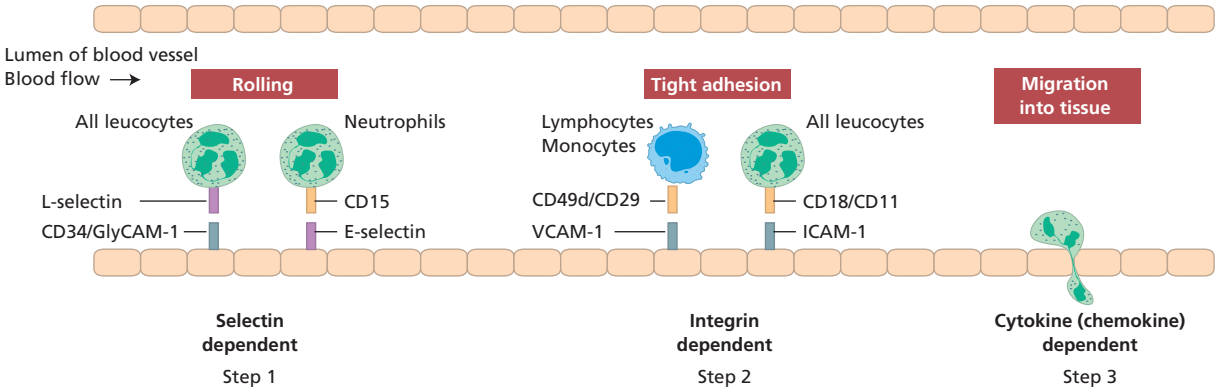


Fig. 1.13 Adhesion molecules and leucocyte–endothelial interactions.

Table 1.9 Proteins controlling classical and alternative complement pathways*

Protein	Function	Clinical consequences of DEFICIENCY
Circulating inhibitors		
C1 esterase inhibitor	Binds to activated C1r, C1s uncoupling it from C1q	Uncontrolled activation of classical pathway leading to hereditary angioneurotic oedema
Factor H	Binds C3b displacing Bb; cofactor for factor I	Total deficiency causes recurrent bacterial infection, glomerulonephritis & renal failure; partial deficiency with familial (atypical) haemolytic uraemic syndrome; a particular allele with adult macular degeneration
Factor I	Serine protease that cleaves C3b; acts synergistically with factor H	As for factor H
Membrane inhibitors		
Complement receptor 1 (CR1; CD35)	Receptor for C3b	Protect mammalian cells. Low CR1 numbers on red cells in SLE is a consequence of fast turnover
Decay accelerating factor (DAF; CD55)	Accelerates decay of C3b Bb by displacing Bb	DAF deficiency alone does not cause disease
Protectin (CD59)	Inhibits formation of lytic pathway complex on homologous cells; widely expressed on cell membranes	In combination with DAF deficiency leads to paroxysmal nocturnal haemoglobinuria (see Section 16.2.4)

SLE, Systemic lupus erythematosus.
*This is not an exhaustive list.

tight adhesion of leucocytes to endothelium is integrin dependent; and transendothelial migration occurs under the influence of chemokines. Cytokines also influence the selectin and integrin-dependent phases.

Integrins are heterodimers composed of non-covalently associated α and β subunits. Depending on the structure of the β subunit, integrins are subdivided into five families (β_1 to β_5 integrins). β_1 and β_2 integrins play a key role in leucocyte–endothelial interaction. β_1 integrins mediate lymphocyte and monocyte binding to the endothelial adhesion receptor called vascular cell adhesion molecule (VCAM-1). β_2 integrins share a common β chain (CD18) that pairs with a different α chain (CD11a, b, c) to form three separate molecules (CD11a CD18, CD11b CD18, CD11c CD18); they also mediate strong binding of leucocytes to the endothelium. Examples in other systems include β_3 to β_5 integrins mediate cell adhesion to extracellular matrix proteins such as fibronectin and vitronectin in the skin and laminin receptor in muscle.

The **selectin** family is composed of three glycoproteins designated by the prefixes E (endothelial), L (leucocyte) and P (platelet) to denote the cells on which they were first described. Selectins bind avidly to carbohydrate molecules on leucocytes and endothelial cells and regulate the homing of the cells to sites of inflammation (see sections 1.6.1, 11.1 and Table 1.9).

1.3 Functional basis of innate responses

The aim of an immune response is to destroy foreign antigens, whether these are inert molecules or invading organisms. To reach the site of invasion and destroy the pathogens, the components of the immune systems have to know where to go and to how to breach the normal barriers, such as the endothelial cells of the vascular system. Humoral factors (such as antibodies and complement) are carried in the blood and enter tissues following an increase in permeability associated with **inflammation**. Immune cells (innate and antigen specific) are actively attracted to a site of inflammation and enter the tissues via specific sites using active processes of adhesion.

Non-specific immunity is older, in evolutionary terms, than antibody production and antigen-specific T cells. The major cells involved in the innate system are phagocytic cells (macrophages and polymorphonuclear leucocytes), which remove antigens including bacteria, and dendritic cells which are the first cells to react to invaders. The major humoral components of the four complement pathways can either directly destroy an organism or initiate/facilitate its phagocytosis. Dendritic cells recognize pathogens in order to provide a rapid initial cytokine response (such as interferon-α in a viral infection by plasmacytoid dendritic cells) and to process antigen for presentation to specific TCRs alongside MHC for activation (classical dendritic cells) (section 1.4.1).

1.3.1 Endothelial cells

The endothelium forms a highly active cell layer lining the inside of blood vessels and thus in present in all tissues. In addition to the critical role in maintaining vasomotor tone, the **endothelium** is closely involved in inflammation, wound healing and the formation of new blood vessels (angiogenesis). Immunologically, endothelial cells are intimately involved in interactions with leucocytes prior to leaving the circulation to enter sites of tissue damage (Fig. 1.13). The endothelium also plays an important role in regulating the turnover of IgG, through the presence of FcRn, a receptor that prevents IgG from undergoing lysosomal degradation (see sections 1.2.4 and 7.4). The immunological importance of the endothelium is summarized in Box 1.4.

Box 1.4 Immunological importance of the endothelium

- Expresses a wide range of molecules on the cell surface (E-selectin, ICAM-1, VCAM-1, complement receptors) and thus plays a critical role in leucocyte–endothelial interactions (Fig. 1.13).
- Major site of IgG turnover due to FcRn.
- Forms important part of the innate immune response by expressing Toll-like receptors to recognize foreign pathogens.
- Capable of antigen presentation.

1.3.2 Neutrophil polymorphonuclear leucocytes

Neutrophils are short-lived cells that play a major role in the body's defence against acute infection. They synthesize and express adhesion receptors so they can stick to, and migrate out of, blood vessels into the tissues. Neutrophils move in response to **chemotactic agents** produced at the site of inflammation; substances include CXCL8, complement-derived factors (such as C3a and C5a), kallikrein, cytokines released by THh1 cells and chemotactic factors produced by mast cells.

Neutrophils are **phagocytic** cells. They are at their most efficient when activated after entering the tissues. Morphologically, the process of phagocytosis is similar in both neutrophils and macrophages. Neutrophils are able to kill and degrade the substances that they ingest. This requires a considerable amount of energy and is associated with a 'respiratory burst' of oxygen consumption, increased hexose monophosphate shunt activity and superoxide production.

1.3.3 Macrophages

Macrophages and monocytes represent the mononuclear phagocytic system, which along with dendritic cells, form the cells of the innate system. Lymphoid and myeloid cells are derived from closely related stem cells in the bone marrow (Fig. 1.1); each cell lineage has a different colony-stimulating factor and, once differentiated, they have entirely different functions. Polymorphonuclear leucocytes develop in the bone marrow and emerge only when mature. *Monocytes circulate for only a few hours before entering the tissues, where they may live for weeks or months as mature macrophages or dendritic cells.* **Macrophages differentiate** in the tissues, principally in subepithelial interstitial and lymphatic sinuses in liver, spleen and lymph nodes, sites where antigens gain entry. Tissue macrophages are heterogeneous in appearance, in metabolism and also in function; they include freely mobile alveolar and peritoneal macrophages, fixed Kupffer cells in the liver and those lining the sinusoids of the spleen. When found in other tissues, they are called histiocytes.

A major function of the mononuclear phagocyte system is to phagocytose invading organisms and other antigens. Macrophages have prominent lysosomal granules containing acid hydrolases and other degradative enzymes with which to destroy phagocytosed material. That material may be an engulfed viable organism, a dead cell, debris, an antigen or an immune complex. In order to carry out their functions effectively, macrophages must be 'activated'; in this state, they show increased **phagocytic and killing** activity. Stimuli include cytokines (see section 1.2), substances which bind to other surface receptors (such as IgG: Fc receptors, Toll-like receptors for endotoxin and other microbial components, receptors for bacterial polysaccharides and for soluble inflammatory mediators such as C5a (see Fig. 1.14). Activation may result in release of cytokines from monocytes or dendritic cells) such as TNF or IL-1, which may cause further damage in already inflamed tissues.

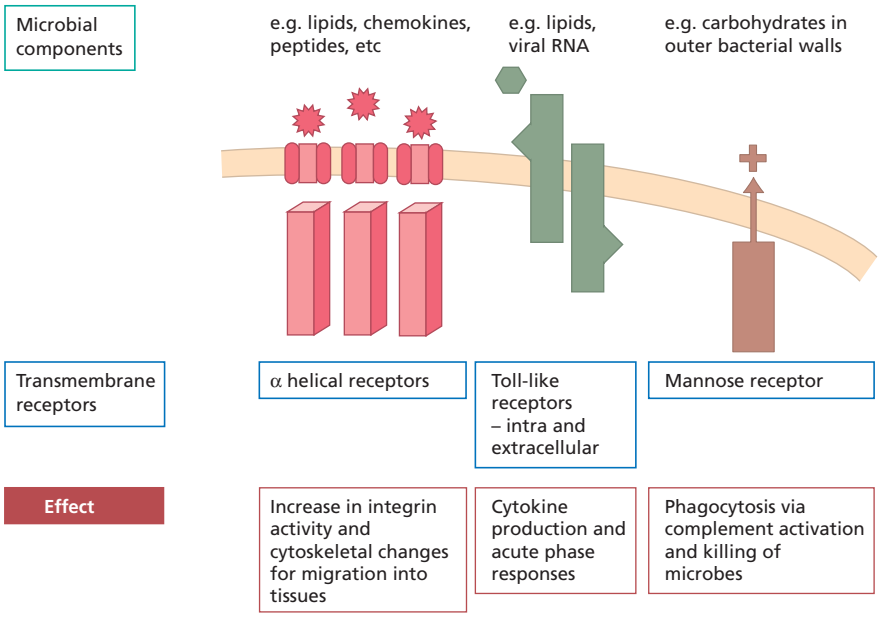


Fig. 1.14 Receptors and functions of mononuclear phagocytic cells.

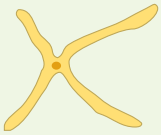
Cell	Appearance	Site	Mobility	Present to:
Interdigitating dendritic cells		Paracortex of lymph node	Mobile	T cells
Langerhans' cells		Skin	Mobile	T cells
Veiled cells		Lymph	Mobile	T cells
Follicular dendritic cells		Lymph node follicles	Static	B cells
Macrophages		Lymph node medulla Liver (Kupffer cells) Brain (astrocytes)	Mobile Static Static	T and B cells
B cell (especially if activated)		Lymphoid tissue	Mobile	T cells

Fig. 1.15 Antigen-presenting cells and their associated sites.

1.3.4 Dendritic cells

Classical or myeloid dendritic cells are mononuclear cells derived from bone marrow precursors and closely related to monocytes. There are many subsets but there are differences between these subsets in mice compared with man and other primates, particularly in their surface markers. So only those relating to humans are described here, though clearly their corresponding functions have been described in all mammalian species studied so far.

Immature dendritic cells are ubiquitous, particularly in epithelia that serve as a portal of entry for microbes, where they capture antigens as well as reacting to pathogen components quickly, within a few hours of invasion. Subsequently, the activated dendritic cells migrate to draining lymph nodes and mature to present antigen to cells of the adaptive system (Fig. 1.15).

Dendritic cells have a range of **functions**; as well as processing antigens (Fig. 1.7), they are able to recognize and respond to pathogens by secreting IFN-α, produce IL-12 and chemok-